Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomized trials

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DEDICATION

I am dedicating this thesis to both my parents, Jean and Nadia. You have sacrificed so much to open so many opportunities for my siblings and me. You inspire me and encourage me to become the best I can be. Thank you for everything you have done and will (undoubtedly) do.

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CONTRIBUTION OF AUTHORS

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PREFACE

This thesis is organized in a manuscript-based format. The research presented in this thesis has been published in the British Medical Journal Open (protocol) and in The Lancet (full report).

ABSTRACT

Background

Excessive opioid prescribing after surgery has contributed to the current opioid crisis; however, the value of prescribing opioids at surgical discharge remains uncertain. We aimed to estimate the extent to which opioid prescribing after discharge affects self-reported pain intensity and adverse events in comparison with an opioid-free analgesic regimen.

Methods

In this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Library, Scopus, AMED, Biosis, and CINAHL from Jan 1, 1990, until July 8, 2021. We included multidose randomized controlled trials comparing opioid versus opioid-free analgesia in patients aged 15 years or older, discharged after undergoing a surgical procedure according to the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) definition (minor, moderate, major, and major complex). We screened articles, extracted data, and assessed risk of bias (Cochrane's risk-of-bias tool for randomized trials) in duplicate. The primary outcomes of interest were self-reported pain intensity on day 1 after discharge (standardized to 0–10 cm visual analogue scale) and vomiting up to 30 days. Pain intensity at further timepoints, pain interference, other adverse events, risk of dissatisfaction, and health-care reutilization were also assessed. We did random-effects meta-analyses and appraised evidence certainty using the Grading of Recommendations, Assessment, Development, and Evaluations scoring system. The review was registered with PROSPERO (ID CRD42020153050).

Results

47 trials (n=6607 patients) were included. 30 (64%) trials involved elective minor procedures (63% dental procedures) and 17 (36%) trials involved procedures of moderate extent (47% orthopedic and 29% general surgery procedures). Compared with opioid-free analgesia, opioid prescribing did not reduce pain on the first day after discharge (weighted mean difference 0.01cm, 95% CI –0.26 to 0.27; moderate certainty) or at other postoperative timepoints (moderate-to-very-low certainty). Opioid prescribing was associated with increased risk of vomiting (relative risk 4.50, 95% CI 1.93 to 10.51; high certainty) and other adverse events, including nausea, constipation, dizziness, and drowsiness (high-to-moderate certainty). Opioids did not affect other outcomes.

Conclusion

Findings from this meta-analysis support that opioid prescribing at surgical discharge does not reduce pain intensity but does increase adverse events. Evidence relied on trials focused on elective surgeries of minor and moderate extent, suggesting that clinicians can consider prescribing opioid-free analgesia in these surgical settings. Data were largely derived from low-quality trials, and none involved patients having major or major-complex procedures. Given these limitations, there is a great need to advance the quality and scope of research in this field.

RÉSUMÉ

Contexte

La surprescription d'opioïdes après les chirurgies est un facteur contributif à la crise des opioïdes ; cependant, la valeur de la prescription d'opioïdes à la suite des interventions chirurgicales demeure incertaine. Nous avons cherché à estimer dans quelle mesure la prescription d'opioïdes après la sortie chirurgicale affecte l'intensité de la douleur et les événements indésirables comparée à un régime analgésique sans opioïdes.

Méthodes

Dans cette revue systématique et méta-analyse, nous avons recherché les bases de données suivantes : MEDLINE, Embase, la bibliothèque Cochrane, Scopus, AMED, Biosis et CINAHL du 1er janvier 1990 au 8 juillet 2021. Nous avons inclus des essais contrôlés randomisés à doses multiples comparant les opioïdes aux médicaments sans opioïdes prescripts aux patients âgés de 15 ans ou plus, sortis après avoir subi une intervention chirurgicale selon la définition du « Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity » (POSSUM) (mineur, modéré, majeur et complexe majeur). Nous avons examiné les articles trouvés, extrait les données et évalué le risque de biais (outil de risque de biais de Cochrane pour les essais randomisés) en double. Les principaux résultats d'intérêt étaient l'intensité de la douleur autodéclarée le premier jour après la sortie chirurgicale (normalisée à une échelle visuelle analogique de 0 à 10 cm) et l'incidence de vomissement jusqu'à 30 jours. L'intensité de la douleur en d'autres jours, l'interférence de la douleur, d'autres événements indésirables, le risque d'insatisfaction et la réutilisation des soins de santé ont également été évalués. Nous avons effectué des méta-analyses à effets aléatoires et nous avons évalué la certitude des preuves à

l’aide du système de notation « Grading of Recommendations, Assessment, Development, and Evaluations » (GRADE). Le protocole de cette étude a été enregistré auprès de PROSPERO (ID CRD42020153050).

Résultats

Quarante-sept essais (n = 6607 patients) ont été inclus. Trente (64 %) essais concernaient des procédures mineures électives (63 % procédures dentaires) et 17 (36 %) essais concernaient des procédures d’ampleur modérée (47 % procédures orthopédiques et 29 % procédures de chirurgie générale). Par rapport à l’analgésie sans opioïdes, la prescription d’opioïdes n’a pas réduit la douleur le premier jour après la sortie chirurgicale (différence moyenne pondérée 0,01 cm, intervalles de confiance à 95 % -0,26 à 0,27 ; certitude modérée) ou à d’autres moments postopératoires (certitude modérée à très faible). La prescription d’opioïdes était associée avec un risque plus élevé de vomissements (risque relatif 4,50, intervalles de confiance à 95 % 1,93 à 10,51 ; certitude élevée) et d’autres événements indésirables, notamment nausées, constipation, étourdissements et somnolence (certitude élevée à modérée). Les opioïdes n’ont pas eu d’effets significatifs sur les autres critères de jugement.

Conclusion

Les résultats de cette méta-analyse confirment que la prescription d’opioïdes à la sortie chirurgicale ne réduit pas l’intensité de la douleur, mais augmente les événements indésirables. Nos résultats sont basés sur des essais cliniques concernant les chirurgies électives d’ampleur mineure et modérée, ce qui suggère que les cliniciens peuvent envisager de prescrire des analgésiques sans opioïdes dans ces contextes chirurgicaux. Les données provenaient en grande partie d’essais de faible qualité, et aucun n’impliquait des patients subissant des procédures

majeures ou complexes majeures. Compte tenu de ces limites, il y a un grand besoin d'améliorer la qualité et la portée de la recherche dans ce domaine.

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PUBLICATIONS, CONFERENCE PRESENTATIONS, AND AWARDS

Publications

1. Fiore JF Jr*, **El-Kefraoui C***, Chay MA, Nguyen-Powanda P, Do U, Olleik G, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised trials. *Lancet*. 2022;399(10343): 2280-2293. *Co-first authors.
2. **El-Kefraoui C**, Olleik G, Chay MA, Kouyoumdjian A, Nguyen-Powanda P, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. *BMJ Open*. 2020;10(1): e035443.
3. Fiore JF Jr, Olleik G, **El-Kefraoui C**, Verdolin B, Kouyoumdjian A, Alldrit A, et al. Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia. *Br J Anaesth*. 2019;123(5): 627-636.
4. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. *JAMA Netw Open*. 2022;5(7): e2221430.
5. Do U, Pook M, Najafi T, Rajabiyazdi F, **El-Kefraoui C**, Balvardi S, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial. *Surg Endosc*. 2022. Doi: 10.1007/s00464-022-09472-8. Online ahead of print.

Conference presentations

1. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-

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2. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at the McGill High Value Healthcare Symposium; April 2022; Montreal, QC.
3. Do U, Pook M, Najafi T, Rajabiyazdi F, **El-Kefraoui C**, Balvardi S, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial. Podium presentation at Society of American Gastrointestinal and Endoscopic Surgeons 2022 Annual Congress; March 2022; Denver, CO.
4. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at 26th Annual McGill Pain Day; January 2022; Montreal, QC.
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6. Do U, Pook M, Najafi T, Rajabiyazdi F, **El-Kefraoui C**, Balvardi S, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial. Poster presentation at 22nd Annual Minimally Invasive Surgery Day; November 2021; Montreal, QC.

7. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Podium presentation at Canadian Surgery Forum 2021 Annual Meeting; September 2021; Halifax, NS.
8. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Podium presentation at Society of American Gastrointestinal and Endoscopic Surgeons 2021 Annual Congress; September 2021; Las Vegas, NV.
9. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at Injury Repair Recovery and Experimental Surgery 2021 Research Day; June 2021; Montreal, QC.
10. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Podium presentation at Injury Repair Recovery and Experimental Surgery 2021 Research Day; June 2021; Montreal, QC.
11. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at 31st Annual Fraser N. Gurd Surgical Research Forum; May 2021; Montreal, QC.
12. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot

randomized controlled trial. Poster presentation at 31st Annual Fraser N. Gurd Surgical Research Forum; May 2021; Montreal, QC.

13. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at L.D. MacLean Visiting Professor Research Day; May 2021; Montreal, QC.
14. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Podium presentation at Experimental Surgery 2021 Seminar Series; February 2021; Montreal, QC.
15. **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised controlled trials. Poster presentation at 21st Annual Minimally Invasive Surgery Day; November 2020; Montreal, QC.
16. Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Poster presentation at 21st Annual Minimally Invasive Surgery Day; November 2020; Montreal, QC.
17. **El-Kefraoui C**, Olleik G, Chay MA, Kouyoumdjian A, Nguyen-Powanda P, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. Poster presentation at Experimental Surgery 2019 Research Day; November 2019; Montreal, QC.

18. Olleik G, **El-Kefraoui C**, Verdolin B, Kouyoumdjian A, Alldrit A, Figueiredo AG, et al. Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia. Poster presentation at Canadian Surgery Forum 2019 Annual Meeting; September 2019; Montreal, QC.

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4. Best podium presentation (Human/Clinical research) – **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta- analysis of randomised controlled trials. 26th Annual McGill Pain Day; January 2022; Montreal, QC.
5. Top 3 podium presentation (Human/Clinical research) – Do U, **El-Kefraoui C**, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Annual McGill Pain Day; January 2022; Montreal, QC.
6. Top 2 podium presentation (Clinical research) – **El-Kefraoui C**, Chay MA, Nguyen-Powanda P, Do U, Olleik G, Rajabiyazdi F et al. Opioid versus opioid-free analgesia after

surgical discharge: A systematic review and meta- analysis of randomised controlled trials. Experimental Surgery 2021 Seminar Series; February 2021; Montreal, QC.

7. Best poster presentation – **El-Kefraoui C**, Olleik G, Chay MA, Kouyoumdjian A, Nguyen-Powanda P, Rajabiyazdi F, et al. Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. Experimental Surgery 2019 Research Day; November 2019; Montreal, QC.

LIST OF ABBREVIATIONS

ATC: Around the clock.

BCE: Before the Common Era

BPI-SF: Brief Pain Inventory Short-Form.

CI: Confidence intervals.

COS: Core outcome sets.

IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

IQR: Interquartile range.

MID: Minimally important difference.

NRS: Numerical rating scale.

NSAIDs: Non-steroidal anti-inflammatory drugs.

OA: Opioid Analgesia.

OFA: Opioid-Free Analgesia.

OME: Oral morphine equivalents.

PICO: Patients, interventions, comparators, outcomes.

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis.

PRN: Pro re nata; taken as needed.

PROMIS-29: Patient-Reported Outcomes Measurement Information System 29 Profile.

RCT: Randomized controlled trial.

RoB: Risk of bias.

RR: Relative risk.

VAS: Visual analogue scale.

WHO: World Health Organization.

WMD: Weighted mean difference.

CHAPTER 1: INTRODUCTION

1. Opioid analgesics

Opioids are natural or synthetic molecules that mediate important biological functions in humans and other animals.[1,2] They play a central role in pain processing and many other aspects of physiology such as mood regulation, stress responses, breathing, gastrointestinal transit, as well as endocrine and immune functions.[1,2] Opioids, whether synthetic or natural, act on opioid receptors, which are G-protein coupled receptors that act via second messengers to translate extracellular stimuli into intracellular responses.[3] There are three major types of opioid receptors: delta, kappa, mu. Although these three receptors share a similar structure, slight differences provide them with unique physiologic functions.[4]

Delta receptors are highly concentrated in the dorsal root ganglia of peripheral nerves.[5] These receptors play minimal role in acute pain management, but they have a substantial role in modulating chronic pain.[6]

Kappa receptors are highly concentrated in the spinal cord.[7] These receptors play an important role in modulating visceral pain and hyperalgesia.[7] Agonism of kappa receptors can cause many adverse events including dysphoria (i.e., state of uneasiness), diuresis, and constipation.[7]

The mu receptors are highly concentrated in the brain, particularly the limbic system.[8] These receptors mediate the analgesic effect of opioids and are also responsible for relevant opioid side-effects, including nausea and vomiting.[8,9] Importantly, while opioid mu receptors are the primary target for most synthetic opioids used to treat pain, their stimulation activates the brain's mesolimbic reward system (mediated by dopamine) leading to feelings of pleasure and euphoria.[8] Unfortunately, this temporary but powerful sense of well-being caused by opioids culminated in an epidemic of opioid misuse, addiction, and overdose in North America.[10,11]

2. The North American Opioid Crisis

Canada and the United States are facing a devastating crisis of opioid addiction and overdose.[12,13] The overprescription of opioids by physicians has been identified as an important contributor to this crisis.[12-14] In fact, the United States and Canada have the highest rate of opioid prescription per-capita in the world,[15] as well as the highest death toll from opioid overdose.[15] In 2019, more than 53,000 individuals lost their lives to opioid overdoses in Canada and the United States.[16,17] The COVID-19 pandemic has further exacerbated the opioid crisis. The number of opioid-related deaths rose to exceed 75,000 in 2020 and 80,000 deaths in 2021.[18,19] This increase has been attributed to an increased use of substances to cope with pandemic-related stress and social isolation, changes in illegal drug supply due to travel restrictions, and decreased access to support services for people who use drugs.[20] In response to these grim statistics, the Canadian and American federal governments have declared a state of public emergency with the aim of reducing unnecessary opioid access and improving prescribing practices.[21,22]

3. Opioid prescribing after surgical discharge

Surgery is one of the gateways for opioid-naïve patients to obtain an opioid prescription[23,24] and spiral into misuse and addiction.[25-29] Reports from Canada and the United States suggest that 6% to 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.[26,30-33] Interestingly, rates of persistent opioid use are similar among patients undergoing major surgeries (conducted in a hospital operating room, e.g. intra-abdominal surgeries)[31,32,34] and minor surgeries (conducted in an office or clinic, e.g. dental procedures).[33] Many surgical patients who do not become persistent opioid users may also contribute to the opioid crisis by

diverting unused tablets for nonmedical use by others. A recent systematic review suggests that of all opioid tablets prescribed to surgical patients, an astounding 42% to 71% go unused.[35] In other words, these prescriptions are unnecessary and become a readily available source for diversion. This is particularly relevant as over 50% of people who misuse opioids obtain the drug from friends or relatives with unused prescriptions.[36] Although the prescription of opioids after surgery stems from good intentions to reduce pain and improve patient comfort, postoperative overprescription is an urgent element of the opioid crisis given how it may contribute to misuse, diversion, addiction, and overdose.[37]

4. Preventing opioid prescribing after surgical discharge

From the perspective of surgeons and other perioperative care clinicians, the answer to the opioid crisis may lie in preventing postoperative opioid prescriptions using opioid-free analgesia [i.e., analgesia interventions using only non-opioid analgesics such as acetaminophen and/or non-steroid anti-inflammatory drugs (NSAIDs)]. Evidence suggests that this practice is common internationally, but not in Canada or the United States where opioid tablets are often prescribed instead of, or in addition to, non-opioid analgesics. In countries such as the Netherlands,[38] China,[39] and Chile[40], 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.[41-45] 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.[46] Interestingly, 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.[41-43] This may, in part, reflect a potential therapeutic superiority of non-opioid drugs or increased adverse events associated with opioid use (i.e., vomiting, constipation).

Although these findings bring into question the value of prescribing opioids to manage acute pain after surgical discharge, prescription decision-making 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 not existent in the literature.[47]

5. Why is a systematic review and meta-analysis needed?

The need for the proposed systematic review and meta-analysis is supported by findings from a scoping review recently completed by our group.[47] We reviewed over 4000 full-text articles (published between January 1990 and February 2019) to map the literature addressing opioid-free postoperative analgesia after major surgery. Of the 424 relevant multi-dose studies identified (i.e., those with analgesic interventions spanning several days), eight were randomized controlled trials (RCTs) comparing opioid versus opioid-free analgesia after postoperative discharge.[48-55] Nevertheless, we did not identify any systematic reviews and/or meta-analysis on this topic. Due to the lack of clear evidence regarding benefits and harms, the decision to prescribe opioids after minor and major surgeries seems to largely depend on clinician preference (or habit) and healthcare culture.[47] Hence, there is an urgent need for a robust knowledge synthesis of RCTs to guide prescription decision-making.

6. Thesis objectives

In light of the research gaps described above, the objective of this thesis project is to summarize the evidence regarding the comparative effectiveness of opioid versus opioid-free analgesia following surgery. Specifically, we aimed to measure the extent to which opioid prescribing at surgical discharge affects pain intensity and adverse events in comparison with opioid-free analgesia. Findings from this research project were published in The Lancet on June 18, 2022.

CHAPTER 2: MANUSCRIPT

Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomized trials

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2.1 ABSTRACT

Background

Excessive opioid prescribing after surgery has contributed to the current opioid crisis; however, the value of prescribing opioids at surgical discharge remains uncertain. We aimed to estimate the extent to which post-discharge opioid prescribing impacts self-reported pain intensity and adverse events in comparison with an opioid-free analgesic regimen.

Methods

In this systematic review and meta-analysis, we searched MEDLINE, EMBASE, the Cochrane Library, Scopus, Amed, Biosis, and CINAHL from January 1990 until July 2021. We included multi-dose randomised trials comparing opioid versus opioid-free analgesia in patients ≥15yo discharged after undergoing a surgical procedure (minor, moderate, major, or major-complex). We screened articles, extracted data, and assessed risk of bias (Cochrane's RoB-2) in duplicate. The primary outcomes of interest were pain intensity on post-discharge day one (standardized to 0-10cm visual analogue scale) and vomiting up to 30 days. Pain intensity at further timepoints, pain interference, other adverse events, risk of dissatisfaction, and healthcare reutilization were also assessed. We conducted random-effects meta-analyses and appraised evidence certainty using GRADE. The review was registered with PROSPERO (CRD42020153050).

Findings

Forty-seven trials (n=6607) were included; 30 involved elective minor procedures (63% dental) and 17 procedures of moderate extent (47% orthopedic, 29% general surgery). Compared with opioid-free analgesia, opioid prescribing did not reduce pain at the first-day post-discharge

[WMD 0.01cm (95% CI -0.26 to 0.27); moderate certainty] or at other postoperative timepoints (moderate-to-very low certainty). Opioid prescribing was associated with increased risk of vomiting [RR 4.50 (95% CI 1.93 to 10.51); high certainty] and other adverse events, including nausea, constipation, dizziness, and drowsiness (high-to-moderate certainty). Opioids did not impact other outcomes.

Interpretation

Findings from this meta-analysis support that opioid prescribing at surgical discharge does not reduce pain intensity but did increase adverse events. Evidence relied on trials focused on elective surgeries of minor and moderate extent, suggesting that clinicians can consider prescribing opioid-free analgesia in these surgical settings. Data were largely derived from low quality trials, and none involved patients undergoing major or major-complex procedures. Given these limitations, there is a great need to advance the quality and scope of research in this field.

Funding

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2.2 INTRODUCTION

Excessive opioid prescribing has contributed to a devastating crisis of addiction and overdose in North America.[12,13] Increasing rates of opioid prescription and opioid-related deaths have also been reported in other parts of the world.[56-59] Surgeons are responsible for the second-highest rate of opioid prescribing among all medical specialties,[24] and thus, are considered to be important contributors to the opioid crisis.[60] Although the prescription of opioids after surgery stems from well-intended efforts to reduce patients' postoperative pain and discomfort, studies have shown that even minor surgeries may serve as an initial event for opioid-naïve patients to become persistent opioid users.[61,62] Patients who do not become persistent users may also contribute to the opioid crisis by diverting unused tablets for nonmedical use by others.[34] Given this scenario, evidence-based strategies are required to support judicious opioid prescribing while ensuring effective postoperative pain management.[63]

Recent literature suggests that to prevent postoperative opioid-related harms, surgeons and other perioperative care clinicians may consider prescribing only non-opioid drugs to manage pain after surgical discharge.[64-66] However, while this practice is common outside North America,[38,39,46,67,68] evidence regarding the comparative-effectiveness of opioid versus opioid-free postoperative analgesia remains uncertain.[47] Hence, we conducted a systematic review and meta-analysis to assess the extent to which opioid prescribing at surgical discharge impacts pain intensity and adverse events in comparison to opioid-free analgesia.

2.3 METHODS

2.3.1 Search strategy and selection criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement[69] and targeted the following PICO question: in patients discharged after undergoing a surgical procedure (P), to what extent does the prescription of opioids (I), in comparison to opioid-free analgesia (C), impact self-reported pain intensity and adverse events (O). Eligible studies were RCTs that (1) had a parallel design, (2) enrolled youth and/or adults patients (≥15 years old) discharged after undergoing a surgical procedure according to the World Health Organization's (WHO) definition (i.e., any intervention involving the incision, excision, manipulation or suturing of tissue and requiring regional or general anesthesia or sedation),[70,71] (3) compared a post-discharge analgesia regimen including opioids versus opioid-free analgesia, and (4) involved a multiple-dose design focused on the overall effect of repeated doses of the analgesics prescribed. Trials targeting both elective and non-elective procedures (i.e., emergency/urgent surgeries) were considered for inclusion. Opioid analgesia was defined as any post-discharge pain management regimen involving the use of drugs that act on opioid receptors. Opioid-free analgesia was defined as any pain management regimen (pharmacological, non-pharmacological, or combined) that does not include opioid drugs. Trials where opioids were offered to the opioid-free group as rescue analgesia were 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).

We excluded cross-over trials as their results can be influenced by the natural history of postoperative pain improving over time regardless of the treatment received.[72] We also excluded single-dose trials as they do not reflect 'real-world' practices where analgesia regimens span

several days postoperatively.[73] Furthermore, single-dose analgesia trials focused on acute pain have been extensively reviewed in previous literature.[73,74] Other exclusion criteria were (1) trials where only placebo was offered to patients (do not reflect standard practice), (2) analgesic administration via invasive routes (e.g., intravenous, epidural; rarely used after discharge), and (3) analgesia for chronic postoperative pain (starting beyond 2 months after surgery).[75]

The following databases were searched: MEDLINE (via Ovid), EMBASE (via Ovid), the Cochrane Library (via Wiley), Scopus (via Elsevier), AMED (via Ovid), Biosis (via Clarivate), and CINAHL (via Ebsco). The search strategies (available in **Appendix pp 84-137**) were developed by a medical librarian (TL) and peer-reviewed (AAZ, AB).[76] Searches were conducted on March 5-7, 2019 and updated on July 8, 2021. We targeted articles published after 1990 as earlier publications do not reflect current standards of surgical care with the widespread use of minimally invasive approaches and care pathways.[77-80] No language restrictions were applied. To ensure literature saturation, we also searched trial registries (ClinicalTrials.gov and the WHO's Clinical Trials Registry Platform, via Cochrane CENTRAL), conference proceedings (via Scopus, Embase, BIOSIS, and the Cochrane Library), reference lists, and citations of the included articles (via Scopus).

2.3.2 Selection of studies and data extraction

Screening of titles, abstracts, and full texts was conducted, independently and in duplicate, by pairs of reviewers (JFF, CEK, MAC, PNP, UD, GO, FR, or AK). Disagreements were resolved by consensus or by consulting an adjudicator (LF). The screening was facilitated by a systematic review online software (Covidence, Veritas Health Innovation). Data extraction was conducted, independently and in duplicate, by pairs of reviewers (CEK, MAC, PNP, or UD) using a customized data extraction form integrated into the Covidence software. Discrepancies in the

extracted data were resolved by consensus after revisiting the full-text article. The data extracted included patient and study characteristics, information about the analgesia intervention [dosage (in oral morphine equivalents (OME) for opioids),[81] frequency of administration, duration, and use of non-pharmacological treatments], and intervention outcomes. Authors were contacted (up to three times via email) if information was missing or unclear.

2.3.3 Outcomes of interest

The first primary outcome of interest was self-reported pain intensity on the first day after surgical discharge (the latest assessment recorded between 13 and 24 hours). This timepoint was chosen to account for the duration of the effect of analgesic interventions used during surgery and/or inpatient stay; e.g., after ambulatory surgery, evidence suggests that patients report most severe pain after approximately 24hrs.[82,83] As per previous recommendations, we prioritized reports of 'dynamic' pain (over pain 'at rest') and 'worst pain' (over 'average pain').[84,85] The co-primary outcome of interest was risk of postoperative vomiting within the study follow-up period (up to 30 days). These outcomes were chosen based on previous literature showing that, according to patients' preference, good pain relief is the most desirable outcome in perioperative care, while postoperative vomiting is the least desirable outcome.[86-88] If data were available, we also assessed other endpoints recommended in core outcomes sets (COS) for perioperative care,[89,90] including: (1) pain intensity at other post-discharge timepoints defined *a priori* [from post-discharge day zero (latest assessment recorded between 6 and 12 hours) up to 30 days],[91] (2) drug adverse events (other than vomiting), (3) pain interference, (4) dissatisfaction with pain management, (5) participant disposition (i.e., withdrawal due to adverse events or ineffective treatment) (6) self-reported health status (overall and domain-based scores, e.g., fatigue, physical, emotional, social, and sleep functions), and (7) healthcare reutilization (i.e., return to

hospital or clinic). We were also interested in postoperative rates of prolonged opioid use, misuse, dependence, and overdose. When eligible RCTs were identified in protocol registries or conference proceedings, authors were contacted (up to three times via email) to obtain further study information and outcome data.

2.3.4 Risk of bias assessment

Risk of bias assessment was carried out independently and in duplicate by two investigators (JF, CEK) using the Cochrane's Risk of Bias Tool 2.0 (RoB 2.0),[92] which addresses five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selective reporting. For each domain, risk of bias was judged as 'low risk', 'some concerns', or 'high risk'. Studies were considered to have an overall 'high risk' of bias if any domain was judged as 'high risk'.[92] Disagreements were resolved by consensus or by consulting an adjudicator (LF).

2.3.5 Protocol registration

Our study protocol (available in **Appendix pp 138-155,** with amendments listed) was registered online (www.crd.york.ac.uk/PROSPERO; ID:CRD42020153050) and published *a priori*.[91]

2.3.6 Data analysis

The extent of agreement between reviewers during full-text screening was assessed using Kappa statistics.[93] When two or more trials assessed the same outcome, data were pooled using random-effects models according to the Hartung-Knapp-Sidik-Jonkman method.[94] Weighted mean differences (WMDs) and 95% confidence intervals (95%CIs) were calculated for pain intensity and other continuous outcomes.[95] For dichotomous measures, we calculated relative risks (RRs) and 95%CIs based on the frequency of events in each treatment arm. For trials reporting zero

events in one or both arms, we employed continuity correction by adding 0.5 to all the cells in 2×2 tables containing empty cells.[96] *Post hoc* sensitivity analyses were conducted using different approaches to address zero cell values: (1) no correction, and (2) correction proportional to the inverse of the opposite arm size.[97] Forest plots were used to display the meta-analyses findings. Analyses were conducted using Stata (Version 16, StataCorp, College Station, Texas, USA). Comparisons were 2-tailed and statistical significance was based on 95%CIs excluding the null.

To prepare continuous data for synthesis, methods described in the Cochrane Handbook were used to impute missing information (e.g., estimating means and standard deviation from medians and other measures of variance).[98] When trials had multiple treatment arms, data from opioid and/or opioid-free arms were aggregated according to Cochrane recommendations.[98] If ordinal or continuous scales were used to assess satisfaction with pain management, data were dichotomized to facilitate interpretation (dissatisfied= very dissatisfied, dissatisfied, or satisfaction score <5/10; not dissatisfied= very satisfied, satisfied, neutral, or satisfaction score ≥5/10).[98] Interpreting effect estimates of '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]. To address this issue, we followed specific guidelines to transform pain intensity measures into a standard metric (as described in the **Appendix, pp 156-157**).[99-101] The standard pain metric chosen was the 10-cm Pain Intensity VAS (score range 0-10 cm; lower score represents less pain), which is the pain measure most commonly used in acute pain trials.[85,102,103] Once VAS WMDs were calculated, we contextualized them in relation to the minimally important difference (MID, the smallest change in score that patients perceive as important[104]) established in previous surgical literature: 1/10cm.[105] To guide the contextualization of VAS data based on this MID, we followed recommendations by the

IMMPACT initiative[106]: a clinically meaningful difference in VAS was deemed *achieved* if WMD 95%CIs laid outside the MID thresholds (-1cm to +1cm), *unlikely* if 95%CIs laid within the MID thresholds, and *inconclusive* if 95%CIs crossed the MID thresholds.

2.3.7 Subgroup analyses

Heterogeneity between the RCTs was assessed using the I^2 test.[107] To explore potential sources of heterogeneity in the analysis of the co-primary outcomes, we conducted subgroup analyses if there were 2 or more trials in each subgroup. We tested *a priori* hypotheses that larger opioid effect sizes would be observed in trials involving: (1) surgeries conducted in an outpatient clinic versus in a hospital operating room (as per WHO's definition of minor versus major surgery),[70,71] (2) day-surgery (i.e., same-day discharge) versus in-patient surgery (i.e., at least one overnight stay), (3) only women as participants [reports of sex-specific data or sex-specific surgeries (e.g., gynecological, breast)] versus men (or both sexes),[72,108] and (4) trials with high versus lower risk of bias.[109,110] In *post hoc* subgroup analyses, we explored the hypotheses that opioid effect sizes would be larger in trials involving: (1) surgeries of larger extent (as classified on based on the POSSUM scoring system [minor (i.e., dental, skin, hand surgery), moderate (e.g. minimally invasive orthopedic, general surgery), major (i.e., bowel, liver, lung resections), major-complex (i.e., thoraco-abdominal, multi-organ resections, procedures under extracorporeal circulation);[111] details in the **Appendix, p 158-159**)], (2) opioid analgesia with 'stronger' opioids (OME ≥1, i.e., morphine, oxycodone, hydrocodone) versus 'weaker' (OME<1, i.e., codeine, dihydrocodeine, tramadol),[112] (3) opioid analgesia prescribed around-the-clock (i.e., at regularly scheduled intervals) versus 'as needed',[113] (4) unimodal opioid-free analgesia (only one non-opioid drug prescribed) versus multimodal (more than one non-opioid drug prescribed),[114] (5) multimodal opioid analgesia (opioid prescribed in addition to non-opioid drug) versus unimodal (only

opioids prescribed),[114] (6) industry funding versus no industry funding,[115] and (7) published versus unpublished data.[116] Tests of interaction were performed to establish if the differences between subgroups were statistically significant.[117] In subgroup analyses of pain outcomes, intervention effects within subgroups were interpreted according to MIDs and 95%CIs.[106]

2.3.8 Certainty of evidence

Certainty of evidence was rated as high, moderate, low, or very low using the GRADE approach.[118] Assessment was conducted, independently and in duplicate (JF, CEK), on an outcome-by-outcome basis.[119] Disagreements were resolved by consensus or by consulting an adjudicator (LF). GRADE items concerning risk of bias, inconsistency, indirectness, imprecision, and publication bias were appraised according to specific criteria (**Appendix pp 160-161**). When there were at least 10 RCTs available for meta-analysis, risk of publication bias was assessed by visual appraisal of funnel plot asymmetry[120] and Begg's test.[121]

2.3.9 Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing, or submission of the report.

2.4 RESULTS

A total of 23977 unique articles were identified and 567 underwent full-text review. Of those, 520 were excluded (articles and reasons for exclusion are listed in the **Appendix pp 162-185**), and 47 met eligibility criteria (Figure 1).[122-168] Among the included trials, 36 addressed pain intensity on the first day post-discharge[122-124,129-134,137,138,140,141,144-157,159-167] and 12 addressed risk of postoperative vomiting (co-primary outcomes).[122,126,127,133-137,140,142,162,165] There was substantial agreement between reviewers during full-text screening ($\kappa = 0.79$).[93] Trial characteristics are described in the **Appendix (summary table, pp 186-191; detailed description, pp 192-342)**. In total, the included trials involved 6607 patients; 59% were female and the average age range was 21 to 63 years. The majority of the trials were conducted in North America (n=25, 53%)[124,126,128-131,135-140,143,145-148,155-158,163,164,167,168] and Europe (n=11, 23%).[125,127,132,142,151,154,159,161,162,165,166] Median duration of patient follow-up was 7 days (IQR 4.25-10). Ten trials (21%) reported industry funding. [126,127,132,135,139,153,155,156,159,168] A total of 17 relevant unpublished RCTs were identified (8 completed, 7 ongoing, 1 terminated, and 1 status unknown). After contacting authors, we obtained data and risk of bias information from 5 unpublished trials. [131,137,145,146,163] Also, we queried missing information from 14 published trials; four authors provided additional data.[127,130,142,147]

Twenty-three trials (49%) involved patients undergoing surgeries conducted in an outpatient clinic[122,123,125,126,128,129,132-135,138,139,141,144,151-154,160,164-166,168] and 24 involved surgeries conducted in a hospital operating room.[124,127,130,131,136,137,140,142,143,145-150,155-159,161-163,167] Forty trials (85%) involved day-surgery[122-126,128-135,137-141,143-148,151-154,156,157,159-168] and 7 (15%) involved in-patient procedures with at least an overnight hospital stay.[127,136,142,149,150,155,158] Among the trials identified, 30 (64%) involved surgeries of minor extent[122,123,125,126,128-135,138,139,141,143,144,149,151-

[154,160,161,163-168] and 17 (36%) involved surgeries of moderate extent.[124,127,136,137,140,142,145-148,150,155-159,162] None of the trials identified involved major or major-complex procedures. All the included trials focused on elective surgeries or did not explicitly report the inclusion of emergency/urgent procedures.

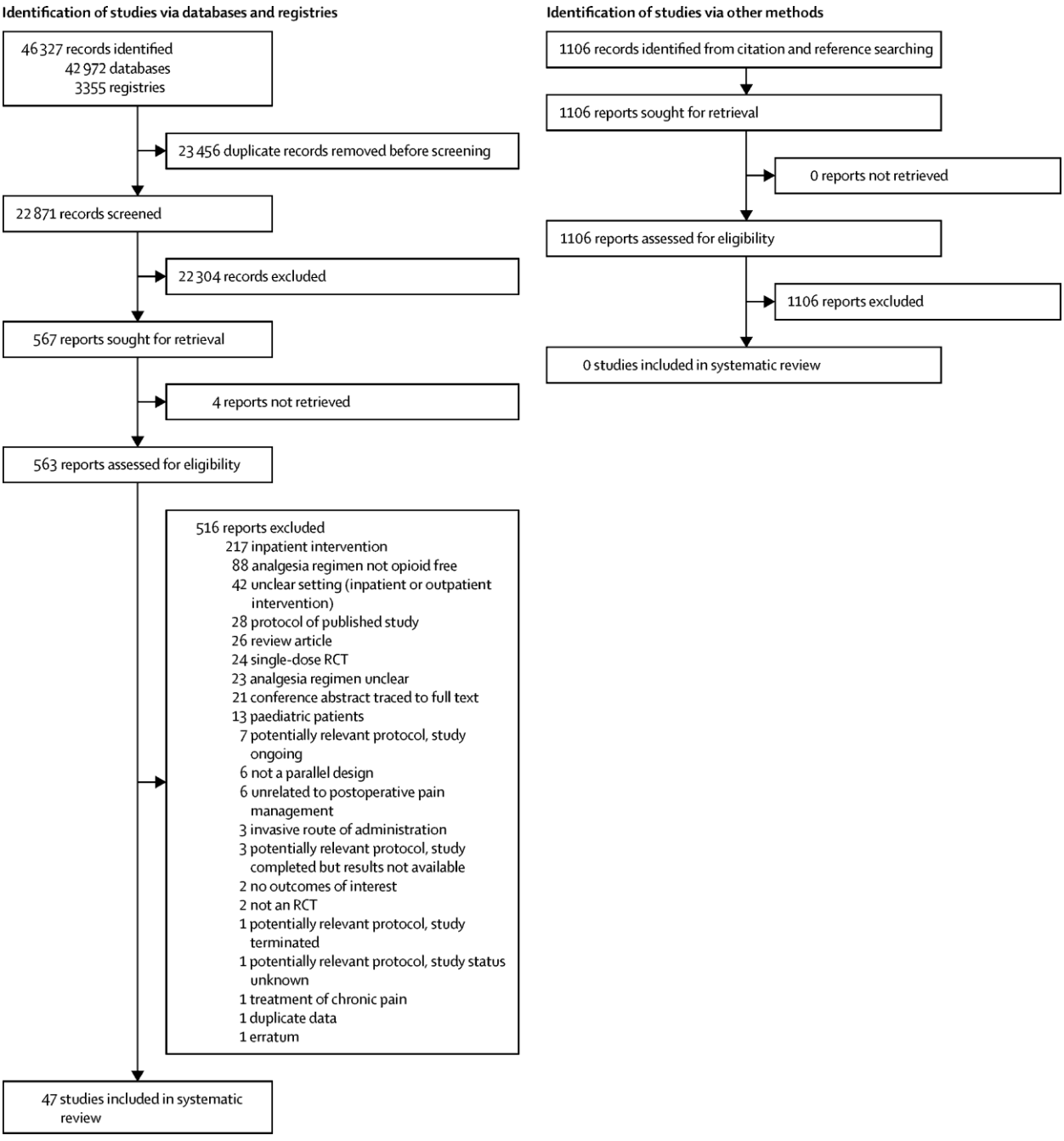
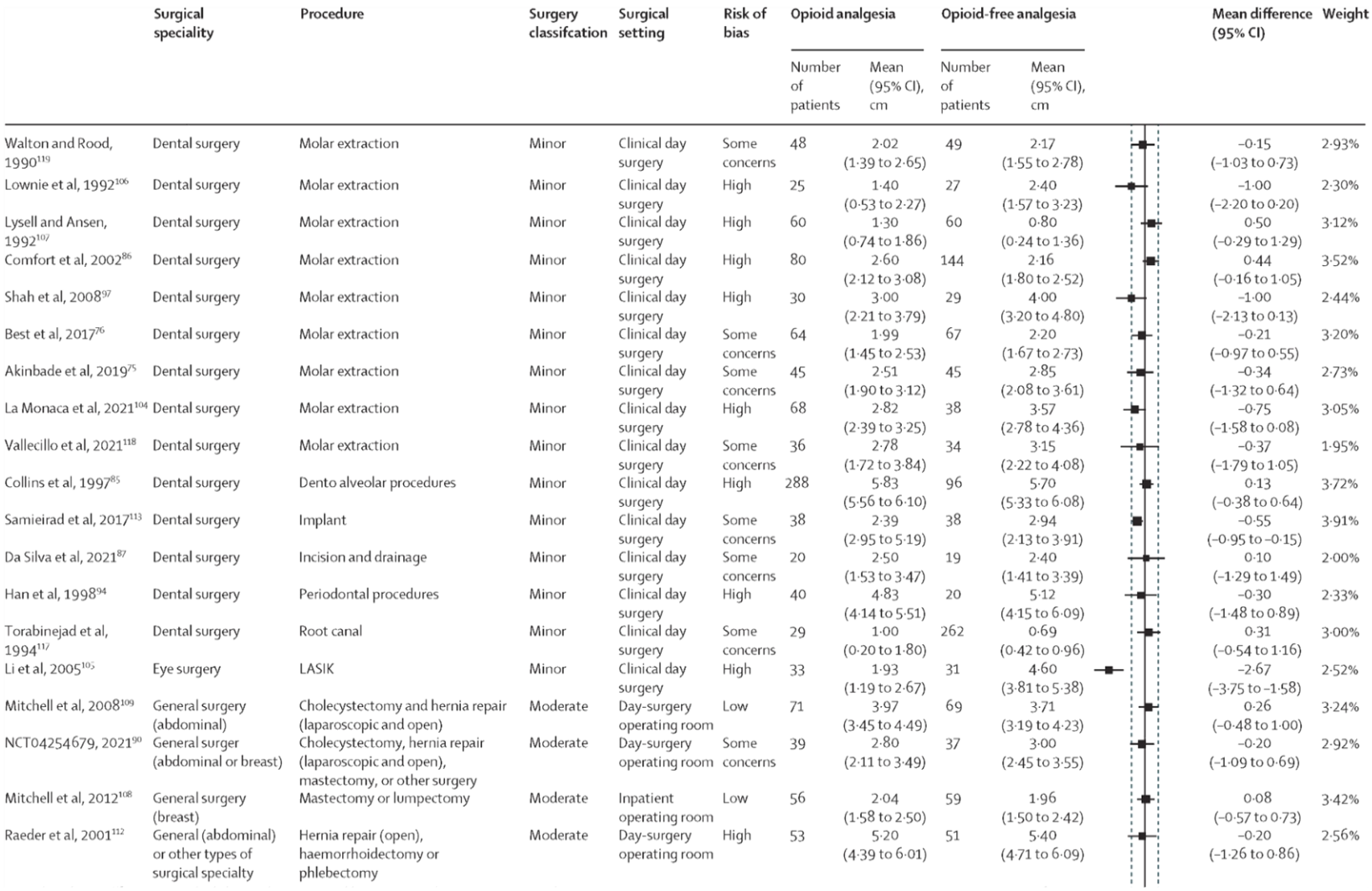


Figure 1: PRISMA diagram

Most opioid-free analgesia regimens were unimodal (n=26, 55%),[122,128,129,131-135,138-141,143,144,149-154,159-161,164,165,168] involved drugs prescribed around-the-clock (n=25, 53%),[122,123,125-127,129,130,133-135,137,141,144,149,150,152-154,159-162,164-166] and included nonsteroidal anti-inflammatory drugs (NSAIDs) (n=42, 89%)[122-128,130,131,133,135-159,162-168] and/or acetaminophen (n=27, 57%).[123-127,130,132,134,136,137,142,143,145-148,155-158,160-164,166,167] Opioid analgesia regimens were most often multimodal (n=42, 89%)[123-142,145-149,151-156,158-168] and had opioids prescribed around-the-clock (n=25, 53%).[122,123,125-127,129,130,132-135,141,144,149,150,152-154,159-162,164-166] The opioid drugs most commonly prescribed were codeine (n=20, 43%),[123,125,126,128,129,133,134,139,141,149,151,153-156,159,160,163,164,166] hydrocodone (n=11, 23%),[130,131,136,138,140,145-148,167,168] and tramadol (n=9, 19%).[122,127,132,135,142,144,152,161,165] The median OME dose prescribed per day was 27mg (IQR 12-41.25). Only one study described the use of non-pharmacological analgesia interventions (ice packs).[158]

A complete description of risk of bias assessment results by outcome measure is reported in the **Appendix (pp 343-382)**. In the 36 RCTs assessing pain on the first day after discharge,[122-124,129-134,137,138,140,141,144-157,159-167] risk of bias was 'low' in 2 trials (6%),[155,156] 'some concerns' in 12 trials (33%),[122,123,134,137,140,150,160,162-166] and 'high' in 22 trials (61%).[124,129-133,138,141,144-149,151-154,157,159,161,167] Of the 12 trials assessing vomiting,[122,126,127,133-137,140,142,162,165] 9 (75%) had 'some concerns',[122,134-137,140,142,162,165] and 3 (25%) had 'high' risk of bias.[126,127,133] The most common reasons for increased risk of bias were potential deviations from intended interventions (e.g., non-compliance with intention-to-treat principle), poor description of the randomization process, and potential selective reporting (i.e., trial protocol not available). There was no clear evidence of publication bias in statistical or visual appraisal of funnel plots (**Appendix pp 383-397**).

Moderate-certainty evidence (36 trials, 3848 patients) [122-124,129-134,137,138,140,141,144-157,159-167] supported that the prescription of opioids was not associated with decreased pain intensity on day one post-discharge [WMD 0.01 cm (95%CI, -0.26 to 0.27 cm)] (Figure 2 and Table 1). The observed 95%CI laid within the MID thresholds, indicating that any potential effect of opioids on postoperative pain relief is unlikely to be clinically meaningful. Subgroup analyses indicated that potential sources of heterogeneity in the pooled intervention effect ($p<0.05$ for interactions) were surgery conducted in an outpatient clinic (versus hospital operating room), weaker (versus stronger) opioids, opioids prescribed around-the-clock (versus 'as needed'), and unpublished (versus published) trials (**Appendix pp 398-408**). Within these subgroups, 95%CIs excluded clinically meaningful benefits of opioids. At other postoperative timepoints, the prescription of opioids was not associated with statistically significant decreases in pain intensity and 95%CIs excluded clinically meaningful benefits (certainty of evidence varied from very low to moderate) (Table 1 and **Appendix pp 420-424**).



	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia		Opioid-free analgesia		Mean difference (95% CI)	Weight
						Number of patients	Mean (95% CI), cm	Number of patients	Mean (95% CI), cm		
Walton and Rood, 1990[119]	Dental surgery	Molar extraction	Minor	Clinical day surgery	Some concerns	48	2·02 (1·39 to 2·65)	49	2·17 (1·55 to 2·78)	−0·15 (−1·03 to 0·73)	2·93%
Lownie et al, 1992[106]	Dental surgery	Molar extraction	Minor	Clinical day surgery	High	25	1·40 (0·53 to 2·27)	27	2·40 (1·57 to 3·23)	−1·00 (−2·20 to 0·20)	2·30%
Lysell and Ansen, 1992[107]	Dental surgery	Molar extraction	Minor	Clinical day surgery	High	60	1·30 (0·74 to 1·86)	60	0·80 (0·24 to 1·36)	0·50 (−0·29 to 1·29)	3·12%
Comfort et al, 2002[86]	Dental surgery	Molar extraction	Minor	Clinical day surgery	High	80	2·60 (2·12 to 3·08)	144	2·16 (1·80 to 2·52)	0·44 (−0·16 to 1·05)	3·52%
Shah et al, 2008[97]	Dental surgery	Molar extraction	Minor	Clinical day surgery	High	30	3·00 (2·21 to 3·79)	29	4·00 (3·20 to 4·80)	−1·00 (−2·13 to 0·13)	2·44%
Best et al, 2017[76]	Dental surgery	Molar extraction	Minor	Clinical day surgery	Some concerns	64	1·99 (1·45 to 2·53)	67	2·20 (1·67 to 2·73)	−0·21 (−0·97 to 0·55)	3·20%
Akinbade et al, 2019[75]	Dental surgery	Molar extraction	Minor	Clinical day surgery	Some concerns	45	2·51 (1·90 to 3·12)	45	2·85 (2·08 to 3·61)	−0·34 (−1·32 to 0·64)	2·73%
La Monaca et al, 2021[104]	Dental surgery	Molar extraction	Minor	Clinical day surgery	High	68	2·82 (2·39 to 3·25)	38	3·57 (2·78 to 4·36)	−0·75 (−1·58 to 0·08)	3·05%
Vallecillo et al, 2021[118]	Dental surgery	Molar extraction	Minor	Clinical day surgery	Some concerns	36	2·78 (1·72 to 3·84)	34	3·15 (2·22 to 4·08)	−0·37 (−1·79 to 1·05)	1·95%
Collins et al, 1997[85]	Dental surgery	Dento alveolar procedures	Minor	Clinical day surgery	High	288	5·83 (5·56 to 6·10)	96	5·70 (5·33 to 6·08)	0·13 (−0·38 to 0·64)	3·72%
Samieirad et al, 2017[113]	Dental surgery	Implant	Minor	Clinical day surgery	Some concerns	38	2·39 (2·95 to 5·19)	38	2·94 (2·13 to 3·91)	−0·55 (−0·95 to −0·15)	3·91%
Da Silva et al, 2021[87]	Dental surgery	Incision and drainage	Minor	Clinical day surgery	Some concerns	20	2·50 (1·53 to 3·47)	19	2·40 (1·41 to 3·39)	0·10 (−1·29 to 1·49)	2·00%
Han et al, 1998[94]	Dental surgery	Periodontal procedures	Minor	Clinical day surgery	High	40	4·83 (4·14 to 5·51)	20	5·12 (4·15 to 6·09)	−0·30 (−1·48 to 0·89)	2·33%
Torabinejad et al, 1994[117]	Dental surgery	Root canal	Minor	Clinical day surgery	Some concerns	29	1·00 (0·20 to 1·80)	262	0·69 (0·42 to 0·96)	0·31 (−0·54 to 1·16)	3·00%
Li et al, 2005[105]	Eye surgery	LASIK	Minor	Clinical day surgery	High	33	1·93 (1·19 to 2·67)	31	4·60 (3·81 to 5·38)	−2·67 (−3·75 to −1·58)	2·52%
Mitchell et al, 2008[109]	General surgery (abdominal)	Cholecystectomy and hernia repair (laparoscopic and open)	Moderate	Day-surgery operating room	Low	71	3·97 (3·45 to 4·49)	69	3·71 (3·19 to 4·23)	0·26 (−0·48 to 1·00)	3·24%
NCT04254679, 2021[90]	General surger (abdominal or breast)	Cholecystectomy, hernia repair (laparoscopic and open), mastectomy, or other surgery	Moderate	Day-surgery operating room	Some concerns	39	2·80 (2·11 to 3·49)	37	3·00 (2·45 to 3·55)	−0·20 (−1·09 to 0·69)	2·92%
Mitchell et al, 2012[108]	General surgery (breast)	Mastectomy or lumpectomy	Moderate	Inpatient operating room	Low	56	2·04 (1·58 to 2·50)	59	1·96 (1·50 to 2·42)	0·08 (−0·57 to 0·73)	3·42%
Raeder et al, 2001[112]	General (abdominal) or other types of surgical specialty	Hernia repair (open), haemorrhoidectomy or phlebectomy	Moderate	Day-surgery operating room	High	53	5·20 (4·39 to 6·01)	51	5·40 (4·71 to 6·09)	−0·20 (−1·26 to 0·86)	2·56%

Figure 2: Forest plot for pain on day 1 after discharge

	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia		Opioid-free analgesia		Mean difference (95% CI)	Weight
						Number of patients	Mean (95% CI), cm	Number of patients	Mean (95% CI), cm		
Stessel et al, 2014[115]	General (abdominal) or orthopaedic surgery	Inguinal hernia repair (laparoscopic and open) or knee repair (arthroscopic)	Moderate	Day-surgery operating room	Some concerns	70	2·92 (2·11 to 3·73)	35	2·67 (1·44 to 3·90)	0·25 (−1·19 to 1·68)	1·93%
Church et al, 2006[83]	Head and neck surgery	Functional endoscopic sinus surgery	Minor	Day-surgery operating room	High	14	2·74 (1·66 to 3·82)	14	2·94 (1·79 to 4·10)	−0·20 (−1·79 to 1·38)	1·72%
NCT03605914, 2021[84]	Head and neck surgery	Functional endoscopic sinus surgery	Minor	Day-surgery operating room	High	26	2·39 (2·06 to 2·72)	31	2·94 (2·71 to 3·17)	1·05 (−0·36 to 2·46)	1·95%
Kim et al, 2005[102]	Head and neck surgery	Tonsillectomy	Minor	Inpatient operating room	High	60	7·45 (6·93 to 7·97)	30	7·90 (7·51 to 8·29)	−0·45 (−1·24 to 0·34)	3·12%
Papoian et al, 2020[110]	Head and neck surgery	Thyroidectomy (total or partial)	Moderate	Day-surgery operating room	High	46	2·40 (1·68 to 3·12)	49	1·60 (0·98 to 2·22)	0·80 (−0·15 to 1·75)	2·80%
Brady et al, 2021[77]	Head and neck surgery	Thyroidectomy (total or partial) or parathyroidectomy	Moderate	Day-surgery operating room	High	62	5·67 (5·12 to 6·22)	64	6·00 (5·64 to 6·36)	−0·33 (−0·99 to 0·33)	3·41%
Gimbel et al, 2001[93]	Orthopaedic surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Day-surgery operating room	Some concerns	181	6·83 (6·50 to 7·16)	185	5·69 (5·37 to 6·02)	1·14 (0·67 to 1·60)	3·80%
NCT03818932, 2021[99]	Orthopaedic surgery	Cruciate ligament repair (arthroscopic)	Moderate	Day-surgery operating room	High	28	4·70 (3·88 to 5·52)	34	3·90 (3·16 to 4·64)	0·80 (−0·31 to 1·91)	2·48%
Jildeh et al, 2021 (A)[100]	Orthopaedic surgery	Labrum repair (arthroscopic)	Moderate	Day-surgery operating room	High	24	4·90 (4·02 to 5·78)	24	4·10 (3·22 to 4·98)	0·80 (−0·45 to 2·05)	2·22%
Jildeh et al, 2021 (B)[101]	Orthopaedic surgery	Meniscus repair (arthroscopic)	Moderate	Day-surgery operating room	High	30	2·80 (2·01 to 3·59)	31	2·70 (1·92 to 3·48)	0·10 (−1·01 to 1·21)	2·47%
NCT03818919, 2021[98]	Orthopaedic surgery	Rotator cuff repair (arthroscopic)	Moderate	Day-surgery operating room	High	27	5·70 (4·95 to 6·45)	17	3·70 (2·65 to 4·75)	2·00 (0·74 to 3·26)	2·20%
Kim et al, 2019[103]	Orthopaedic or neurosurgery	Laminectomy or discectomy	Moderate	Inpatient operating room	Some concerns	47	4·46 (4·09 to 4·83)	46	4·95 (4·59 to 5·31)	−0·49 (−1·01 to 0·03)	3·70%
Spagnoli et al, 2011[114]	Orthopaedic or plastic surgery	Hand and foot repair (carpal tunnel, bunion, or other types of repair)	Minor	Day-surgery operating room	High	57	0 (0 to 0)	57	0·90 (0·33 to 1·47)	−0·90 (−1·71 to −0·09)	3·08%
NCT02647788, 2019[116]	Orthopaedic or plastic surgery	Hand repair (carpal tunnel or trigger finger)	Minor	Day-surgery operating room	Some concerns	53	3·51 (2·79 to 4·23)	49	2·90 (2·28 to 3·52)	0·61 (−0·35 to 1·57)	2·76%
Weinheimer et al, 2019[120]	Orthopaedic or plastic surgery	Hand repair (carpal tunnel, trigger finger, or other types of repair)	Minor	Day-surgery operating room	High	30	3·00 (2·21 to 3·79)	30	2·20 (1·41 to 2·99)	0·80 (−0·32 to 1·92)	2·46%
Chen and Adamson, 2009[82]	Plastic surgery	Rhinoplasty, rhytidectomy, otoplasty, or other types of surgery)	Minor	Clinical day surgery	High	17	2·12 (1·07 to 3·17)	18	2·37 (1·35 to 3·39)	−0·25 (−1·71 to 1·21)	1·88%
Frants et al, 2021[91]	Plastic surgery	Rhinoplasty	Minor	Clinical day surgery	High	26	2·46 (1·73 to 3·19)	38	1·84 (1·43 to 2·25)	0·62 (−0·16 to 1·40)	3·15%
Overall										**0·01 (−0·26 to 0·27)**	

Heterogeneity: χ^2=103·72, df=35 (p<0·001); I^2=71·44%
Test for overall effect: Z=0·04, p=0·97

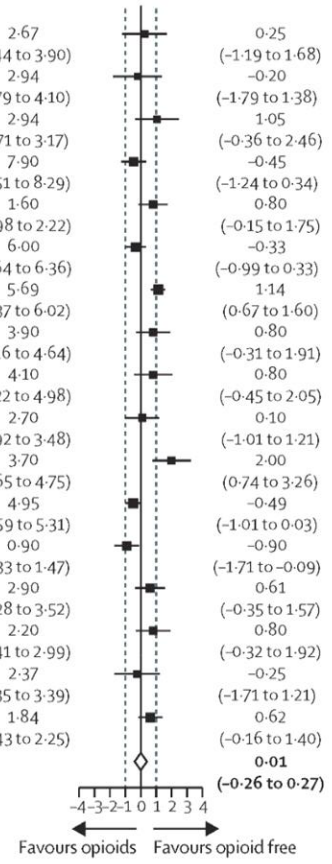


Figure 2: Forest plot for pain on day 1 after discharge

High-certainty evidence (12 trials, 2789 patients)[122,126,127,133-137,140,142,162,165] supported that opioid prescribing was associated with increased risk of vomiting in comparison to opioid-free analgesia [10.9% versus. 1.3%, RR 4.50 (95%CI 1.93 to 10.51)] (Figure 3 and Table 1). *Post hoc* sensitivity analyses using different approaches to address zero cell values were consistent with our primary analysis (**Appendix pp 409-410**). Subgroup analyses indicated that potential sources of heterogeneity ($p<0.05$ for interactions) were surgery conducted in an outpatient clinic (versus hospital operating room) and minor surgery (versus moderate extent) (**Appendix pp 411-419**). The prescription of opioids was also significantly associated with increased risk of overall adverse events (composite outcome), as well as nausea, constipation, dizziness, and drowsiness (certainty of evidence varied from moderate to high; Table 1 and **Appendix pp 425-429**). No between-group differences were observed in risk for other adverse events (certainty of evidence varied from very low to moderate; Table 1 and **Appendix pp 430-445**).

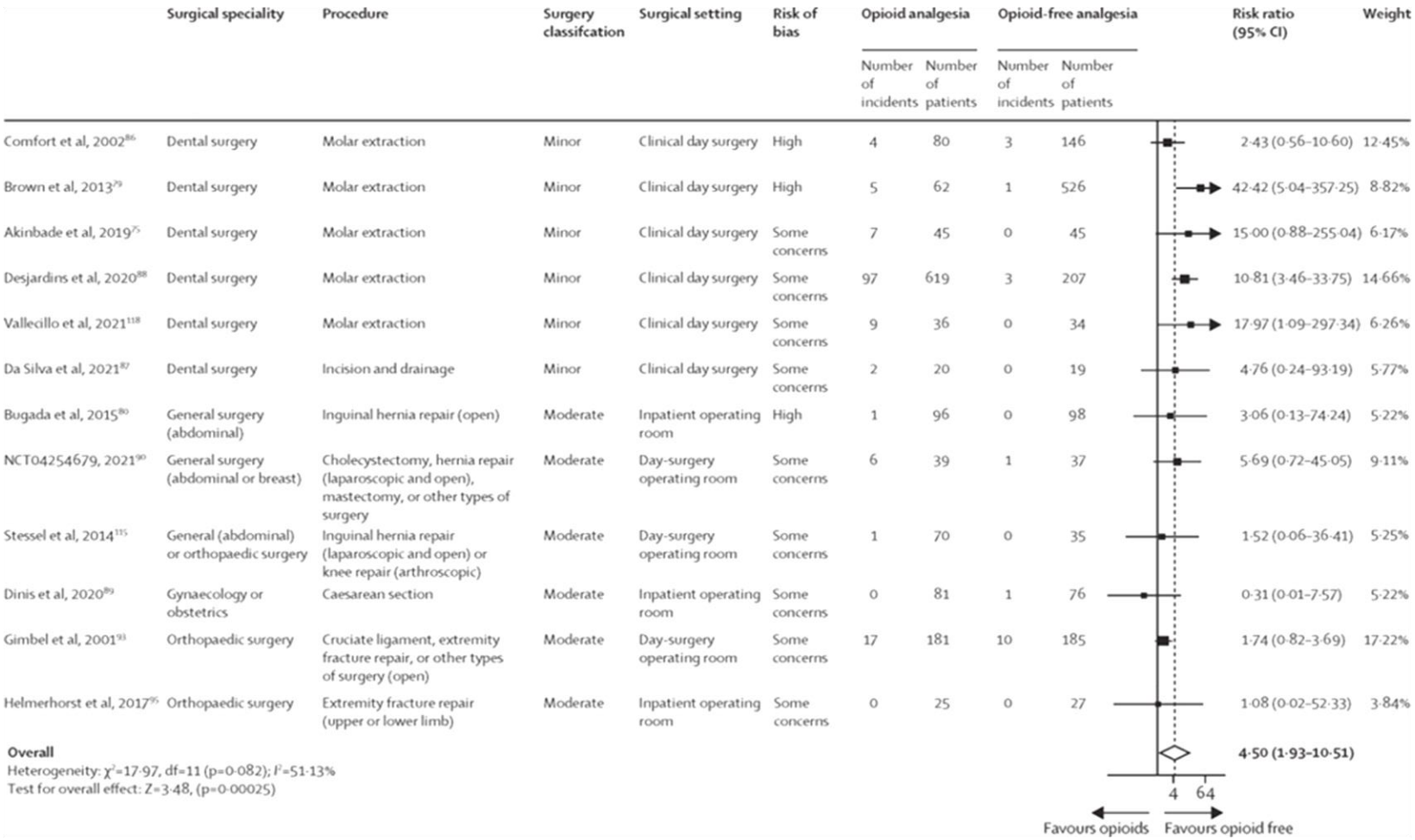


Figure 3: Forest plot for vomiting after surgical discharge

The prescription of opioids was not associated with increased rates of dissatisfaction with pain management [risk ratio 1.14 (95%CI 0.67 to 1.94); low-certainty], participant disposition [risk ratio 2.05 (95%CI 0.95 to 4.42); high-certainty], or healthcare reutilization [risk ratio 0.88 (95%CI 0.30 to 2.61); very low-certainty] (Table 1 and **Appendix pp 446-448**). Opioid prescribing also did not reduce pain interference [WMD 3.51 (95%CI 1.01, 6.02); low certainty] (Table 1 and **Appendix p 449**) and self-reported postoperative health status (quality of recovery) [WMD -0.34 (95%CI -0.87, 0.19); moderate certainty] (Table 1 and **Appendix p 450**). No trials reported on prolonged opioid use, misuse, dependence, or overdose after surgical discharge.

Table 1. GRADE evidence profile

Outcome measure	No. of trials	No. of patients	Serious risk of bias	I^2	Serious indirectness or imprecision	Likelihood of publication bias	Effect size [WMD (95% CI) or RR (95% CI)]	Quality of evidence
Postoperative pain								
Post-discharge day 0	21	2317	↓1 level	82.23%	No	No	-0.25 (-0.74, 0.24)[a]	Low
Post-discharge day 1 (co-primary outcome)	36	3848	↓1 level	71.44%	No	No	0.01 (-0.26, 0.27)[a]	Moderate
Post-discharge day 2	29	3054	↓1 level	68.82%	No	No	0.01 (-0.26, 0.28)[a]	Moderate
Post-discharge day 3	26	2321	↓1 level	63.00%	No	No	0.44 (0.18, 0.70)[a]	Moderate
Post-discharge day 4-7[c]	22	1946	↓1 level	54.09%	↓1 level	No	0.23 (-0.01, 0.47)[a]	Low
Post-discharge day 8-30[d]	9	677	↓1 level	87.09%	↓1 level	No	0.33 (-0.32, 0.99)[a]	Very low
Adverse events								
Nausea	21	3544	No	60.82%	No	No	2.37 (1.59, 3.55)[b]	High
Overall adverse events; non-specific	19	2804	No	84.16%	↓1 level	No	1.78 (1.20, 2.66)[b]	Low
Constipation	16	2227	No	65.00%	No	No	1.63 (1.04, 2.57)[b]	High
Dizziness	14	2878	No	42.31%	No	No	2.22 (1.20, 4.08)[b]	High
Drowsiness	14	1695	No	58.39%	↓1 level	No	1.57 (1.02, 2.42)[b]	Moderate

Vomiting (co-primary outcome)	12	2789	No	51.13%	No	No	4.50 (1.93 to 10.51)[b]	High
Pruritus	10	1730	No	32.08%	↓2 levels	No	1.27 (0.73, 2.21)[b]	Low
Headache	8	1892	No	58.95%	↓1 level	No	1.40 (0.72, 2.70)[b]	Moderate
Confusion	5	671	↓1 level	22.95%	↓2 levels	No	0.73 (0.27, 1.97)[b]	Very low
Diarrhea	5	370	↓1 level	2.08%	↓2 levels	No	1.53 (0.48, 4.91)[b]	Very low
Difficulty urinating	4	670	No	2.29%	↓2 levels	No	0.93 (0.33, 2.60)[b]	Low
Indigestion	4	588	No	23.33%	↓2 levels	No	0.58 (0.17, 1.95)[b]	Low
Nausea or Vomit	4	373	↓1 level	37.77%	↓2 levels	No	1.88 (0.57, 6.26)[b]	Very low
Bleeding	4	358	No	3.10%	↓2 levels	No	1.05 (0.26, 4.18)[b]	Low
Dry mouth	3	920	No	32.94%	↓2 levels	No	1.57 (0.57, 4.32)[b]	Low
Sleep problems	3	570	↓2 levels	35.90%	↓3 levels	No	1.01 (0.38, 2.71)[b]	Very low
Hypotension	2	919	No	1.88%	↓2 levels	No	2.01 (0.19, 21.33)[b]	Low
Difficulty concentrating	2	537	No	25.91%	↓2 levels	No	0.89 (0.31, 2.54)[b]	Low

Acid reflux	2	262	No	10.04%	↓2 levels	No	0.90 (0.24, 3.42)[b]	Low
Skin rash	2	316	↓2 levels	0.00%	↓2 levels	No	1.63 (0.14, 19.18)[b]	Very low
Upset stomach	2	177	↓1 level	0.44%	↓2 levels	No	1.23 (0.67, 2.26)[b]	Very low
Difficulty breathing	2	91	↓2 levels	5.48%	↓2 levels	No	0.35 (0.03, 3.99)[b]	Very low
Pain interference (first week post-discharge)[e]	6	657	↓1 level	64.92%	↓1 level	No	3.51 (1.01, 6.02)[a]	Low
Quality of recovery (post-discharge day 2)[f]	2	156	No	0.44%	↓1 level	No	-0.34 (-0.87, 0.19)[a]	Moderate
Patient disposition	15	2612	No	54.40%	No	No	2.05 (0.95, 4.42)[b]	High
Patient dissatisfaction	14	1750	No	42.46%	↓2 levels	No	1.14 (0.67, 1.94)[b]	Low
Healthcare reutilization	8	778	No	51.69%	↓3 levels	No	0.88 (0.30, 2.61)[b]	Very low

[a] Effect estimate measured as weighted mean difference (WMD) and 95% CI on the visual analogue scale (VAS).
[b] Effect estimate measured as relative risk (RR) and 95% CI.
[c] In studies with multiple timepoints, we extracted data from the timepoint closest to 7 days. Median post-discharge days until assessment = 7 (range 4 – 7).
[d] In studies with multiple timepoints, we extracted data from the timepoint closest to 30 days. Median post-discharge days until assessment = 12 (range 10 – 28).
[e] Pain interference was measured using the questionnaires Patient Reported Outcomes Measurement Information System-Pain Interference (PROMIS-PI), American Pain Society (APS) questionnaire, and Brief Pain Inventory (BPI). For meta-analysis, measures were standardized to PROMIS-PI scores [minimal important difference ≈ 9 (J Hand Surg Am 2019;44(8):635-640)].
[f] Quality of recovery was measured using the questionnaires Quality of Recovery-9 (QoR-9) and QoR-40. For meta-analysis, measures were standardized to QoR-9 scores [minimal important difference = 0.9 (Anesthesiology 2016;125(1):39-45)].

2.5 DISCUSSION

In this meta-analysis, opioid prescribing at surgical discharge following elective procedures of minor and moderate extent did not reduce self-reported pain intensity compared to opioid-free analgesia. Furthermore, the prescription of opioids was associated with an increased risk of vomiting and other adverse events including nausea, constipation, dizziness, and drowsiness. There were no meaningful differences in other outcomes. These findings contribute important new knowledge and the best available evidence to inform analgesia prescribing for patients discharged after undergoing surgery.

A major strength of this meta-analysis is that it fills a critical knowledge gap regarding the comparative-effectiveness of multidose opioid versus opioid-free analgesia after surgical discharge.[47] Previous meta-analyses in this field targeted single-dose RCTs which are often placebo-controlled, of short duration, and conducted under strict experimental conditions (i.e. with patients kept in a research facility).[73,74] Although these trials are important to ascertain drug efficacy for regulatory approval purposes, they do not reflect 'real-world' settings where postoperative pain management spans several days after discharge.[73] It is important to note that the results from single-dose analgesia meta-analyses corroborate that opioids are not superior to non-opioid drugs (NSAIDs, acetaminophen, or combinations) in managing acute/postoperative pain,[73] and that they increase adverse events.[74] Other major strengths of our meta-analysis include: use of a comprehensive search strategy to identify relevant RCTs in any language, compliance with PRISMA methodological standards, inclusion of unpublished trials, subgroup analyses to address heterogeneity, interpretation of results in light of MIDs, and use of the GRADE approach to appraise certainty of evidence.

Results from this meta-analysis support current analgesia practices in several countries where, as opposed to North America, opioids are rarely prescribed after postoperative discharge.[38,39,46,67,68] In a recent study focused on international prescribing patterns after discharge following general surgery, opioids were prescribed to 95% of patients undergoing surgery in the United States compared to only 5% in European, Asian, South American, and Middle Eastern countries.[67] While patient and procedure characteristics may have affected these findings (e.g. preoperative opioid use, emergency surgery), similar results were observed in other international comparisons focused on different surgical specialties.[38,39,46, 68] The reasons contributing to the widespread prescribing of postoperative opioids in North America are multifactorial but include clinicians' concerns regarding inadequate pain control, patient dissatisfaction, and risk of increased healthcare reutilization due to uncontrolled pain.[169] Findings from this meta-analysis indicate that none of these concerns are supported by comparative-effectiveness evidence. Although current guidelines support the prescription of opioids as part of multimodal analgesia after surgical discharge,[114,170,171] we found no evidence that this approach is superior to opioid-free analgesia. Our results are in line with recent reports supporting that the removal of opioids from postoperative discharge prescriptions does not impact patient satisfaction or postoperative outcomes after minor and moderate elective surgeries.[64-66]

2.6 LIMITATIONS

This review must be interpreted considering several limitations. There are inherent challenges in performing and interpreting meta-analyses including heterogeneous populations and interventions.[172] In fact, heterogeneity between the trials included was substantial (>50% for primary outcomes), which may impact the interpretation of overall effect estimates. To address this concern, we conducted *a priori* and *post hoc* subgroup analyses which identified potential sources of statistical heterogeneity but excluded clinically meaningful benefits of opioids within subgroups. Given our focus on MIDs, there was limited attention to statistically significant findings in secondary analyses, which may have been impacted by Type I error given multiple comparisons. We prioritized the assessment of dynamic pain scores,[84,85] but pain at rest (not relieved by staying still) is also concerning to patients and clinicians. Our findings are not generalizable to surgeries that were not subject to RCTs on this topic, including major and major-complex procedures. While these procedures are associated with higher levels of postoperative pain and analgesic requirements,[173] they are usually conducted in in-patient settings where acute pain (in the first postoperative days) is treated during hospital stay; therefore, the need to prescribe opioids for these patients at discharge remains uncertain. Also, our results are not generalizable to emergency/urgent procedures, which were not addressed in the available trials. Most of the RCTs involved the prescription of 'weak' opioids (i.e., codeine, tramadol), with limited attention to 'stronger' opioids that are commonly used in surgical practice (i.e., oxycodone, hydromorphone).[174] Also, there was limited attention to non-pharmacological interventions that may contribute to postoperative pain management (e.g., expectation setting, relaxation, ice packs).[114] The included trials did not report on risk of postoperative opioid use disorder and overdoses, which are relevant outcomes considering the

current opioid crisis. Poorly controlled acute pain is a known risk factor for chronic postoperative pain,[175] but we did not target this outcome *a priori*. Only one of the identified trials (open inguinal hernia repair, high risk of bias) reported on risk of chronic pain supporting no difference between groups.[127] Factors known to impact opioid consumption and prolonged opioid use after surgery (i.e., preoperative pain and opioid use, anxiety, depression, pain catastrophizing)[176-178] were rarely considered in trial design. While many trials focused on adverse events common to opioid analgesia (e.g., vomiting, nausea, constipation), there was limited focus on the potential side effects of non-opioid drugs, including NSAIDs (e.g., bleeding, kidney failure) and acetaminophen (i.e., liver failure), hindering robust conclusions. Although subgroup analysis indicated that study quality (high versus lower risk of bias) did not have a significant impact on effect estimates, 28 (60%) of the RCTs identified were deemed at 'high' risk of bias, supporting the need to improve the quality of research in this field. Our findings support the equipoise of post-discharge opioid versus opioid-free analgesia, which justifies and encourages the conduct of high-quality trials to address the above-mentioned knowledge gaps.

2.7 CONCLUSIONS

Findings from this meta-analysis suggest that opioid prescribing at surgical discharge does not reduce pain intensity and is associated with increased adverse events compared to opioid-free analgesia. Evidence largely relied on low-quality trials focused on elective surgeries of minor and moderate extent. None of the identified trials targeted patients undergoing major or major-complex procedures. While our findings support that clinicians may consider excluding opioids from discharge prescriptions in many surgical settings, there is a great need to advance the quality and scope of research to support evidence-based pain management and mitigate opioid-related harms after surgery.

2.8 CONTRIBUTORS

JFF, CEK, AD, TL, AAZ, RA, MM, LL, GB, and LSF designed the study. JFF and CEK coordinated the study. TL, AAZ, AB, JFF, and CEK designed the literature search; TL, AAZ, and AB ran the search. JFF, CEK, MAC, PNP, UD, GO, FR, and AK screened records. CEK, MAC, PNP, and UD extracted data. JFF and CEK assessed risk of bias and GRADE. CEK, JFF, and RA conducted statistical analyses. All authors contributed to the data interpretation. JFF and CEK drafted the manuscript. All authors provided critical conceptual input and critically revised the manuscript. All authors were responsible for the decision to submit the manuscript. JFF and CEK have accessed and verified the data reported.

2.9 DECLARATION OF INTERESTS

JFF declares receiving research funding from Merck and honorarium from Shionogi outside the submitted work. LF declares receiving research funding from Merck and Johnson & Johnson outside the submitted work. LL declares receiving research funding from Johnson & Johnson outside the submitted work. No other authors reported relevant disclosures.

2.10 DATA SHARING

Extracted data are available on request to the corresponding author.

2.11 ACKNOWLEDGMENTS

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CHAPTER 3: CONCLUSION & FUTURE DIRECTION

The overprescription of opioids after surgery is recognized as one of the driving forces behind the current opioid crisis in North America. Patients undergoing surgery are often prescribed opioids after postoperative discharge, while alternative pain management strategies are often overlooked by clinicians. Results from this thesis project support that analgesia with opioids are not superior to opioid-free analgesia in controlling pain after surgical discharge from minor and moderate procedures. These findings support that, after selected surgical procedures, opioid-free analgesia can be safely incorporated into practice to prevent postoperative opioid-related harms. This may prevent more people from becoming addicted to opioids in the future (it is impossible to become addicted without exposure) and, also importantly, reduce the diversion of unused prescriptions to others. By addressing the overprescription element of the opioid crisis, our research program tackles the first pillar of the New Canadian Drugs and Substances Strategy (CDSS), i.e., preventing problematic drug and substance use supported by a strong evidence base.[179]

While our meta-analysis findings do challenge indiscriminate opioid prescription after surgical discharge, evidence largely relied on low-quality trials focused on elective surgeries ranging from minor (e.g., dental, hand procedures) and moderate surgical extent (e.g., minimally invasive orthopedic, general surgery procedures), with none of the trials including patients undergoing major (e.g., lung, bowel, liver resections) or major-complex surgeries (e.g., thoraco-abdominal procedures, multi-organ resections). To advance the quality and scope of evidence in this field, our team will lead a series of methodologically robust, multicenter RCTs to assess the comparative-effectiveness of opioid versus opioid-free analgesia after surgical discharge. This collaborative endeavor, conducted with a multidisciplinary team of researchers from across

Canada (Alberta, Manitoba, Ontario, and Quebec), will target several surgical populations, including general abdominal, breast, colorectal, bariatric, and obstetric (c-section) procedures. The feasibility of conducting such trials has been supported by a pilot RCT recently completed by our team.[180,181] This research program will build a strong body of evidence to inform perioperative care guidelines and mitigate the negative downstream effects of opioid overprescribing after surgery.

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APPENDIX

Table of Contents (Appendix)

Literature search strategies

MEDLINE search strategy

#	Searches	Results
1	Pain, Postoperative/	35796
2	Postoperative Care/	57576
3	Postoperative Period/	46330
4	((after or following) adj3 (procedur* or resect* or surg*)).tw,kf.	409930
5	(post-operat* or postoperat* or post-surg* or postsurg*).tw,kf.	570419
6	or/2-5	880998
7	(analgaes* or analges* or pain).tw,hw,kf.	732418
8	6 and 7	114032
9	1 or 8	122798
10	Acetaminophen/	17092
11	exp Adrenal Cortex Hormones/	382792
12	Amitriptyline/	6458
13	exp Analgesics, Non-Narcotic/	322105
14	Anesthesia, Local/	16529
15	exp Anesthetics, Local/	101526
16	exp Anticonvulsants/	137214
17	exp Anti-Inflammatory Agents, Non-Steroidal/	196247
18	Aspirin/	43105
19	Baclofen/	5418
20	Bupivacaine/	11523
21	Carbamazepine/	10751
22	Celecoxib/	4115
23	Clonidine/	13085

24	exp Cyclooxygenase 2 Inhibitors/	12883
25	Desipramine/	5522
26	Dexamethasone/	49489
27	Dexmedetomidine/	2943
28	Diclofenac/	7415
29	Diflunisal/	490
30	Dipyrone/	1493
31	Duloxetine Hydrochloride/	1448
32	Fenoprofen/	285
33	Flurbiprofen/	1826
34	Gabapentin/	3467
35	gamma-Aminobutyric Acid/	37175
36	Ibuprofen/	8321
37	Indomethacin/	27875
38	Ketamine/	11509
39	Ketoprofen/	2654
40	Ketorolac/	1384
41	Ketorolac Tromethamine/	579
42	Lidocaine/	23688
43	Mefenamic Acid/	1025
44	Mepivacaine/	1968
45	Methocarbamol/	209
46	Methylprednisolone/	18170
47	Methylprednisolone Hemisuccinate/	708
48	Naproxen/	3926
49	exp Neuromuscular Agents/	75200
50	Nortriptyline/	2116

51	Phenytoin/	13327
52	Piroxicam/	2733
53	Prednisolone/	31868
54	Prednisone/	38253
55	Pregabalin/	1730
56	Prilocaine/	2097
57	Procaine/	9750
58	Triamcinolone/	3717
59	Triamcinolone Acetonide/	5557
60	Venlafaxine Hydrochloride/	2432
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.	65843
62	(acetaminophen or paracetamol or tylenol).mp.	26582
63	(acetylsalicylic-acid or aspirin).mp.	66646
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.	88250
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.	52148
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.	13887
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	9094

	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.	6530
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.	18277
70	(alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil).mp.	629
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.	1130
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.	7520
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.	17339
74	(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*).mp.	292
75	(anti-inflammatory-analges* or antiinflammatory-analges*).tw,kf.	1199
76	(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia).mp.	703
77	(ariclaim or cymbalta or duloxetine or xeristar or yentreve).mp.	2446
78	(aristospan or kenalog or triamcinolone or zilretta).mp.	11185

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.	502
80	(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex).mp.	12314
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.	3064
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.	282
83	(baclofen* or gablofen* or kemstro or lioresal).mp.	7771
84	(bupivacaine or exparel or marcaine or sensorcaine or vivacaine).mp.	16031
85	(carbocaine or mepivacaine or polocaine or scandonest).mp.	2622
86	(catapres or clonidine or clorpres or duraclon or kapvay).mp.	17955
87	(celebrex or celecox*).mp.	6484
88	(chloroprocaine or procaine).mp.	13339
89	(corticoid* or corticosteroid* or cortico-steroid*).tw,kf.	101651
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.	2036
91	(daypro or deflam or oxaprozin*).mp.	157
92	(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane).mp.	8133
93	(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*).mp.	4349
94	(dexmedetomidine or precedex).mp.	4973
95	diflunisal.mp.	772
96	(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi).mp.	4682
97	(feldene or piroxicam).mp.	3850
98	(fenoprofen or nalfon).mp.	487
99	flurbiprofen.mp.	2572

100	(frotek or ketoprofen).mp.	4083
101	(gabapentin* or gralise or horizant or neurontin).mp.	6519
102	(gabatril or gabitril or tiagabine).mp.	963
103	(indocin or indomethacin or novo-methacin or pro-indo or tivorbex).mp.	41922
104	(ketalar or ketamine).mp.	18433
105	(lidocaine or xylocaine or xylocard).mp.	31445
106	(local-infiltration adj2 analgesia).tw,kf.	227
107	(lumiracoxib or prexige).mp.	244
108	(lyrica or pregabalin).mp.	3260
109	(mefenamic-acid or ponstan or ponstel).mp.	1610
110	(metassalone or metaxalon* or skelaxin or zorane).mp.	43
111	(narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*).tw,kf.	2795
112	(narop or naropin or noropine or ropivacain*).mp.	4526
113	(nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*).tw,kf.	43217
114	(opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*).tw,kf.	914
115	(oxcarbazepin* or oxtellar or timox or trileptal).mp.	1945
116	parecoxib.mp.	535
117	(prialt or ziconotide).mp.	391
118	(sirdalud or ternelin or tizanidin* or zanaflex).mp.	554
119	or/10-118	1199905
120	9 and 119	25335
121	Alfentanil/	1646
122	exp Analgesics, Opioid/	109011
123	Buprenorphine/	4731
124	Butorphanol/	1063
125	Codeine/	4393

126	Dextropropoxyphene/	1456
127	Fentanyl/	12994
128	Hydrocodone/	565
129	Hydromorphone/	1208
130	Meperidine/	5627
131	Methadone/	11802
132	Morphine/	37212
133	Morphine Derivatives/	2217
134	Nalbuphine/	655
135	Oxycodone/	2025
136	Pentazocine/	2218
137	Pirinitramide/	260
138	Remifentanil/	3111
139	Sufentanil/	1741
140	Tramadol/	2886
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.	2298
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.	21482
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.	6743
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	56235

	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.	5225
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.	16091
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.	1966
148	(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen).mp.	2394
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.	47704
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.	6852
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	3743

	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.	1564
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.	2026
154	(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl).mp.	2798
155	(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide).mp.	513
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.	3035
157	(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor).mp.	969
158	(Nicomorfin* or Nicomorphin* or Vilan).mp.	54
159	(Remifentanil or Remifentanyl or Ultiva).mp.	4885
160	or/121-159	179741
161	120 and 160	10596
162	Animals/ not (Animals/ and Humans/)	4519604
163	Disease models, animal/ or Models, animal/	345171
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.	2285707
165	or/162-164	4977063
166	161 not 165	10017
167	(exp child/ or exp infant/) not (adolescent/ or exp adult/)	1214356

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.	1724797
169	167 or 168	2137539
170	166 not 169	8925
171	Clinical trials as topic/	186145
172	Controlled clinical trial/	92938
173	Randomized controlled trial/	476954
174	(placebo or randomized or randomly).tw.	818082
175	trial.ti.	194961
176	171 or 172 or 173 or 174 or 175	1209154
177	170 and 176	6088

Following peer review, the search was rerun on July 23, 2019 with a revised age filter that retrieved 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.

As a consequence, 199 additional results were screened.

EMBASE search strategy

#	Searches	Results
1	postoperative pain/	61149
2	postoperative period/ or postoperative care/	280290
3	((after or following) adj3 (procedur* or resect* or surg*)).tw,kw.	593422
4	(post-operat* or postoperat* or post-surg* or postsurg*).tw,kw.	823022
5	or/2-4	1304577
6	(analgaes* or analges* or pain).tw,hw,kw.	1308384
7	5 and 6	195632
8	postoperative analgesia/	15417
9	1 or 7 or 8	212203
10	paracetamol/	84707
11	exp corticosteroid/	964030
12	amitriptyline/	38645
13	exp analgesic agent/	884691
14	local anaesthesia/	37619
15	exp local anesthetic agent/	244075
16	exp anticonvulsive agent/	400317
17	exp nonsteroid antiinflammatory agent/	713474
18	acetylsalicylic acid/	203502
19	baclofen/	17297
20	bupivacaine/	35549
21	carbamazepine/	62456
22	celecoxib/	20777
23	clonidine/	40865
24	exp cyclooxygenase 2 inhibitor/	49707
25	desipramine/	21980
26	dexamethasone/	143999
27	dexmedetomidine/	9349
28	diclofenac/	37768
29	diflunisal/	2648
30	dipyrone/	8234
31	duloxetine/	9985
32	fenoprofen/	2653
33	flurbiprofen/	7427
34	gabapentin/	27980
35	4 aminobutyric acid/	53017
36	ibuprofen/	47002
37	indometacin/	77953
38	ketamine/	36300
39	ketoprofen/	12598
40	ketorolac/	9025
41	ketorolac trometamol/	1930
42	lidocaine/	72590
43	mefenamic acid/	5795

44	mepivacaine/	6476
45	methocarbamol/	868
46	methylprednisolone/	88876
47	methylprednisolone sodium succinate/	6658
48	naproxen/	25278
49	exp muscle relaxant agent/	150929
50	nortriptyline/	14618
51	phenytoin/	64331
52	piroxicam/	11108
53	prednisolone/	123585
54	prednisone/	168885
55	pregabalin/	12491
56	prilocaine/	4572
57	procaine/	19322
58	triamcinolone/	14766
59	triamcinolone acetonide/	14595
60	venlafaxine/	20113
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.	213198
62	(acetaminophen or paracetamol or tylenol).mp.	90343
63	(acetylsalicylic-acid or aspirin).mp.	213892
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.	214063
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.	175943
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.	48922
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.	39409
68	(aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen).mp.	26146
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	67193

	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.	2101
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.	2914
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.	23491
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.	64291
74	(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*).mp.	2040
75	(anti-inflammatory-analges* or antiinflammatory-analges*).tw,kw.	1876
76	(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia).mp.	2799
77	(ariclaim or cymbalta or duloxetine or xeristar or yentreve).mp.	10212
78	(aristospan or kenalog or triamcinolone or zilretta).mp.	29925
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.	2046
80	(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex).mp.	39573
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.	14899
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.	922
83	(baclofen* or gablofen* or kemstro or lioresal).mp.	18091
84	(bupivacaine or exparel or marcaine or sensorcaine or vivacaine).mp.	36943
85	(carbocaine or mepivacaine or polocaine or scandonest).mp.	6724
86	(catapres or clonidine or clorpres or duraclon or kapvay).mp.	42887
87	(celebrex or celecox*).mp.	21259
88	(chloroprocaine or procaine).mp.	27049
89	(corticoid* or corticosteroid* or cortico-steroid*).tw,kw.	163764
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.	6615
91	(daypro or deflam or oxaprozin*).mp.	731
92	(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane).mp.	22713
93	(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*).mp.	20983
94	(dexmedetomidine or precedex).mp.	9583

95	diflunisal.mp.	2729
96	(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi).mp.	21166
97	(feldene or piroxicam).mp.	11445
98	(fenoprofen or nalfon).mp.	2884
99	flurbiprofen.mp.	7943
100	(frotek or ketoprofen).mp.	13118
101	(gabapentin* or gralise or horizant or neurontin).mp.	29015
102	(gabatril or gabitril or tiagabine).mp.	3924
103	(indocin or indomethacin or novo-methacin or pro-indo or tivorbex).mp.	42777
104	(ketalar or ketamine).mp.	39799
105	(lidocaine or xylocaine or xylocard).mp.	76873
106	(local-infiltration adj2 analgesia).tw,kw.	328
107	(lumiracoxib or prexige).mp.	1146
108	(lyrica or pregabalin).mp.	12817
109	(mefenamic-acid or ponstan or ponstel).mp.	5943
110	(metassalone or metaxalon* or skelaxin or zorane).mp.	317
111	(narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*).tw,kw.	4599
112	(narop or naropin or noropine or ropivacain*).mp.	11034
113	(nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*).tw,kw.	67113
114	(opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*).tw,kw.	1402
115	(oxcarbazepin* or oxtellar or timox or trileptal).mp.	10338
116	parecoxib.mp.	1843
117	(prialt or ziconotide).mp.	738
118	(sirdalud or ternelin or tizanidin* or zanaflex).mp.	2703
119	or/10-118	2704158
120	9 and 119	77464
121	alfentanil/	6546
122	exp narcotic analgesic agent/	325470
123	buprenorphine/	15859
124	butorphanol/	3170
125	codeine/	20815
126	dextropropoxyphene/	7568
127	fentanyl/	59509
128	hydrocodone/	5207
129	hydromorphone/	9122
130	pethidine/	24907
131	methadone/	31419
132	morphine/	104728
133	morphine derivative/	1765
134	exp nalbuphine/	2941
135	oxycodone/	15825
136	pentazocine/	9424
137	piritramide/	1673
138	remifentanil/	12416
139	sufentanil/	8547
140	tramadol/	19118

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.	9394
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.	64335
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.	23553
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.	120666
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.	20439
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.	34366
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.	7928
148	(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen).mp.	6747
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.	110136
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.	17197

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.	17569
152	(Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol).mp.	3829
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.	9473
154	(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl).mp.	9013
155	(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide).mp.	1781
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.	9761
157	(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor).mp.	3035
158	(Nicomorfin* or Nicomorphin* or Vilan).mp.	206
159	(Remifentanil or Remifentanyl or Ultiva).mp.	12830
160	or/121-159	413991
161	120 and 160	42863
162	limit 161 to (conference abstract or conference paper or "conference review")	7441
163	(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*).ti,kw,dq,jx. not (human* or patient*).mp.	2369024
164	162 not 163	7336
165	161 not 162	35422
166	(exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/	7076523
167	165 not (166 or 163)	33929
168	exp child/ not (exp adolescent/ or exp adult/)	1744903
169	(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,jx.	2204108
170	167 not (168 or 169)	30351
171	("crossover procedure" or "double-blind procedure" or "randomized controlled trial" or "single-blind procedure").hw. or (random* or factorial* or crossover* or (cross adj1 over*) or placebo* or (doubl* adj1 blind*) or (singl* adj1 blind*) or assign* or allocat* or volunteer*).ti,ab,hw.	2392225
172	170 and 171	13499
207	or/173-206 PMIDS	5213
208	172 not 207	8960
209	164 not 169 (Conferences NOT peds)	6810
210	209 and 171 (Conference AND RCTs)	2451

211	210 not 207 (Conferences NOT PMIDS)	2392

Following peer review, the search was rerun on July 29, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The queries at lines 168 and 169 of the original strategy were modified as follows:

168 exp child/ not (exp adolescent/ or exp adult/)

169 (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,jx.

As a consequence, 1180 additional results were screened.

Cochrane Library search strategy

ID	Search	Hits
#1	((after or following) NEAR/3 (procedur* or resect* or surg*)):ti,ab,kw	49107
#2	((post near/1 operat*) or postoperat* or (post near/1 surg*) or postsurg*):ti,ab,kw	94841
#3	#2 OR #1	115523
#4	(analgaes* or analges* or pain):ti,ab,kw	136894
#5	#4 AND #3	39681
#6	((a near/1 methapred) or artisone or besonia or dopomedrol or esametone or firmacort or lemod or medesone or medixon or medlone or medrate or (m near/1 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 near/1 n) or prednisolone or prednol or promacortine or reactonol or sieropresol or solomet or solumedrol or summicort or suprametil or urbason* or wyacort):ti,ab,kw	8490
#7	(acetaminophen or paracetamol or tylenol):ti,ab,kw	7701
#8	((acetylsalicylic near/1 acid) or aspirin):ti,ab,kw	12867
#9	(accufix or (aeroseb near/1 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 near/1 dec) or endomethasone or hexadrol or maxidex or maxitrol or neodecadron or neomycin or ozurdex or septomixine or tobradex or tobramycin):ti,ab,kw	9916
#10	(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 near/1 cortelan) or (delta near/1 cortisone) or (delda near/1 dome) or (delta near/1 e) or (delta near/1 some) or deltacordene or deltacortisone or deltacortone or deltasone or deltison* or deltra or (di near/1 adreson) or diadreson or econosone or encorton* or fernisone or fiasone or hostacortin or (in near/1 sone) or incocortyl or juvason or lisacort or lodotra or lodtra or (me near/1 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):ti,ab,kw	7565
#11	(addaprin or advil or caldolor or dyspel or europrofen or genpril or (i near/1 prin) or (IBU near/1 200) or ibuprofen or motrin or neoProfen or (novo near/1 profen) or provil):ti,ab,kw	3677
#12	(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 near/1 peram) or belpax or (damilen near/1 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 near/1 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	2303

	tripta or triptizol or triptyn or trynol or (tryptacap near/1 hydrochloride) or tryptine or tryptizol or trytomer or vanatrip):ti,ab,kw	
#13	(aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen):ti,ab,kw	1983
#14	(aleviatin or auranile or causoin or cerebyx or comitoina or convul or danten or dantinal or dantoinal or dantoine or denyl or (di near/1 hydan) or (di near/1 lan) or (di near/1 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 near/1 d) or epilantin or epinat or epised or eptal or fenantoin or fenidantoin or fenitoina or fentoin or fenylepsin or fenytoin* or (fosphenytoin near/1 sodium) or hidan or hidantal or hidantilo or hidantina or hidantomin or hydantal or hydantoinal or (ictalis near/1 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):ti,ab,kw	1222
#15	(alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil):ti,ab,kw	382
#16	(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 near/1 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 near/1 dalgin)):ti,ab,kw	420
#17	(alphatrex or (beta near/1 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 near/1 b) or (pro near/1 sone) or sernivo or taclonex or uticort or valisone or valnac):ti,ab,kw	1969
#18	(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):ti,ab,kw	1882
#19	(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*):ti,ab,kw	144
#20	((anti near/1 inflammatory near/1 analges*) or (antiinflammatory near/1 analges*)):ti,ab,kw	303
#21	(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia):ti,ab,kw	327
#22	(ariclaim or cymbalta or duloxetine or xeristar or yentreve):ti,ab,kw	950
#23	(aristospan or kenalog or triamcinolone or zilretta):ti,ab,kw	2256
#24	(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):ti,ab,kw	165

#25	(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex):ti,ab,kw	3973
#26	(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):ti,ab,kw	760
#27	(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):ti,ab,kw	52
#28	(baclofen* or gablofen* or kemstro or lioresal):ti,ab,kw	571
#29	(bupivacaine or exparel or marcaine or sensorcaine or vivacaine):ti,ab,kw	9689
#30	(carbocaine or mepivacaine or polocaine or scandonest):ti,ab,kw	831
#31	(catapres or clonidine or clorpres or duraclon or kapvay):ti,ab,kw	3416
#32	(celebrex or celecox*):ti,ab,kw	1599
#33	(chloroprocaine or procaine):ti,ab,kw	652
#34	(corticoid* or corticosteroid* or (cortico near/1 steroid*)):ti,ab,kw	15465
#35	(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):ti,ab,kw	454
#36	(daypro or deflam or oxaprozin*):ti,ab,kw	56
#37	(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane):ti,ab,kw	701
#38	(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*):ti,ab,kw	1641
#39	(dexmedetomidine or precedex or diflunisal):ti,ab,kw	2812
#40	(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi):ti,ab,kw	1106
#41	(feldene or piroxicam):ti,ab,kw	1112
#42	(fenoprofen or nalfon or flurbiprofen):ti,ab,kw	860
#43	(frotek or ketoprofen):ti,ab,kw	1060
#44	(gabapentin* or gralise or horizant or neurontin):ti,ab,kw	1718
#45	(gabatril or gabitril or tiagabine):ti,ab,kw	170

#46	(indocin or indomethacin or (novo near/1 methacin) or (pro near/1 indo) or tivorbex):ti,ab,kw	2654
#47	(ketalar or ketamine):ti,ab,kw	3503
#48	(lidocaine or xylocaine or xylocard):ti,ab,kw	9484
#49	((local near/1 infiltration) NEAR/2 analgesia):ti,ab,kw	182
#50	(lumiracoxib or prexige):ti,ab,kw	79
#51	(lyrica or pregabalin):ti,ab,kw	1324
#52	((mefenamic near/1 acid) or ponstan or ponstel):ti,ab,kw	296
#53	(metassalone or metaxalon* or skelaxin or zorane):ti,ab,kw	9
#54	((narcotic* near/1 free) or (narcotic* near/1 less) or (narcotic* near/1 spar*) or (non near/1 narcotic*) or (non near/1 opioid*)):ti,ab,kw	2416
#55	(narop or naropin or noropine or ropivacain*):ti,ab,kw	3930
#56	((nonsteroidal near/1 antiinflammatory) or (nonsteroidal near/1 anti near/1 inflammatory) or (non near/1 steroidal near/1 antiinflammatory) or (non near/1 steroidal near/1 anti near/1 inflammatory) or nsaid*):ti,ab,kw	6347
#57	((opiat* near/1 free) or (opiat* near/1 less) or (opiat* near/1 spar*) or (opioid* near/1 free) or (opioid* near/1 less) or (opioid* near/1 spar*)):ti,ab,kw	602
#58	(oxcarbazepin* or oxtellar or timox or trileptal or parecoxib):ti,ab,kw	769
#59	(prialt or ziconotide):ti,ab,kw	18
#60	(sirdalud or ternelin or tizanidin* or zanaflex):ti,ab,kw	187
#61	#60 OR #59 OR #58 OR #57 OR #56 OR #55 OR #54 OR #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6	110782
#62	#5 AND #61	17048
#63	(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 near/1 hydrochloride) or Dolan or Dolene or Dolorphe or Doloxene or Doloxyne or Femadol or (Kesso near/1 gesic) or Levitan or Leviton or Liberan or Piril or (Pro near/1 gesic) or (Prophene near/1 65) or Propoxyphen* or Propoxyphine or Proxagesic or Proxyvon or Regredol or Tawasan):ti,ab,kw	420
#64	(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	10736

	Mezolar or Onsolis or PecFent or Phentanyl or Rapinyl or Recuvyra or Sentonil or Sublimase or Sublimaze or Subsys or Tanyl or Transfenta):ti,ab,kw	
#65	(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):ti,ab,kw	1379
#66	(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 near/1 Ediat) or Meslon or (M near/1 Eslon) or Mitigo or Moraxen or Morcontin or Morficontin or Morphabond or Morphanton or Morphgesic or Morphia or Morphine* or Moscontin or (MS near/1 Contin) or (M near/1 S near/1 Contin) or Noceptin or Oblioser or Oramorph or (Rapi near/1 ject) or Relimal or Roxanol or Rylomine or Sevredol or Skenan or (S near/1 morphine) or Statex or Vendal or Zomorph):ti,ab,kw	10541
#67	(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 near/1 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 near/1 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):ti,ab,kw	2745
#68	(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 near/1 Rapide) or Sinalgin or Symoron or Westadone):ti,ab,kw	2404
#69	(Allay or Anexsia or Apadaz or Azdone or Bancap or Bekadid or Codamine or Codinovo or (CO near/1 GESIC) or Dico or Dicodid or Dihydrocodeinone or Dihydrocodone or (Duradyne near/1 DHC) or Flowtuss or Hidrocodona or Hycodan or Hycofenix or Hycon or Hydrocodeinonebitartrate or Hydrocodon* or Hydrocon* or Hydropane or (Hy near/1 Phen) or Hysingla or Idrocodone or (Lorcet near/1 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 near/1 ER) or Vicodin or Vicoprin or Vicoprofen or Vituz or Xtrelus or Zohydro or Zutripro or Zydone):ti,ab,kw	595
#70	(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen):ti,ab,kw	1347
#71	(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	5492

	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):ti,ab,kw	
#72	(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):ti,ab,kw	1995
#73	(Avridi or Bionine or Bionone or Bolodorm or Broncodal or Bucodal or Cafacodal or Cardanon or Codeinone or Codenon or (Codix near/1 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 near/1 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 near/1 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):ti,ab,kw	1742
#74	(Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol):ti,ab,kw	367
#75	(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 near/1 Contin) or (Hydromorphinone near/1 hydrochloride) or Hydromorphon* or (Hydrostat near/1 ir) or Hymorphan or Idromorfone or Jurnista or Laudacon* or Novolaudon or Opidol or Paliadon or Palladon* or Rexaphon or Semcox or Sophidone):ti,ab,kw	775
#76	(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl):ti,ab,kw	1996
#77	(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide):ti,ab,kw	315
#78	(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):ti,ab,kw	577
#79	(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor):ti,ab,kw	497
#80	(Nicomorfin* or Nicomorphin* or Vilan):ti,ab,kw	29
#81	(Remifentanil or Remifentanyl or Ultiva):ti,ab,kw	3483
#82	#81 OR #80 OR #79 OR #78 OR #77 OR #76 OR #75 OR #74 OR #73 OR #72 OR #71 OR #70 OR #69 OR #68 OR #67 OR #66 OR #65 OR #64 OR #63	36566
#83	#62 AND #82	8951

#84	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti,so	115842
#85	#83 NOT #84	8184
#86	(MEDLINE):an	11967
#87	(EMBASE):an	454766
#88	#85 NOT (#86 OR #87)	4708

Following peer review, the search was rerun on July 30, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The query at line 84 of the original strategy was modified as follows:

84 (newborn* or new-born* or neonat* or neo-nat* or infan* or baby* or babies* or toddler* or kid or kids or boy* or girl* or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti,so

As a consequence, 871 additional results were screened.

Scopus search strategy

3	#1 AND NOT #2	1380
2	ALL PMIDS	4881
1	((((((TITLE-ABS-KEY ((after OR following) W/3 (procedur* OR resect* OR surg*)) OR TITLE-ABS-KEY (post-operat* OR postoperat* OR post-surg* OR postsurg*)) AND TITLE-ABS-KEY (analgaes* OR analges* OR pain)) AND (TITLE-ABS-KEY (sirdalud OR ternelin OR tizanidin* OR zanaflex OR prialt OR ziconotide OR oxcarbazepin* OR oxtellar OR timox OR trileptal OR parecoxib OR opiat*-free OR opiat*-less OR opiat*-spar* OR opioid*-free OR opioid*-less OR opioid*-spar* OR nonsteroidal-antiinflammatory OR nonsteroidal-anti-inflammatory OR non-steroidal-antiinflammatory OR non-steroidal-anti-inflammatory OR nsaid* OR narop OR naropin OR noropine OR ropivacain* OR narcotic*-free OR narcotic*-less OR narcotic*-spar* OR non-narcotic* OR non-opioid* OR metassalone OR metaxalon* OR skelaxin OR zorane OR mefenamic-acid OR ponstan OR ponstel OR lyrica OR pregabalin OR lumiracoxib OR prexige OR (local-infiltration W/2 analgesia) OR lidocaine OR xylocaine OR xylocard OR ketalar OR ketamine OR indocin OR indomethacin OR novo-methacin OR pro-indo OR tivorbex OR gabatril OR gabitril OR tiagabine OR gabapentin* OR gralise OR horizant OR neurontin OR frotek OR ketoprofen OR fenoprofen OR nalfon OR flurbiprofen OR feldene OR piroxicam OR epitomax OR qsymia OR qudexy OR tipiramat* OR topamax OR topax OR topiragen OR topiramat* OR trokendi OR dexmedetomidine OR precedex OR diflunisal OR desvenlafaxine OR effexor OR elafax OR khedezla OR pristiq OR venlafaxin* OR demethylimipramine OR desimipramine OR desipramin* OR desmethylimipramine OR dezipramine OR dimethylimipramine OR norimipramine OR norpramin OR pertofrane OR daypro OR deflam OR oxaprozin* OR 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 OR corticoid* OR corticosteroid* OR cortico-steroid* OR chloroprocaine OR procaine OR celebrex OR celecox* OR catapres OR clonidine OR clorpres OR duraclon OR kapvay OR carbocaine OR mepivacaine OR polocaine OR scandonest OR bupivacaine OR exparel OR marcaine OR sensorcaine OR vivacaine OR baclofen* OR gablofen* OR kemstro OR lioresal OR 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 OR 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 OR arthrotec OR diclofenac OR dyloject OR flector OR pennsaid OR solaraze OR voltaren OR zipsor OR zorvolex OR 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 OR aristospan OR kenalog OR triamcinolone OR zilretta OR ariclaim OR cymbalta OR duloxetine OR xeristar OR yentreve OR arcoxia OR etoricoxib* OR etoxib OR etropain OR kingcox OR tauxib OR torcoxia OR anti-inflammatory-analges* OR antiinflammatory-analges* OR amrix OR cyclobenzaprin* OR fexmid OR flexeril OR lisseril OR proeptatriene OR proheptatrien* OR 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 OR alphatrex OR beta-val OR betacort OR betaderm OR betagel OR betaject OR betamethasone OR betamycin OR betaprolene OR betaprone OR betatrex OR beteflam	2,382

	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 OR 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 OR alganex OR liman OR mobiflex OR octiveran OR rexalgan OR tenoxicam* OR tilcotil OR 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 OR aleve OR anaprox OR flanax OR maxidol OR mediproxen OR naprelan OR naprosyn OR naproxen OR 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 OR 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 OR 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 OR 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 OR acetylsalicylic-acid OR aspirin OR acetaminophen OR paracetamol OR tylenol OR 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))) AND (TITLE-ABS-KEY (remifentanil OR remifentanyl OR ultiva OR nicomorfin* OR nicomorphin* OR vilan OR nalbufin* OR nalbuphin* OR nalcryn OR nalpain OR nubain* OR onfor OR 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 OR dipidolor OR dipiritramide OR dipydolor OR piridolan OR pirinitramide OR piritramid* OR pyritramide OR chronogesic OR dsuvia OR fentathianyl OR fentathienyl OR fentatienil OR sufenta OR sufentanil* OR sufentanyl OR 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 OR beforal OR butorfanol OR butorphanol OR butorphanolum OR dolorex OR moradol OR stadol OR 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 OR 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 OR 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 OR alfenil OR alfenta OR alfentanil* OR alfentanyl OR brevafen OR fanaxal OR limifen OR rapifen OR 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 OR 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 AND 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 OR 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 OR 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 OR 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 OR 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 OR 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))) AND NOT (TITLE (animals OR animal 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*) AND NOT TITLE (human* OR patient*))) AND NOT (TITLE (newborn* OR new-born* OR neonat* OR neo-nat* OR infan* OR	

	child* OR adolesc* OR paediatr* OR pediatr* OR baby* OR babies* OR toddler* OR kid OR kids OR boy* OR girl* OR juvenile* OR teen* OR youth* OR pubescen* OR preadolesc* OR prepubesc* OR preteen OR tween) OR SRCTITLE (pediatr* OR paediatr*))) AND (TITLE-ABS (placebo OR randomized OR randomly) OR TITLE (trial)) ...	

Following peer review, the search was rerun on July 30, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The pediatric restriction portion of the original strategy was modified as follows:

AND NOT (TITLE (newborn* OR new-born* OR neonat* OR neo-nat* OR infan* OR child* OR adolesc* OR paediatr* OR pediatr* OR baby* OR babies* OR toddler* OR kid OR kids OR boy* OR girl* OR juvenile* OR teen* OR youth* OR pubescen* OR preadolesc* OR prepubesc* OR preteen OR tween))

As a consequence, 196 additional results were screened.

AMED search strategy

#	Searches	Results
1	(following adj3 (procedure* or resect* or surg*)).ti,ab,et.	18158
2	(post-operat* or postoperat* or post-surg* or postsurg*).ti,ab,et.	4417
3	1 or 2	19544
4	(analgaes* or analges* or pain).mp,et.	32806
5	3 and 4	4631
6	(sirdalud or ternelin or tizanidin* or zanaflex or prialt or ziconotide or oxcarbazepin* or oxtellar or timox or trileptal or parecoxib or opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar* or nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid* or narop or naropin or noropine or ropivacain* or narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid* or metassalone or metaxalon* or skelaxin or zorane or mefenamic-acid or ponstan or ponstel or lyrica or pregabalin or lumiracoxib or prexige or (local-infiltration adj2 analgesia) or lidocaine or xylocaine or xylocard or ketalar or ketamine or indocin or indomethacin or novo-methacin or pro-indo or tivorbex or gabatril or gabitril or tiagabine or gabapentin* or gralise or horizant or neurontin or frotek or ketoprofen or fenoprofen or nalfon or flurbiprofen or feldene or piroxicam or epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi or dexmedetomidine or precedex or diflunisal or desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin* or demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane or daypro or deflam or oxaprozin* or 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 or corticoid* or corticosteroid* or cortico-steroid* or chloroprocaine or procaine or celebrex or celecox* or catapres or clonidine or clorpres or duraclon or kapvay or carbocaine or mepivacaine or polocaine or scandonest or bupivacaine or exparel or marcaine or sensorcaine or vivacaine or baclofen* or gablofen* or kemstro or lioresal or 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,et.	1953
7	(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 or arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex or 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 or aristospan or kenalog or triamcinolone or zilretta or ariclaim or cymbalta or duloxetine or xeristar or yentreve or arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia or anti-inflammatory-analges* or antiinflammatory-analges* or amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien* or 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 or 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	414

	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,et.	
8	(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 or alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil or 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 or aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen).mp,et.	98
9	(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 or 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 or 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,et.	657
10	(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 or acetylsalicylic-acid or aspirin or acetaminophen or paracetamol or tylenol or 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	753

	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,et.	
11	6 or 7 or 8 or 9 or 10	3425
12	5 and 11	239
13	(Remifentanil or Remifentanyl or Ultiva or Nicomorfin* or Nicomorphin* or Vilan or Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor or 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 or Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide or Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl or 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 or Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol).mp,et.	85
14	(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,et.	61
15	(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 or 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 or Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen or 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	281

	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,et.	
16	(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 or 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,et.	191
17	(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 or 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 or 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 or 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,et.	809
18	13 or 14 or 15 or 16 or 17	1209
19	12 and 18	42
20	(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*).ti,hw,jx. not (human* or patient*).mp.	11419
21	19 not 20	39

22	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween).ti,jw.	20124
23	21 not 22	38
24	(placebo or randomized or randomly).ti,ab. or trial.ti.	17190
25	23 and 24	17

Following peer review, the search was rerun on July 30, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The query at line 22 of the original strategy was modified as follows:

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

As a consequence, 0 additional results were screened.

Institutional access to AMED (the Allied and Complementary Medicine Database) was discontinued in June of 2020; the June 8, 2021 update therefore does not include records from this database.

Biosis search strategy

Indexes=BCI Timespan=All years

#104	466	#89 NOT 103
#90-103	2800	PMIDS
# 89	2,337	#87 AND #88
# 88	649,332	TS=(placebo or randomized or randomly) OR TI=(trial)
# 87	3,670	#85 NOT #86
# 86	933,680	TI=(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween) OR SO=(pediatr* or paediatr*)
# 85	4,038	#83 NOT #84
# 84	8,647,500	TA=(animal* NOT hominidae)
# 83	4,392	#62 AND #82
# 82	148,102	#81 OR #80 OR #79 OR #78 OR #77 OR #76 OR #75 OR #74 OR #73 OR #72 OR #71 OR #70 OR #69 OR #68 OR #67 OR #66 OR #65 OR #64 OR #63
# 81	3,011	TS=(Remifentanil or Remifentanyl or Ultiva)
# 80	45	TS=(Nicomorfin* or Nicomorphin* or Vilan)
# 79	955	TS=(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor)
# 78	2,948	TS=(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)
# 77	356	TS=(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide)
# 76	2,697	TS=(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl)
# 75	1,399	TS=(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)
# 74	1,621	TS=(Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol)
# 73	2,720	TS=(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)
# 72	5,137	TS=(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)
# 71	47,284	TS=(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)
# 70	2,348	TS=(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen)
# 69	1,661	TS=(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)
# 68	11,272	TS=(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)
# 67	3,627	TS=(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)
# 66	63,419	TS=(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)
# 65	6,014	TS=(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)
# 64	15,510	TS=(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)
# 63	1,901	TS=(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)
# 62	9,588	#5 AND #61
# 61	551,869	#60 OR #59 OR #58 OR #57 OR #56 OR #55 OR #54 OR #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6
# 60	524	TS=(sirdalud or ternelin or tizanidin* or zanaflex)
# 59	219	TS=(prialt or ziconotide)
# 58	2,761	TS=(oxcarbazepin* or oxtellar or timox or trileptal or parecoxib)
# 57	371	TS=(opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*)
# 56	37,432	TS=(nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*)

# 55	2,834	TS=(narop or naropin or noropine or ropivacain*)
# 54	1,996	TS=(narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*)
# 53	45	TS=(metassalone or metaxalon* or skelaxin or zorane)
# 52	1,539	TS=(mefenamic-acid or ponstan or ponstel)
# 51	2,495	TS=(lyrica or pregabalin)
# 50	266	TS=(lumiracoxib or prexige)
# 49	79	TS=(local-infiltration NEAR/2 analgesia)
# 48	21,708	TS=(lidocaine or xylocaine or xylocard)
# 47	17,407	TS=(ketalar or ketamine)
# 46	44,605	TS=(indocin or indomethacin or novo-methacin or pro-indo or tivorbex)
# 45	1,173	TS=(gabatril or gabitril or tiagabine)
# 44	5,848	TS=(gabapentin* or gralise or horizant or neurontin)
# 43	4,302	TS=(frotek or ketoprofen)
# 42	3,456	TS=(fenoprofen or nalfon or flurbiprofen)
# 41	3,638	TS=(feldene or piroxicam)
# 40	5,338	TS=(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi)
# 39	3,468	TS=(dexmedetomidine or precedex or diflunisal)
# 38	4,111	TS=(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*)
# 37	8,977	TS=(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane)
# 36	219	TS=(daypro or deflam or oxaprozin*)
# 35	2,153	TS=(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)
# 34	90,289	TS=(corticoid* or corticosteroid* or cortico-steroid*)
# 33	8,524	TS=(chloroprocaine or procaine)
# 32	6,718	TS=(celebrex or celecox*)
# 31	17,325	TS=(catapres or clonidine or clorpres or duraclon or kapvay)

# 30	1,923	TS=(carbocaine or mepivacaine or polocaine or scandonest)
# 29	10,989	TS=(bupivacaine or exparel or marcaine or sensorcaine or vivacaine)
# 28	7,730	TS=(baclofen* or gablofen* or kemstro or lioresal)
# 27	195	TS=(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)
# 26	3,034	TS=(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)
# 25	11,775	TS=(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex)
# 24	589	TS=(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)
# 23	7,233	TS=(aristospan or kenalog or triamcinolone or zilretta)
# 22	1,975	TS=(ariclaim or cymbalta or duloxetine or xeristar or yentreve)
# 21	650	TS=(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia)
# 20	1,645	TS=(anti-inflammatory-analges* or antiinflammatory-analges*)
# 19	314	TS=(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*)
# 18	18,316	TS=(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)
# 17	5,186	TS=(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)
# 16	1,144	TS=(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)
# 15	793	TS=(alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil)
# 14	15,700	TS=(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)
# 13	7,268	TS=(aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen)
# 12	8,299	TS=(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)
# 11	14,274	TS=(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)
# 10	41,848	TS=(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)
# 9	87,896	TS=(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)
# 8	55,703	TS=(acetylsalicylic-acid or aspirin)
# 7	23,680	TS=(acetaminophen or paracetamol or tylenol)
# 6	45,555	TS=(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)
# 5	41,368	#4 AND #3
# 4	408,320	TS=(analgaes* or analges* or pain)
# 3	394,514	#2 OR #1
# 2	236,997	TS=(post-operat* or postoperat* or post-surg* or postsurg*)
# 1	220,884	TS=((after or following) NEAR/3 (procedur* or resect* or surg*))

Following peer review, the search was rerun on July 30, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The queries at line 86 of the original strategy were modified as follows:

86 TI=(newborn* or new-born* or neonat* or neo-nat* or infan* or baby* or babies* or toddler* or kid or kids or boy* or girl* or pubescen* or preadolesc* or prepubesc* or preteen or tween)

As a consequence, 203 additional results were screened.

CINAHL search strategy

#	Query	Results
S151	S147 AND S150	1,632
S150	S148 OR S149	370,152
S149	TI (placebo or randomized or randomly or trial) OR AB (placebo or randomized or randomly)	258,807
S148	(MH "Clinical Trials") OR (MH "Randomized Controlled Trials")	219,102
S147	S145 NOT S146	2,601
S146	TI (newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween) OR SO (pediatr* or paediatr*)	546,059
S145	S143 NOT S144	2,864
S144	TI ((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*) NOT (human* or patient*))	80,613
S143	S106 AND S142	2,892
S142	S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141	38,804
S141	TI (Remifentanil or Remifentanyl or Ultiva) OR AB (Remifentanil or Remifentanyl or Ultiva)	1,362
S140	TI (Nicomorfin* or Nicomorphin* or Vilan) OR AB (Nicomorfin* or Nicomorphin* or Vilan)	8
S139	TI (Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor) OR AB (Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor)	124
S138	TI (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) OR AB (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)	140
S137	TI (Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide) OR AB (Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide)	60

S136	TI (Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl) OR AB (Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl)	506
S135	TI (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) OR AB (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)	533
S134	TI (Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol) OR AB (Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol)	81
S133	TI (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) OR AB (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)	1,483
S132	TI (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) OR AB (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	2,666

	or Probuphine or Somnena or Sublocade or Suboxone or Subutex or Temgesic or Transtec or Vetergesic or Zubsolv)	
S131	TI (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) OR AB (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)	2,135
S130	TI (Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen) OR AB (Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen)	447
S129	TI (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) OR AB (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)	850
S128	TI (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) OR AB (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	4,403

	Physepton* or Polamidon or Polamivet or Polamivit or Sedo-Rapide or Sinalgin or Symoron or Westadone)	
S127	TI (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) OR AB (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)	1,283
S126	TI (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) OR AB (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)	7,090
S125	TI (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) OR AB (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)	811
S124	TI (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	3,826

	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) OR AB (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)	
S123	TI (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) OR AB (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)	300
S122	(MH "Tramadol")	1,038
S121	(MH "Sufentanil")	422
S120	(MH "Pentazocine")	127
S119	(MH "Oxycodone")	1,391
S118	(MH "Nalbuphine")	101
S117	(MH "Morphine")	6,264
S116	(MH "Methadone")	4,327
S115	(MH "Meperidine")	902
S114	(MH "Dihydromorphinone")	457
S113	(MH "Fentanyl")	3,924
S112	(MH "Propoxyphene")	158
S111	(MH "Codeine")	968
S110	(MH "Butorphanol")	67
S109	(MH "Buprenorphine")	2,644
S108	(MH "Alfentanil")	450
S107	(MH "Analgesics, Opioid+")	30,340

S106	S9 AND S105	7,118
S105	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104	143,377
S104	TI (sirdalud or ternelin or tizanidin* or zanaflex) OR AB (sirdalud or ternelin or tizanidin* or zanaflex)	117
S103	TI (prialt or ziconotide) OR AB (prialt or ziconotide)	90
S102	TI (oxcarbazepin* or oxtellar or timox or trileptal or parecoxib) OR AB (oxcarbazepin* or oxtellar or timox or trileptal or parecoxib)	510
S101	TI (opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*) OR AB (opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*)	339
S100	TI (nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*) OR AB (nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*)	8,095
S99	TI (narop or naropin or noropine or ropivacain*) OR AB (narop or naropin or noropine or ropivacain*)	1,128
S98	TI (narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*) OR AB (narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*)	587
S97	TI (metassalone or metaxalon* or skelaxin or zorane) OR AB (metassalone or metaxalon* or skelaxin or zorane)	14
S96	TI (mefenamic-acid or ponstan or ponstel) OR AB (mefenamic-acid or ponstan or ponstel)	79
S95	TI (lyrica or pregabalin) OR AB (lyrica or pregabalin)	1,182
S94	TI (lumiracoxib or prexige) OR AB (lumiracoxib or prexige)	61
S93	TI (local-infiltration N2 analgesia) OR AB (local-infiltration N2 analgesia)	130
S92	TI (lidocaine or xylocaine or xylocard) OR AB (lidocaine or xylocaine or xylocard)	3,385
S91	TI (ketalar or ketamine) OR AB (ketalar or ketamine)	3,148
S90	TI (indocin or indomethacin or novo-methacin or pro-indo or tivorbex) OR AB (indocin or indomethacin or novo-methacin or pro-indo or tivorbex)	1,547
S89	TI (gabatril or gabitril or tiagabine) OR AB (gabatril or gabitril or tiagabine)	104

S88	TI (gabapentin* or gralise or horizant or neurontin) OR AB (gabapentin* or gralise or horizant or neurontin)	1,818
S87	TI (frotek or ketoprofen) OR AB (frotek or ketoprofen)	218
S86	TI (fenoprofen or nalfon or flurbiprofen) OR AB (fenoprofen or nalfon or flurbiprofen)	118
S85	TI (feldene or piroxicam) OR AB (feldene or piroxicam)	159
S84	TI (epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi) OR AB (epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi)	1,224
S83	TI (dexmedetomidine or precede or diflunisal) OR AB (dexmedetomidine or precede or diflunisal)	4,582
S82	TI (desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*) OR AB (desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*)	1,045
S81	TI (demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane) OR AB (demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane)	163
S80	TI (daypro or deflam or oxaprozin*) OR AB (daypro or deflam or oxaprozin*)	8
S79	TI (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) OR AB (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)	163
S78	TI (corticoid* or corticosteroid* or cortico-steroid*) OR AB (corticoid* or corticosteroid* or cortico-steroid*)	15,385
S77	TI (chloroprocaine or procaine) OR AB (chloroprocaine or procaine)	181
S76	TI (celebrex or celecox*) OR AB (celebrex or celecox*)	1,099
S75	TI (catapres or clonidine or clorpres or duraclon or kapvay) OR AB (catapres or clonidine or clorpres or duraclon or kapvay)	1,128
S74	TI (carbocaine or mepivacaine or polocaine or scandonest) OR AB (carbocaine or mepivacaine or polocaine or scandonest)	234
S73	TI (bupivacaine or exparel or marcaine or sensorcaine or vivacaine) OR AB (bupivacaine or exparel or marcaine or sensorcaine or vivacaine)	2,632
S72	TI (baclofen* or gablofen* or kemstro or lioresal) OR AB (baclofen* or gablofen* or kemstro or lioresal)	1,057
S71	TI (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	21

	robax or robaxacet or robaximol or robaxin or robaxisal or robinax or romethocarb or spasmhalt or surquetil or tresortil) OR AB (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)	
S70	TI (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) OR AB (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)	294
S69	TI (arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex) OR AB (arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex)	1,278
S68	TI (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) OR AB (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)	41
S67	TI (aristospan or kenalog or triamcinolone or zilretta) OR AB (aristospan or kenalog or triamcinolone or zilretta)	998
S66	TI (ariclaim or cymbalta or duloxetine or xeristar or yentreve) OR AB (ariclaim or cymbalta or duloxetine or xeristar or yentreve)	861
S65	TI (arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia) OR AB (arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia)	195
S64	TI (anti-inflammatory-analges* or antiinflammatory-analges*) OR AB (anti-inflammatory-analges* or antiinflammatory-analges*)	107
S63	TI (amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*) OR AB (amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*)	87
S62	TI (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) OR AB (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)	1,336
S61	TI (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) OR AB (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	570

	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)	
S60	TI (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) OR AB (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)	108
S59	TI (alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil) OR AB (alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil)	60
S58	TI (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) OR AB (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)	1,130
S57	TI (aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen) OR AB (aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen)	695

S56	TI (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) OR AB (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)	742
S55	TI (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) OR AB (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)	1,868
S54	TI (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) OR AB (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)	3,033
S53	TI (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) OR AB (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)	5,608

S52	TI (acetylsalicylic-acid or aspirin) OR AB (acetylsalicylic-acid or aspirin)	9,781
S51	TI (acetaminophen or paracetamol or tylenol) OR AB (acetaminophen or paracetamol or tylenol)	4,818
S50	TI (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) OR AB (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)	3,738
S49	(MH "Venlafaxine")	604
S48	(MH "Triamcinolone")	1,190
S47	(MH "Procaine")	190
S46	(MH "Prilocaine")	409
S45	(MH "Pregabalin")	490
S44	(MH "Prednisone")	3,768
S43	(MH "Prednisolone")	2,624
S42	(MH "Piroxicam")	155
S41	(MH "Phenytoin+")	1,020
S40	(MH "Nortriptyline")	270
S39	(MH "Neuromuscular Agents+")	9,182
S38	(MH "Naproxen")	600
S37	(MH "Methylprednisolone")	2,369
S36	(MH "Lidocaine")	4,416
S35	(MH "Ketorolac")	653
S34	(MH "Ketamine")	2,796
S33	(MH "Indomethacin")	1,172
S32	(MH "Ibuprofen")	1,819

S31	(MH "GABA")	2,069
S30	(MH "Gabapentin")	912
S29	(MH "Flurbiprofen")	69
S28	(MH "Fenoprofen")	4
S27	(MH "Duloxetine Hydrochloride")	290
S26	(MH "Diclofenac")	1,150
S25	(MH "Dexamethasone")	4,559
S24	(MH "Desipramine")	131
S23	(MH "Clonidine")	1,221
S22	(MH "Cox-2 Inhibitors")	3,496
S21	(MH "Carbamazepine")	1,227
S20	(MH "Bupivacaine")	3,221
S19	(MH "Baclofen")	979
S18	(MH "Aspirin")	9,997
S17	(MH "Antiinflammatory Agents, Non-Steroidal+")	27,434
S16	(MH "Anticonvulsants+")	16,772
S15	(MH "Anesthetics, Local")	7,594
S14	(MH "Anesthesia, Local")	2,669
S13	(MH "Analgesics, Nonnarcotic+")	35,219
S12	(MH "Amitriptyline")	703
S11	(MH "Adrenal Cortex Hormones+")	29,468
S10	(MH "Acetaminophen")	4,731
S9	S1 OR S8	34,464
S8	S6 AND S7	28,253
S7	TI (analgaes* or analges* or pain) OR AB (analgaes* or analges* or pain)	212,862
S6	S2 OR S3 OR S4 OR S5	156,397

S5	TI (post-operat* or postoperat* or post-surg* or postsurg*) OR AB (post-operat* or postoperat* or post-surg* or postsurg*)	94,188
S4	TI ((after or following) N3 (procedur* or resect* or surg*)) OR AB ((after or following) N3 (procedur* or resect* or surg*))	76,586
S3	(MH "Postoperative Period")	10,785
S2	(MH "Postoperative Care")	15,872
S1	(MH "Postoperative Pain")	14,722

Following peer review, the search was rerun on July 29, 2019 with a revised age filter that retrieved articles from pediatric journals and studies including pediatric patients.

The query at line 146 of the original strategy was modified as follows:

S146 TI (newborn* or new-born* or neonat* or neo-nat* or infan* or baby* or babies* or toddler* or kid or kids or boy* or girl* or pubescen* or preadolesc* or prepubesc* or preteen or tween)

As a consequence, 123 additional results were screened.

Study protocol and amendments

Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. BMJ Open. 2020;10(1):e035443. doi: 10.1136/bmjopen-2019-035443.

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. 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 ($\leq$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. 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. 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.

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 anaesthesia 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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List of protocol amendments

All the protocol amendments have been decided in consultation with the review steering committee comprised of librarians, researchers, knowledge users, statisticians, and patient representatives.

Amendment	Reason
Change in eligibility criteria (prior to literature search): Exclusion of cross-over trials.	We decided to exclude cross-over trials from the meta-analysis. When used to assess postoperative pain management strategies, cross-over trials can be influenced by the natural history of postoperative pain improving over time regardless of the treatment received. The inclusion of such trials would have added statistical complexity to our analysis and, potentially, increased risk of bias.
Change in the search strategy (prior to literature search): PsycINFO database was not part of the search strategy.	Our librarians determined that searching in PsycINFO was unlikely to retrieve any unique records qualified for inclusion in our review, while adding a high number of irrelevant records to screen. Based on previous experience reviewing the literature on opioid-free analgesia, which did not identify unique relevant records via PsycINFO (https://www.bjanaesthesia.org/article/S0007-0912(19)30640-3/fulltext), as well as pilot searches, we are confident that the range of bibliographic databases and trial registries searched for this meta-analysis provided a robust coverage of the eligible RCTs.
Change in outcome-related terminology (prior to data analysis): Vomiting deemed as a co-primary outcome.	Our initial protocol deemed vomiting as a 'secondary *a priori* outcome', but this terminology was confusing to some members of our team. Given that postoperative vomiting is considered the least desirable outcome in perioperative care according to patient preference, we decided to designate vomiting a 'co-primary outcome'. This change was purely terminological and did not impact our analysis nor the interpretation of results.
Change in outcome assessment (prior to data analysis): The outcome 'satisfaction with pain management' was assessed as a dichotomous measure and termed 'dissatisfaction with pain management'.	After data extraction, we noticed that authors used a variety of instruments to assess satisfaction with pain management (dichotomous, ordinal, and continuous measures). When preparing this data for analysis we decided to (1) dichotomize all the available data (dissatisfied= very dissatisfied, dissatisfied, or satisfaction score <5/10; not dissatisfied= very satisfied, satisfied, neutral, or satisfaction score >5/10) and (2) focus our meta-analysis on risk of dissatisfaction (rather than satisfaction) to facilitate interpretation. We also considered combining binary, ordinal and continuous data into a common scale such as a standardized difference. However, we believe that assessing satisfaction with pain management using standardized differences would generate effect estimates that have limited meaning to clinicians (how much standardized difference is clinically meaningful?). Besides, combining data into standardized differences assumes that the continuous scale follows a logistic distribution, which is often not the case for satisfaction scales (where responses are often skewed towards higher scores).
Change in outcome assessment (prior to data analysis): 'Emergency department visits', 'unplanned clinic visits', and 'hospital readmissions' were assessed as one composite outcome named 'healthcare reutilization'.	Not many trials assessed the outcomes 'emergency department visits', 'unplanned clinic visits', and 'hospital readmissions'. As analysing these outcomes separately would have prevented robust meta-analyses, we decided to combine these data into one composite outcome named 'healthcare reutilization' (https://jamanetwork.com/journals/jamasurgery/article-abstract/2772622).
Change in analysis plan (prior to data analysis): Decision to not analyse pain as a dichotomous outcome (cut-off <3/10cm in VAS).	None of the studies identified by the search strategy reported pain as a dichotomous outcome. Also, many studies reporting postoperative pain did not report measures of variance (e.g., standard deviations) which are crucial for accurate dichotomization of continuous outcomes. Therefore, the dichotomization of pain outcomes was deemed not feasible.

Change in method of data interpretation (prior to data analysis): Pain data were interpreted according to recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).	In the initial protocol, we proposed interpreting the magnitude of between-group differences in VAS as 'very large' (WMD>2 MIDs), 'large' (WMD>1 MID, but <2 MIDs), 'moderate' (WMD>0.5 MID, <1 MID), or 'small' (WMD<0.5 MID). However, this interpretation, proposed by OMERACT in 2015 (https://www.jrheum.org/content/42/10/1962.long), is complex and somewhat arbitrary. In November 2020, new recommendations for the interpretation of pain trials were proposed by the IMMPACT group (https://pubmed.ncbi.nlm.nih.gov/32520773/). Our group agreed that this newly proposed method, based on the relationship between confidence intervals and MID thresholds, would be a better fit for our meta-analyses.
Change in data analysis (suggested during peer-review): An additional subgroup analysis was conducted with surgeries classified according to the POSSUM System (minor, moderate, major, major-complex).	Peer-reviewers suggested that using the WHO classification of minor and major surgery weakens our analysis as several procedures classified as major (e.g., laparoscopic hernia repairs, arthroscopies, hand surgery) are not associated with substantial tissue trauma and should not be grouped with more extensive procedures (e.g., pancreaticoduodenectomy, thoraco-abdominal esophagectomies). Following the reviewers' suggestion, we further classified our procedures by surgery extent (minor, moderate, major, major-complex) based on the criteria proposed in the POSSUM System (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) (https://jamanetwork.com/journals/jamasurgery/fullarticle/212013). Furthermore, we conducted a subgroup analysis based on this classification, which allowed a more balanced assessment of existing evidence and detection of knowledge gaps to be filled by future trials.
Change in data analysis (suggested during peer-review): Sensitivity analyses were conducted assessing different methods to address zero cells in our primary binary outcomes (vomiting).	Pooled estimates and standard errors derived from meta-analyses of binary outcomes may be biased when there are trials with zero events (0 cells) in one or both study arms. To deal with this issue, we used Stata's default continuity correction approach which adds 0.5 to all the cells in 2×2 table containing empty cells. However, this is a controversial approach, which receives both support (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-7-5; https://www.valueinhealthjournal.com/article/S1098-3015(16)01783-6/fulltext) and criticism in the literature (https://pubmed.ncbi.nlm.nih.gov/15116347/; https://onlinelibrary.wiley.com/doi/full/10.1002/jrsm.1460). Given concerns raised by one of the peer-reviewers of our manuscript, we conducted and reported two *post hoc* sensitivity analyses focused on alternative approaches to address zero cells: (1) no continuity correction, and (2) treatment-arm continuity correction (TACC; https://pubmed.ncbi.nlm.nih.gov/15116347/).

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

We followed specific guidelines to concert pain intensity measures into a standard metric.[1-3] Our standard metric of choice was the 10-cm Pain Intensity VAS (score range 0-10 cm; lower score represents less pain) as this is the scale most commonly used in acute pain trials.[4-6] The process of standardization followed the steps below:

Step 1	• Non-VAS pain scores were initially converted into standardized mean differences (SMD), by dividing the between-group differences in means (MD) in each trial by the pooled standard deviation (SD) of the two trial arms. • The SMD expresses the intervention effect in SD units, rather than the original units of measurement.
Step 2	• Standardization of other pain scales into VAS scores was done by multiplying the SMD obtained from original trials (calculated as above) by the VAS SD. • The VAS SD used for this conversion was the pooled SD obtained from the largest trial where pain intensity was assessed via VAS.
Step 3	• Trials that assessed pain outcomes using a VAS score or had non-VAS scores converted into VAS were meta-analysed to calculate a pooled weighted mean difference (WMD) in VAS scores.

Step 1	• The authors assessed pain using a numerical rating scale (NRS) ranging from 0-10. On post-discharge day 3, 96 patients in the opioid group had a mean NRS score of 2.74 ± 2.04, and 98 patients in the opioid-free group had a mean NRS score of 2.62 ± 1.90. • The mean difference (MD) between groups in NRS scores was 0.12 (2.74 minus 2.62) and the pooled standard deviation was 1.97, calculated according to the formula described in Cochrane handbook:[7] $\sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}(M_1^2+M_2^2-2M_1M_2)}{N_1+N_2-1}}$ • The calculated standardized mean differences (SMD) in NRS between groups was 0.06 (MD / SD = 0.12 / 1.97).
Step 2	• To convert NRS results into VAS scores, we multiplied the SMD previously calculated (0.06) by the pooled SD obtained from the largest trial where pain intensity was assessed via VAS (Mitchell 2008; pooled SD = 1.94). • When the data was converted, the mean between-group difference in VAS scores calculated for Bugada et al was 0.12 (SMD * SD_{VAS} = 0.06 * 1.94).
Step 3	• The VAS score at post-discharge day 3 calculated from Bugada et al (0.12) was meta-analysed with other trials that assessed pain outcomes at the same timepoint using a VAS score, or with non-VAS scores converted into VAS.

Working example: Bugada et al 2015

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Classification of surgical procedures

(Adapted from the POSSUM System of Surgical Audit; https://jamanetwork.com/journals/jamasurgery/fullarticle/212013)

Classification/criteria	Procedures addressed in the trials identified
Minor • The procedure can be done in an outpatient clinic (may not require a hospital operating room). • Conducted under local/regional anesthesia. • Tissue manipulation and trauma are minimal. • Rarely leads to long-term functional impairment. • Discharge is on the same day.	• Dental surgery (i.e., molar, root canal, implant, incision &drainage). • Laser eye surgery (i.e., LASIK). • Cosmetic facial surgery (i.e., rhinoplasty, otoplasty, blepharoplasty, rhytidectomy). • Sinus surgery. • Tonsillectomy. • Vasectomy. • Hand repair (i.e., carpal tunnel, trigger finger). • Foot repair (i.e., bunion, tarsal tunnel release). • Hemorrhoidectomy. • Varicose vein surgery. *Other examples (not addressed): Excision of skin or subcutaneous lesions, adenoidectomy, circumcision, tubal ligation, anal fissure repairs.*
Moderate • The procedure is usually done in a hospital operating room. • Conducted under general or regional anesthesia. • Tissue manipulation and trauma are minimal or minimized using minimally invasive surgical techniques. • Rarely leads to long-term functional impairment. • Discharge on the same day or after an overnight stay is often feasible.	• Thyroidectomy/Parathyroidectomy. • Mastectomy/Partial Mastectomy. • Laparoscopic/open cholecystectomy. • Laparoscopic/open inguinal hernia repair. • Laparoscopic/open umbilical hernia repair. • Laparoscopic/open appendectomy. • Transvaginal procedures (i.e., hysterectomy, prolapse repair, vaginal sling) • Caesarian section. • Spinal decompression (i.e., discectomy, laminectomy). • Shoulder arthroscopic repair (i.e., labrum, rotator cuff repair). • Knee arthroscopic repair (i.e., meniscus, cruciate ligament). • Extremity fracture repair (i.e., upper, lower limb). *Other examples (not addressed): Prostatectomy, salpingectomy, oophorectomy.*
Major • The procedure is done in a hospital operating room. • Conducted under general or regional anesthesia. • Tissue manipulation and trauma are considerable but can be reduced using minimally invasive surgical techniques. • May lead to long-term functional impairment.	• No procedures addressed in the trials identified. *Examples (not addressed): Surgeries via craniotomy, sternotomy, or thoracotomy (excluding major extended), gastric, bowel, liver, kidney, or distal pancreatic resections, abdominal wall reconstruction, joint replacement (i.e., knee, hip), spinal reconstruction/fusion.*

• Often requires postoperative hospitalization for a few days.	
Major-complex • The procedure is done in a hospital operating room. • Conducted under general anesthesia. • Tissue manipulation and trauma are extensive. • May require planned postoperative ICU stay. • Often leads to long-term functional impairment. • Often require postoperative hospitalization for many days.	• No procedures addressed in the trials identified. *Examples (not addressed): Skull-base resections, laryngectomy, thoraco-abdominal procedures (i.e., esophagectomy, aortic repair), cardiac surgery with extracorporeal circulation, pancreaticoduodenectomy, radical cystectomy, abdominal perineal resection, transplant of thoraco-abdominal organs, multi-visceral resections.*

GRADE assessment rules

Grade domain	Rules to <u>decrease</u> certainty
Methodological limitations of the included study[1]	'No serious methodological limitation' if (1) studies with 'high' risk of bias contributed < 50% to the effect estimate and (2) subgroup analysis does not indicate a significant difference in effect estimates between studies with 'high risk' of bias and studies with lower risk of bias ('low risk' or 'some concerns'). ↓1 level if (1) studies with 'high' risk of bias contributed > 50% to the effect estimate and (2) subgroup analysis does not indicate a significant difference in effect estimates between studies with 'high risk' of bias and studies with lower risk of bias ('low risk' or 'some concerns'). ↓2 levels if subgroup analysis indicates a significant difference in effect estimates between studies with 'high risk' of bias and studies with lower risk of bias ('low risk' or 'some concerns'). ↓2 levels if all studies were 'high risk' of bias.
Indirectness[2]	'No serious indirectness' if studies evaluated the interventions of interest, applied to the populations of interest and outcomes were measured consistently (i.e., in a standardized manner). ↓1 level if the outcome measure was assessed using various criteria (e.g., overall adverse event) or different timepoints.
Imprecision[3]	<u>Continuous outcomes:</u> Calculate optimal sample size based on alpha, beta, minimally important difference, and highest SD of studies included. https://clincalc.com/stats/samplesize.aspx 'No serious imprecision' if the optimal sample size was met and the CI of the overall estimate does not cross zero (i.e., the no effect line). 'No serious imprecision' if the optimal sample size was met and the CI of the overall estimate crosses zero (i.e., the no effect line) but does not include the minimal important difference (MID). ↓1 level if optimal sample size was not met. ↓1 level if optimal sample size was met but CI crosses zero (i.e., the no effect line) and includes the MID. ↓2 levels if CI include both important benefits and harms (potential reduction or increase above the MID). <u>Dichotomous outcomes:</u>

	Calculate optimal sample size based on alpha, beta, control group event rate and accounting for a relative risk (RR) reduction (or increase) threshold of 30%. https://clincalc.com/stats/samplesize.aspx 'No serious imprecision' if the total sample size was > 2000. 'No serious imprecision' if the optimal sample size was met and the CI of the overall estimate does not cross 1.0 (i.e., the no effect line). 'No serious imprecision' if the optimal sample size was met and the CI of the overall estimate crosses 1.0 (i.e., the no effect line), but does not include an important benefit/harm (RR reduction or increase > 30%). ↓1 level if optimal sample size was not met. ↓1 level if optimal sample size was met but CI of the overall estimate crosses 1.0 (i.e., the no effect line) and includes an important benefit or harm (RR reduction or increaser = 30%). ↓2 levels if CI of the overall estimate include both important benefits and harms (potential RR reduction or increase > 30%).
Inconsistency[4]	'No serious inconsistency' if I^2<75%. 'No serious inconsistency' if CIs of individual studies overlap. 'No serious inconsistency' if CIs of individual studies don't overlap, but they are all in the same direction (supporting harms or benefits). ↓1 level if I^2>75%, CIs of individual studies don't overlap and some (<20%) are in complete opposite directions (i.e., support benefits or harms, while not crossing zero). ↓2 levels if I^2>75%, CIs of individual studies don't overlap and many (>20%) are in complete opposite directions (i.e., support benefits or harms, while not crossing zero).
Likelihood of publication bias[5]	'Undetected' if examination of funnel plots and trial registries do not suggest publication bias. <u>If ≥ 10 studies</u> ↓1 level if funnel plot is asymmetrical and Begg's test indicates asymmetry. <u>If < 10 studies</u> ↓1 level there is discrepancy in findings between published and unpublished studies (reported in trial registries).

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Excluded articles and reasons

Exclusion reason	Reference
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Not an RCT (N=2)	1. Patel HD, Faisal FA, Patel ND, et al. Effect of a prospective opioid reduction intervention on opioid prescribing and use after radical prostatectomy: results of the Opioid Reduction Intervention for Open, Laparoscopic, and Endoscopic Surgery (ORIOLES) initiative. BJU Int. 2020;125(3):426-432. 2. Zheng Y, Margulis R, Kostenbader K, et al. Open-label 14-day safety extension of a randomized, double-blind, placebo-controlled trial of biphasic immediate-release/extended-release hydrocodone bitartrate/acetaminophen tablets for acute postoperative pain. J Pain. 2015;16(4 Suppl 1):S80.
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Summary of trial characteristics

Study	Country	Industry funding	Procedure	Surgical setting	Sample size	Age[a]	Female sex, n (%)	Opioid-free analgesia regimen	Opioid analgesia regimen	Oral morphine equivalent (OME)	Opioids prescribed 'as needed' (PRN) only
Minor surgery											
Walton, 1990	United Kingdom	No	Dental - Molar extraction	Clinic/day-surgery	97	24.2 ± 5.3	Not reported	**Multimodal:** Ibuprofen slow release (ATC) + Acetaminophen, (PRN)	**Multimodal:** Ibuprofen slow release (ATC) + Codeine (ATC) + Acetaminophen, (PRN)	4 mg/day	No
Lownie, 1992	South Africa	Yes	Dental - Molar extraction	Clinic/day-surgery	52	22.5	25 (48%)	**Unimodal:** Mefenamic acid (ATC)	**Multimodal:** Ibuprofen (ATC) + Acetaminophen (ATC) + Codeine (ATC)	6 mg/day	No
Lysell, 1992	Sweden	Unclear	Dental - Molar extraction	Clinic/day-surgery	120	26.0	58 (48%)	**Unimodal:** Ibuprofen (ATC)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	9 mg/day	No
Torabinejad, 1994	United States	No	Dental - Root canal	Clinic/day-surgery	291	Not reported	173 (53%)	**Unimodal:** Acetaminophen (ATC) OR NSAID (ATC)[b]	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	24 mg/day	No
Casey, 1997	Canada	No	Urology - Vasectomy	Clinic/day-surgery	40	35.4 ± 3.9	0 (0%)	**Unimodal:** Etodolac (PRN)	**Multimodal:** Acetaminophen (PRN) + Codeine (PRN)	12 mg/day	Yes
Collins, 1997	United Kingdom	Yes	Dental - Dento-alveolar procedures	Clinic/day-surgery	384	24.0 [18-83]	180 (47%)	**Unimodal:** Acetaminophen (PRN)	**Multimodal:** Tramadol (ATC) + Acetaminophen (PRN)	20, 40, 80 mg/day	No
Breivik, 1998	Norway	No	Dental - Molar extraction	Clinic/day-surgery	20	26.5 [19-35]	8 (40%)	**Multimodal:** Acetaminophen (ATC) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC) + Ibuprofen (PRN)	24 mg/day	No
Han, 1998	South Korea	Unclear	Dental - Periodontal procedures	Clinic/day-surgery	60	45.6 ± 11.4	29 (48%)	**Unimodal:** Ibuprofen (ATC)	**Multimodal:** Ibuprofen (ATC) + Acetaminophen (ATC) + Codeine (ATC)	4 mg/day	No

									OR **Unimodal:** Codeine (ATC)	8 mg/day	No
Comfort, 2002	China	Unclear	Dental - Molar extraction	Clinic/day-surgery	224	26.0 [21-32]	141 (65%)	**Unimodal:** NSAID (ATC)[c]	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	3.2 mg/day	No
Garibaldi, 2002	United States	Yes	Dental - Molar extraction	Clinic/day-surgery	67	25.0 [18-32]	33 (49%)	**Unimodal:** Ketorolac (PRN)	**Multimodal:** Codeine (PRN) ± Ketorolac (PRN)	3, 6, 12 mg/day	Yes
Kim, 2005	South Korea	Unclear	Head and Neck - Tonsillectomy	Operating room/in-patient	90	Mean 29.1, Range [17-49]	49 (54%)	**Unimodal:** Piroxicam (ATC)	**Multimodal:** Ibuprofen (ATC) + Acetaminophen (ATC) + Codeine (ATC)	9 mg/day	No
									OR **Unimodal:** Dihydrocodeine (ATC)	4 mg/day	No
Li, 2005	China	Unclear	Eye - LASIK	Clinic/day-surgery	64	29.8 ± 7.4	43 (67%)	**Unimodal:** Diclofenac (ATC)[d]	**Multimodal:** Diclofenac (ATC)[d] + Tramadol (ATC)	40 mg/day	No
Church, 2006	United States	No	Head and Neck - Sinus surgery	Operating room/day-surgery	28	44.6	9 (32%)	**Multimodal:** Rofecoxib (ATC) + Acetaminophen (PRN)	**Multimodal:** Acetaminophen (ATC) + Hydrocodone (ATC) + Acetaminophen (PRN)	36 mg/day	No
Shah, 2008	Pakistan	No	Dental - Molar extraction	Clinic/day-surgery	59	34.5	28 (47%)	**Unimodal:** Diclofenac (ATC)	**Unimodal:** Tramadol (ATC)	30 mg/day	No
Chen, 2009	United States	No	Plastic - Rhinoplasty, others	Clinic/day-surgery	35	Not reported	Not reported	**Unimodal:** Ibuprofen (ATC)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	24 mg/day	No
Spagnoli, 2011	Italy	No	Orthopaedic/Plastic - Hand and foot repair	Operating room/day-surgery	114	56.8	66 (58%)	**Unimodal:** Acetaminophen (ATC)	**Multimodal:** Acetaminophen (ATC) + Tramadol (ATC)	15 mg/day	No
Brown, 2013	United States	Yes	Dental - Molar extraction	Clinic/day-surgery	588	21.3 ± 3.6	340 (58%)	**Multimodal:** Acetaminophen (PRN) ± NSAID (ATC)[e]	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC) ± Acetaminophen (PRN)	24 mg/day	No
Best, 2017	New Zealand	No	Dental - Molar extraction	Clinic/day-surgery	131	23.6 ± 4.9	84 (64%)	**Multimodal:** Acetaminophen (ATC) + Ibuprofen (ATC)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC) + Ibuprofen (ATC)	24 mg/day	No

Samieirad, 2017	Iran	No	Dental - Implant	Clinic/day-surgery	76	41.0 ± 5.1	38 (50%)	**Unimodal:** Acetaminophen (ATC)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	8 mg/day	No
Weinheimer, 2019[h]	United States	No	Orthopaedic/Plastic - Hand repair	Operating room/day-surgery	60	Mean 52.5, Range [18-86]	35 (58%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	36 mg/day	Yes
Akinbade, 2019	Nigeria	No	Dental - Molar extraction	Clinic/day-surgery	90	25.0 [18-45]	59 (66%)	**Unimodal:** Celecoxib (ATC)	**Unimodal:** Tramadol (ATC)	60 mg/day	No
Ilyas, 2019	United States	No	Orthopaedic/Plastic - Hand repair	Operating room/day-surgery	188	Mean 60.5, Range [19-94]	108 (57%)	**Unimodal:** Acetaminophen (PRN) OR Ibuprofen (PRN)	**Unimodal:** Oxycodone (PRN)	30 mg/day	Yes
Zuniga, 2019	United States	Yes	Dental - Molar extraction	Clinic/day-surgery	461	22.4 ± 5.0	337 (73%)	**Unimodal:** Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	36 mg/day	Yes
Desjardins, 2020	United States, Mexico	Yes	Dental - Molar extraction	Clinic/day-surgery	826	23.6 ± 5.5	529 (64%)	**Unimodal:** Diclofenac (ATC)	**Multimodal:** Tramadol (ATC) ± Diclofenac (ATC)	15, 30 mg/day	No
Da Silva, 2021	Brazil	No	Dental - Incision and drainage	Clinic/day-surgery	39	43.5 ± 14.5	26 (67%)	**Unimodal:** Acetaminophen (ATC) ± Acetaminophen (PRN)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC) ± Acetaminophen (PRN)	12 mg/day	No
Frants, 2021	United States	No	Plastic - Rhinoplasty	Clinic/day-surgery	70	32.0	31 (44%)	**Unimodal:** Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	36 mg/day	Yes
La Monaca, 2021	Italy	No	Dental - Molar extraction	Clinic/day-surgery	106	20.5 ± 3.6	66 (62%)	**Unimodal:** Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Codeine (PRN)	12 mg/day	Yes
Vallecillo, 2021	Spain	No	Dental - Molar extraction	Clinic/day-surgery	70	26 ± 0.4	40 (57%)	**Unimodal:** Ibuprofen (ATC)	**Multimodal:** Dexketoprofen (ATC) + Tramadol (ATC)	45 mg/day	No
NCT02647788	United States	No	Orthopaedic/Plastic - Hand repair	Operating room/day-surgery	111	59.5 ± 12.5	75 (68%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Codeine (PRN)	12 mg/day	Yes
NCT03605914	United States	Unclear	Head and Neck - Sinus surgery	Operating room/day-surgery	100	45.7 ± 15.5	37 (37%)	**Unimodal:** Diclofenac	**Multimodal:** Acetaminophen + Hydrocodone	Unclear	Unclear

Moderate surgery

Gimbel, 2001	United States	No	Orthopaedic - Various procedures[f]	Operating room/day-surgery	366	45.5 ± 15.7	221 (60%)	**Unimodal:** Celecoxib (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	36 mg/day	Yes
Raeder, 2001	Norway	Yes	General (abdominal)/Others - Various procedures[g]	Operating room/day-surgery	104	Not reported	Not reported	**Unimodal:** Ibuprofen (ATC)	**Multimodal:** Acetaminophen (ATC) + Codeine (ATC)	18 mg/day	No
Mitchell, 2008	Canada	Yes	General (abdominal) - Hernia/Gallbladder	Operating room/day-surgery	146	Median 48.0, IQR [33-56]	79 (54%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Codeine (PRN)	12 mg/day	Yes
Mitchell, 2012	Canada	Yes	General (breast) – Mastectomy, lumpectomy	Operating room/in-patient	141	Median 51.4, IQR [44-61]	141 (100%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Codeine (PRN)	24 mg/day	Yes
Stessel, 2014	Netherlands	No	General (abdominal) - Hernia repair/ Orthopaedic - Knee repair	Operating room/day-surgery	105	46.3 ± 13.0	28 (27%)	**Multimodal:** Acetaminophen (ATC) + Naproxen (ATC)	**Multimodal:** Acetaminophen (ATC) + Oxycodone, slow release (ATC)	60 mg/day	No
Bugada, 2015	Italy	Yes	General (abdominal) - Hernia repair	Operating room/in-patient	194	57.0 ± 15.0	14 (7%)	**Multimodal:** Ketorolac (ATC) + Acetaminophen (PRN)	**Multimodal:** Acetaminophen (ATC) + Tramadol (ATC) + Acetaminophen (PRN)	23 mg/day	No
Helmerhorst, 2017[h]	Netherlands	No	Orthopaedic - Fracture repair	Operating room/in-patient	52	43.6 ± 18.4	24 (46%)	**Multimodal:** Acetaminophen (PRN) + Diclofenac (PRN)	**Multimodal:** Acetaminophen (PRN) + Tramadol (PRN) + Diclofenac (PRN)	30 mg/day	Yes
Kim, 2019	South Korea	No	Orthopaedic/Neuro – Laminectomy, discectomy	Operating room/in-patient	93	63.2 ±10.9	54 (58%)	**Unimodal:** Celecoxib (ATC)	**Unimodal:** Oxycodone, slow release (ATC)	30 mg/day	No
Dinis, 2020[h]	United States	Unclear	Gynaecology/Obstetrics - Caesarean section	Operating room/in-patient	170	28 [23-33]	170 (100%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN) + Ibuprofen (PRN)	48 mg/day	Yes
Petrikovets, 2019	United States	Unclear	Gynaecology/Obstetrics – Various procedures[i]	Operating room/in-patient	63	60.8 ± 11.5	63 (100%)	**Multimodal:** Acetaminophen (PRN) + Ketorolac (PRN)	**Multimodal:** Ibuprofen (PRN) + Acetaminophen (PRN) + Oxycodone (PRN)	45 mg/day	Yes

Papoian, 2020	United States	No	Head and Neck - Thyroidectomy	Operating room/day-surgery	95	54.0	75 (79%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Unimodal:** Oxycodone (PRN)	90 mg/day	Yes
Brady, 2021	United States	No	Head and Neck – Thyroidectomy, parathyroidectomy	Operating room/day-surgery	126	54.4 ± 14.3	108 (86%)	**Multimodal:** Acetaminophen (PRN) + Ibuprofen (PRN)	**Multimodal:** Acetaminophen (PRN) + Oxycodone (PRN)	30 mg/day	Yes
Jildeh 2021 (A)	United States	No	Orthopaedic – Labrum repair	Operating room/day-surgery	48	25.9 ± 8.7	10 (21%)	**Multimodal:** Acetaminophen (PRN) + Ketorolac (PRN) + Gabapentin (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	72 mg/day	Yes
Jildeh 2021 (B)	United States	No	Orthopaedic – Meniscus repair	Operating room/day-surgery	61	45.0 ± 15.3	17 (28%)	**Multimodal:** Acetaminophen (PRN) + Ketorolac (PRN) + Gabapentin (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	72 mg/day	Yes
NCT04254679[j]	Canada	No	General (abdominal, breast) - Cholecystectomy, hernia repair, mastectomy, others	Operating room/day-surgery	76	55.5 ± 14.6	50 (66%)	**Multimodal:** Acetaminophen (ATC) ± NSAID (ATC) + NSAID (PRN)[k]	**Multimodal:** Acetaminophen (ATC) ± NSAID (ATC)[k] + Opioid (PRN)[l]	45-68 mg/day	Yes
NCT03818932[j]	United States	Unclear	Orthopaedic - Cruciate ligament repair	Operating room/day-surgery	62	27.3 ± 12.8	28 (45%)	**Multimodal:** Acetaminophen (PRN) + Ketorolac (PRN) + Gabapentin (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	72 mg/day	Yes
NCT03818919[j]	United States	No	Orthopaedic - Rotator cuff repair	Operating room/day-surgery	44	55.1 ± 8.0	19 (43%)	**Multimodal:** Acetaminophen (PRN) + Ketorolac (PRN) + Gabapentin (PRN)	**Multimodal:** Acetaminophen (PRN) + Hydrocodone (PRN)	72 mg/day	Yes

ATC = around-the-clock, PRN = *pro re nata* (as needed).

[a] Data are presented as mean, mean±SD, median [range], unless otherwise stated.

[b] Multiple opioid-free groups using Acetylsalicylic acid (ATC), Ibuprofen (ATC) or Ketoprofen (ATC).

[c] Multiple opioid-free groups using Diflunisal (ATC) or Etodolac (ATC).

[d] Analgesia given as eye drops.

[e] Multiple opioid-free groups using Etoricoxib (ATC) or Ibuprofen (ATC).

[f] Multiple orthopaedic procedures including open reduction internal fixation, anterior cruciate ligament (ACL) repair, bunionectomy, laminectomy, and osteotomy.

[g] Multiple surgical procedures including abdominal hernia repair, haemorrhoidectomy, and varicose veins resection.

[h] Patients in the opioid-free and opioid regimen had access to a narcotic prescription after additional contact with a healthcare provider.

[i] Multiple gynaecologic procedures including hysterectomy, trachelectomy, sacrospinous ligament fixation, uterosacral ligament suspension, colpocleisis, retropubic midurethral sling, colporrhaphy, perineorrhaphy, McCall culdoplasty, bilateral salpingectomy, bilateral salpingoophorectomy, cystoscopy.

[j] Unpublished study.

[k] NSAIDs prescribed depended on surgeon preference. NSAIDs included Celecoxib, Ibuprofen or Naproxen.

[l] Opioids prescribed depended on surgeon preference. Opioids included Oxycodone or Hydromorphone.

Trial characteristics

Akinbade 2019 (https://pubmed.ncbi.nlm.nih.gov/31187764/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare analgesic efficacy and tolerability of celecoxib and tramadol following mandibular third molar extraction. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 45; opioid-free group: 45. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: mean 25 (range 19-44); opioid-free group: mean 25 (range 18-45). **Sex (female):** Not reported. **Ethnicity:** Not reported. **Inclusion criteria:** Age 18-45, at least one impacted mandibular 3rd molar indicated for extraction. **Exclusion criteria:** Comprised cardiac function, hematological abnormalities, metabolic disorders, central nervous system disorders, impaired renal or hepatic function, depressed respiratory functions, history of allergy or hypersensitivity to celecoxib and tramadol, patients with peptic ulcer disease, pregnant and breastfeeding women, patients with history suggestive of psychological or physical dependence on opioids, use of analgesics 24h prior to the extraction.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (lignocaine hydrochloride 2% + epinephrine 1:100,000). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group***

	Medication: Tramadol 100 mg, every 8 hours around the clock, PO. *Duration:* 2 days. ***Opioid-free group*** *Medication:* Celecoxib 400 mg 1st dose, all other doses 200 mg, every 12 hours, around the clock, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain score, visual analogue scale 0-100 mm, median (range). **Timepoints:** Just after extraction, 4 hours, 8 hours, 16 hours, 24 hours, and 48 hours. **Secondary outcomes:** Adverse events (drowsiness, vomiting, nausea, dizziness), reason for cessation of primary analgesia. **Total length of follow up:** 2 days.
Country and setting	**Country:** Nigeria. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Randomization sequence was generated before the commencement of the study. Drugs were dispensed in non-transparent sealed envelopes, labelled according to randomization sequence. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Surgeons and patients were blinded. The authors describe the use of an intention-to-treat analysis.
Risk of bias due to missing outcome data.	Low risk.	Only 3 patients did not return assessment forms.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score just after extraction, VAS (0-100)	Median 24.5 (Range 0-98)*	Median 22 (Range 0-100)*
Pain score 4h after surgery, VAS (0-100)	Median 51.5 (Range 5-100)*	Median 24 (Range 0-97)*
Pain score 8h after surgery, VAS (0-100)	Median 32 (Range 0-98)*	Median 23 (Range0-83)*
Pain score 16h after surgery, VAS (0-100)	Median 15.5 (Range 0-78)*	Median 15 (Range 0-98)*
Pain score 24h after surgery, VAS (0-100)	Median 10 (Range 0-79)*	Median 7 (Range 0-98)*
Pain score 48h after surgery, VAS (0-100)	Median 8 (Range 0-80)*	Median 4 (Range 0-89)*
Drowsiness	Incidence rate 6/45	Incidence rate 0/45
Vomiting	Incidence rate 7/45	Incidence rate 0/45
Nausea	Incidence rate 5/45	Incidence rate 0/45
Dizziness	Incidence rate 4/45	Incidence rate 0/45

*Median and range data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Best 2017 (https://pubmed.ncbi.nlm.nih.gov/28586638/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; non-inferiority design (not adaptive). **Study objective:** To assess the efficacy of codeine when added to a regimen of paracetamol and ibuprofen for pain relief after third molar surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The authors estimated the number per group as 51 for an anticipated effect size of 0.5, α value of 0.05, and a power of 0.8 to detect a difference.
Participants	**N randomised:** Opioid group: 64; opioid-free group: 67. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: mean 23 (SD 3); opioid-free group: mean 24 (SD 6). **Sex (female):** Opioid group: 61%; opioid-free group: 67%. **Ethnicity:** Opioid group: Pakeha 66%, other 34%; opioid-free group: Pakeha 66%, other 34%. **Inclusion criteria:** At least one impacted mandibular 3rd molar indicated for extraction, medically fit for surgery under intravenous sedation. **Exclusion criteria:** Patients younger than 17 years, patients with an existing medical condition requiring a medication with analgesic properties that could not be ceased before and for the duration of the study, patients who needed to drive a motor vehicle or operate machinery within 48 hours after surgery, patients who had a history of asthma sensitive to nonsteroidal anti-inflammatory drugs, peptic ulceration, bleeding disorder, renal or hepatic impairment, cardiovascular disease, systemic lupus erythematosus, lactose intolerance, respiratory depression, chronic obstructive pulmonary disease, opioid addiction, alcoholism, glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to morphine or benzodiazepines, phenylketonuria, myasthenia gravis, glaucoma, osteoporosis, or psychosis, patients who were currently pregnant or breastfeeding, patients who were taking an anticoagulant, hepatic enzyme inducer, or central nervous system depressant, patients who had systemic viral, bacterial or fungal infection, if the clinician deemed for any other reason that participation in the study might be contraindicated.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.

Interventions	**Intraoperative anaesthesia:** Sedation (midazolam IV + dexamethasone IV) + local infiltration (mepivacaine 2% + epinephrine 1:100,000) **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 1000 mg, every 6 hours around the clock, PO + Ibuprofen 400 mg, every 8 hours around the clock, PO + Codeine 60 mg, every 6 hours around the clock, PO. *Duration:* 2 days. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 6 hours around the clock, PO + Ibuprofen 400 mg, every 8 hours around the clock, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain score, visual analogue scale 0-100 mm, mean. **Timepoints:** Just after extraction, 3 hours, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 27 hours, 30 hours, 33 hours, 36 hours, 39 hours, 42 hours, 45 hours, and 48 hours. **Secondary outcomes:** Medical practitioner visit, use of rescue analgesia, pain relief. **Total length of follow up:** 2 days.
Country and setting	**Country:** New Zealand. **Number of centres:** Single centre. **Study period:** 2013-2014.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Block randomization was used to generate the random allocation sequence and ensure balanced randomization (i.e., groups of approximately equal number). Block sizes were unclear. Implementation of the random allocation sequence was delegated to the hospital pharmacist, the only nonblinded person involved in the study. Based offsite at the Dunedin Public Hospital (Dunedin, New Zealand), this individual was the only person in possession of the random allocation sequence. Allocation done preoperatively (at recruitment).

		Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Placebo and intervention pills were similar in appearance. This assisted in ensuring the blinding of patients, clinicians, and researchers. The authors describe the use of an intention-to-treat analysis. They called it 'modified' because 1 patient with missing data was excluded.
Risk of bias due to missing outcome data.	Low risk.	Only 1 participant from the intervention group was excluded due to missing data.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score just after extraction, VAS (0-100)	Mean 6.5*	Mean 6.5*
Pain score 3h after surgery, VAS (0-100)	Mean 24.9*	Mean 24.9*
Pain score 6h after surgery, VAS (0-100)	Mean 23.6*	Mean 26.1*
Pain score 9h after surgery, VAS (0-100)	Mean 19.6*	Mean 29.9*
Pain score 12h after surgery, VAS (0-100)	Mean 24.1*	Mean 30.7*
Pain score 15h after surgery, VAS (0-100)	Mean 23.6*	Mean 25.6*
Pain score 18h after surgery, VAS (0-100)	Mean 22.9*	Mean 23.8*
Pain score 21h after surgery, VAS (0-100)	Mean 21.9*	Mean 24.5*
Pain score 24h after surgery, VAS (0-100)	Mean 19.9*	Mean 22.0*
Pain score 27h after surgery, VAS (0-100)	Mean 19.8*	Mean 24.0*
Pain score 30h after surgery, VAS (0-100)	Mean 20.4*	Mean 25.7*
Pain score 33h after surgery, VAS (0-100)	Mean 26.9*	Mean 28.2*
Pain score 36h after surgery, VAS (0-100)	Mean 27.2*	Mean 31.8*
Pain score 39h after surgery, VAS (0-100)	Mean 23.7*	Mean 30.2*
Pain score 42h after surgery, VAS (0-100)	Mean 24.0*	Mean 31.3*
Pain score 45h after surgery, VAS (0-100)	Mean 21.5*	Mean 32.5*

Pain score 48h after surgery, VAS (0-100)	Mean 18.4*	Mean 31.5*
Medical practitioner visit	Incidence rate 2/64	Incidence rate 0/67

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Brady 2021 (https://pubmed.ncbi.nlm.nih.gov/32416981/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To determine whether patients undergoing thyroidectomy and parathyroidectomy have similar postoperative pain if managed with an opioid-sparing medication regimen versus an opioid-containing medication regimen. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The authors assumed a standard deviation of 2 (/10) for postoperative pain scores, to detect a 1-point difference in pain scores. Based on that, 126 patients (63 per arm) provided 80% power to declare equivalency with a 2-sided a of 0.05.
Participants	**N randomised:** Opioid group: 62; opioid-free group: 64. **Diagnosis (% of participants):** Opioid group: nontoxic multinodular goiter or multiple thyroid nodules (32%), thyrotoxicosis with toxic multinodular goiter (16%), thyroid cancer (11%), Grave's disease (7%), hyperparathyroidism (16%), follicular neoplasm (8%), Hurthle cell neoplasm (5%), Hashimoto thyroiditis (2%), thyroid nodule (8%); opioid-free group: nontoxic multinodular goiter or multiple thyroid nodules (39%), thyrotoxicosis with toxic multinodular goiter (14%), thyrotoxicosis with single thyroid nodule (2%), thyroid cancer (11%), Grave's disease (13%), hyperparathyroidism (17%), Hurthle cell neoplasm (3%), Hashimoto thyroiditis (3%), thyroid nodule (14%) **Surgery:** Opioid group: total thyroidectomy (55%), thyroid lobectomy (29%), total thyroidectomy with central neck dissection (3%), total thyroidectomy with parathyroidectomy (2%), parathyroidectomy (15%), parathyroid autotransplantation (22%); opioid-free group: total thyroidectomy (50%), thyroid lobectomy (30%), total thyroidectomy with central neck dissection (3%), total thyroidectomy with parathyroidectomy (3%), parathyroidectomy (16%), parathyroid autotransplantation (22%). **Age:** Opioid group: mean 55 (SD 15); opioid-free group: mean 54 (SD 14). **Sex (female):** Opioid group: 87%; opioid-free group: 84%. **Ethnicity:** Opioid group: non-Hispanic 92%, Hispanic 8%; opioid-free group: non-Hispanic 89%, Hispanic 11%. **Inclusion criteria:** Age > 18 years, undergoing elective total thyroidectomy, partial thyroidectomy, parathyroidectomy, or combination of thyroidectomy with parathyroidectomy. **Exclusion criteria:** Use of narcotic pain medication at the time of surgery, patients undergoing additional concomitant operations.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room **Surgical discharge:** Same day. **Surgery classification:** Moderate.

	Surgery status: Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Acetaminophen + Ibuprofen + Dyclonine throat lozenge + Oxycodone for breakthrough pain. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 1000 mg, every 8 hours as needed, PO + Oxycodone 5 mg, every 6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 8 hours as needed, PO + Ibuprofen 800 mg, every 8 hours as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain score, visual analogue scale 0-10 cm, median (IQR). **Timepoints:** Day 0, Day 1, Day 2, Day 3, Day 4, and Day 5. **Secondary outcomes:** Medical practitioner calls, emergency department visits, adverse events (unspecified). **Total length of follow up:** 6 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2018-2019.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	High risk.	Unclear how the randomization sequence was generated. Unclear how/if concealment of allocation was conducted. Group characteristics were not balanced: patients who received narcotics after discharge from the PACU were more likely to have a history of substance abuse, including a history of alcohol and opioid abuse, and were more likely to be smokers and actively engaged in illicit drug use at the time of surgery.

Risk of bias due to deviation from intended interventions.	Some concerns.	There is no mention of blinding of participants or carers. They were likely not blinded. There were no apparent deviations from the intended interventions. The authors reported an intention-to-treat analysis, as well as a per protocol analysis (8 patients in the opioid-free group (12%) crossed over to the opioid group because of refractory pain)
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. It is unclear if assessments of other outcomes (e.g., ED visits, readmissions) were blinded. Knowledge of group assignment could have influenced outcome reporting (e.g., pain).
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score day 0, VAS (0-10)	Median 7 (IQR 5-8)*	Median 7.5 (IQR 6-9)*
Pain score day 1, VAS (0-10)	Median 6 (IQR 4-7)*	Median 6 (IQR 5-7)*
Pain score day 2, VAS (0-10)	Median 5 (IQR 3-7)*	Median 5 (IQR 4-7)*
Pain score day 3, VAS (0-10)	Median 4 (IQR 3-5)*	Median 4 (IQR 3-6)*
Pain score day 4, VAS (0-10)	Median 3 (IQR 1-5)*	Median 3 (IQR 2-5)*
Pain score day 5, VAS (0-10)	Median 2.5 (IQR 0-4)*	Median 2 (IQR 2-4)*
Adverse event (unspecified)	Incidence rate 0/62	0/64
Emergency department visit	Incidence rate 5/62	Incidence rate 7/64

*Median and range data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Breivik 1998 (https://pubmed.ncbi.nlm.nih.gov/10700313/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To improve upside assay sensitivity in dental pain model by selecting patients with high baseline pain intensity. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Sample sizes were estimated from the nomogram in Young et al. (1983) using sum of pain intensities with paracetamol alone from a selection of patients with high baseline pain in a previous study. A reduction of sum of pain intensities by 50% when adding codeine and assuming a coefficient of variation of 40%, with $\alpha = 0.05$ and $\beta = 0.20$, would require 8-10 patients in each group.
Participants	**N randomised:** Opioid group: 10; opioid-free group: 10. **Diagnosis (% of participants):** Asymptomatic 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: median 28 (range 22-35); opioid-free group: median 25 (range 19-30). **Sex (female):** Opioid group: 40%; opioid-free group: 40%. **Ethnicity:** Not reported. **Inclusion criteria:** Healthy, young (18-40 years) outpatients undergoing surgical removal of asymptomatic wisdom teeth, preoperative pain intensity ≥50 mm on a 100 mm VAS. **Exclusion criteria:** Patients with pericoronitis or other regional infections, patients with known sensitivity to acetaminophen or codeine, patients using concomitant medication (except oral contraceptives), patients with any chronic or acute disease.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Acetaminophen + Ibuprofen + Dyclonine throat lozenge + Oxycodone for breakthrough pain. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 500 mg, every 3 hours around the clock, PO + Codeine 30 mg, every 3 hours around the clock, PO + Ibuprofen 600 mg, as needed for breakthrough pain, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Acetaminophen 500 mg, every 3 hours around the clock, PO + Ibuprofen 600 mg, as needed for breakthrough pain, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain score, visual analogue scale 0-100 mm, mean (SD). **Timepoints:** Just after extraction, 0.5 hours, 1 hour, 2 hours, 3 hours, 3.5 hours, 4 hours, 5 hours, 6 hours, 6.5 hours, 7 hours, 8 and hours. **Secondary outcomes:** Use of rescue analgesia, adverse events (all adverse events, drowsiness, dizziness, nausea, sweating). **Total length of follow up:** 1 day.
Country and setting	**Country:** Norway. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Unclear how randomization sequence was generated. Medications were kept in sealed opaque envelopes. There were more patients with double extraction in the opioid-free group (30%) vs the opioid group (10%), which may have influenced results. Age was significantly lower in the opioid-free group. Due to small sample, differences may be due to chance.
Risk of bias due to deviation from intended interventions.	High risk.	The study is described as double-blinded, but there is no specific information about blinding of participants. There were no apparent deviations from the intervention because of the trial context. The analysis was conducted 'per protocol'. Patients not taking the medication as prescribed were excluded. The exclusion of 1 patient (10% of the group sample) may have influenced the study results.

Risk of bias due to missing outcome data.	High risk.	Five patients (20%; 4 in the opioid-free group, 1 in the opioid group) did not respond the last questionnaire. Imputation was conducted (last value carried forward). There are differences between intervention groups in the proportions of missing outcome data. Bias due to missing outcome data cannot be excluded.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score just after extraction, VAS (0-100)	Mean 62.0 (SD 7.4)	Mean 63.0 (SD 10.7)
Pain score 0.5h after surgery, VAS (0-100)	Mean 38.6*	Mean 56.0*
Pain score 1h after surgery, VAS (0-100)	Mean 22.5*	Mean 47.5*
Pain score 2h after surgery, VAS (0-100)	Mean 24.9*	Mean 53.1*
Pain score 3h after surgery, VAS (0-100)	Mean 30.0*	Mean 57.4*
Pain score 3.5h after surgery, VAS (0-100)	Mean 22.4*	Mean 47.9*
Pain score 4h after surgery, VAS (0-100)	Mean 15.7*	Mean 45.8*
Pain score 5h after surgery, VAS (0-100)	Mean 18.9*	Mean 50.9*
Pain score 6h after surgery, VAS (0-100)	Mean 19.0*	Mean 53.0*
Pain score 6.5h after surgery, VAS (0-100)	Mean 13.0*	Mean 52.0*
Pain score 7h after surgery, VAS (0-100)	Mean 11.9*	Mean 48.7*
Pain score 8h after surgery, VAS (0-100)	Mean 11.1*	Mean 48.1*
Adverse events (any)	Incidence rate 5/10	Incidence rate 1/10
Drowsiness	Incidence rate 4/10	Incidence rate 1/10
Dizziness	Incidence rate 3/10	Incidence rate 0/10
Nausea	Incidence rate 2/10	Incidence rate 0/10

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Brown 2013 (https://pubmed.ncbi.nlm.nih.gov/23247002/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To evaluate the analgesic effects of etoricoxib and comparator agents on the second and third days after oral surgery. **Number of arms:** 5 (1 opioid analgesia, 4 opioid-free analgesia). **Randomization ratio:** 4:3:12:6:12 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 62; opioid-free group 1: 46, opioid-free group 2: 191, opioid-free group 3: 97, opioid-free group 4: 192. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: mean 20.5 (SD 2.8); opioid-free group 1: mean 21 (SD 3), opioid-free group 2: mean 21.8 (SD 3.6), opioid-free group 3: mean 21.8 (SD 3.5), opioid-free group 4: mean 21.6 (SD 3.8). **Sex (female):** Opioid group: 60%; opioid-free group 1: 54%, opioid-free group 2: 59%, opioid-free group 3: 52%, opioid-free group 4: 60%. **Ethnicity:** Not reported. **Inclusion criteria:** Healthy, young (18-40 years) outpatients undergoing surgical removal of asymptomatic wisdom teeth, preoperative pain intensity ≥50 mm on a 100 mm VAS. **Exclusion criteria:** Patients with pericoronitis or other regional infections, patients with known sensitivity to acetaminophen or codeine, patients using concomitant medication (except oral contraceptives), patients with any chronic or acute disease.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Nerve block (lidocaine 2%, epinephrine 1:100,000) ± nitrous oxide. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 600 mg, every 6 hours around the clock, PO + Codeine 60 mg, every 3 hours around the clock, PO + Acetaminophen 325 mg, every 6 hours as needed for breakthrough pain, PO. *Duration:* 2 days. ***Opioid-free group 1*** *Medication:* Acetaminophen 325 mg, every 6 hours as needed, PO. *Duration:* 2 days. ***Opioid-free group 2*** *Medication:* Etoricoxib 90 mg, once a day, PO + Acetaminophen 325 mg, every 6 hours as needed, PO. *Duration:* 2 days. ***Opioid-free group 3*** *Medication:* Etoricoxib 120 mg, once a day, PO + Acetaminophen 325 mg, every 6 hours as needed, PO. *Duration:* 2 days. ***Opioid-free group 4*** *Medication:* Ibuprofen 600 mg, every 6 hours around the clock, PO + Acetaminophen 325 mg, every 6 hours as needed, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain relief, visual analogue scale 0-100 mm, least squares. **Timepoints:** 48 hours, 72 hours. **Secondary outcomes:** Patient satisfaction, adverse events (headache, dizziness, nausea, vomiting). **Total length of follow up:** 14 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2008-2009.
Source of funding	Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA.
Source of data	Peer-reviewed article.
Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)	
Bias	**Author's judgement** **Support for judgement**

Risk of bias arising from the randomization process.	Low risk.	Treatment allocation was undertaken with a computer- generated allocation schedule (performed in-house by the study sponsor). Supplies were packaged in kit boxes containing 3 blister cards per kit for each patient. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	The patient, investigators, and the study sponsor were not aware of the treatment group to which any patient had been assigned. No explicit information was provided regarding type of analysis, but it can be interpreted that the analysis was 'per protocol' as the analysis population included 'randomized patients who received ≥1 dose of study medication'. A substantial number of patients were excluded from the analysis (up to 38% on day 2, and up to 57% on day 3).
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data (adverse events) may depend on its true value.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group 1***	**Opioid-free group 2***	**Opioid-free group 3***	**Opioid-free group 4***
Headache	Incidence rate 4/62	Incidence rate 3/46	Incidence rate 3/191	Incidence rate 1/97	Incidence rate 1/192
Dizziness	Incidence rate 0/62	Incidence rate 1/46	Incidence rate 1/191	Incidence rate 0/97	Incidence rate 2/192
Nausea	Incidence rate 6/62	Incidence rate 1/46	Incidence rate 2/191	Incidence rate 1/97	Incidence rate 4/192
Vomiting	Incidence rate 5/62	Incidence rate 0/46	Incidence rate 0/191	Incidence rate 0/97	Incidence rate 1/192
Patient satisfaction[†]					
Poor	Incidence rate 2%	Incidence rate 42%	Incidence rate 5%	Incidence rate 6%	Incidence rate 5%
Fair	Incidence rate 19%	Incidence rate 30%	Incidence rate 7%	Incidence rate 7%	Incidence rate 10%
Good	Incidence rate 32%	Incidence rate 9%	Incidence rate 17%	Incidence rate 21%	Incidence rate 26%
Very good	Incidence rate 32%	Incidence rate 7%	Incidence rate 41%	Incidence rate 31%	Incidence rate 34%
Excellent	Incidence rate 15%	Incidence rate 12%	Incidence rate 30%	Incidence rate 36%	Incidence rate 26%

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[†]Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = poor; not dissatisfied = fair, good, very good, or excellent).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Bugada 2015 (https://pubmed.ncbi.nlm.nih.gov/26329661/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To identify differences in postoperative pain management between Tramadol and ketorolac after inguinal hernia repair. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Authors based the sample size calculation on data from a pilot study (unpublished). They hypothesized that the proportion of patients with NRS ≥4 would be 35% in the ketorolac group at 96 hours after surgery and that it would decrease to 15% in the tramadol group. They calculated that a Fisher exact test with a 0.05 two-sided significance level would have 84% power to detect such a difference between these 2 groups, when the sample size in each group is 90. Assuming a drop-out percentage of 10%, approximately 100 patients per group were planned to be enrolled in the study.
Participants	**N randomised:** Opioid group: 96; opioid-free group: 98. **Diagnosis (% of participants):** Inguinal hernia (100%). **Surgery:** Inguinal hernia repair with tension-free technique (100%). **Age:** Mean 57 (SD 15). **Sex (female):** Opioid group: 9%; opioid-free group: 5%. **Ethnicity:** Not reported. **Inclusion criteria:** Age > 18 years, undergoing unilateral inguinal hernia repair for type 2, 3A and 3B inguinal hernia, ASA I or II. **Exclusion criteria:** ASA III or IV, emergency surgery, postsurgical admission to intensive care unit, type 1, 3c, and 4 inguinal hernia, laparoscopic surgery, cognitive or psychiatric disorders, allergy to the study drugs (ketorolac or tramadol), use of opioids and/or NSAIDs in the 5 days before surgery.
Procedure characteristics	**Surgical setting:** In-patient. **Surgery location:** Hospital operating room. **Surgical discharge:** Overnight stay. **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** General anesthesia or local anesthesia (ropivacaine 0.2% + lidocaine 2%) + ketorolac 30 mg IV + tramadol 100 mg IV. **Inpatient analgesia (after surgery, prior to discharge):** Opioid group: Tramadol 100 mg, every 8 hours around the clock, IV + Acetaminophen 1000 mg, as needed for breakthrough pain, PO; opioid-free group:

	Ketorolac 30 mg, every 8 hours around the clock, IV + Acetaminophen 1000 mg, as needed for breakthrough pain, PO. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 325 mg, every 8 hours around the clock, PO + Tramadol 37.5 mg, every 8 hours around the clock, PO + Acetaminophen 1000 mg, as needed for breakthrough pain, PO *Duration:* 3 days. ***Opioid-free group*** *Medication:* Ketorolac 10 mg, every 8 hours around the clock, PO + Acetaminophen 1000 mg, as needed for breakthrough pain, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Proportion of patients with pain score >4, numerical rating scale 0-10. **Timepoints:** 4 days. **Secondary outcomes:** Pain score, use of rescue analgesia, adverse events (any, nausea, vomiting), chronic pain incidence. **Total length of follow up:** 90 days.
Country and setting	**Country:** Italy. **Number of centres:** Single centre. **Study period:** 2012.
Source of funding	This study was supported by a grant from IRCCS Foundation Policlinico S Matteo. Alfa Wassermann provided acetaminophen/tramadol combination (Patrol).
Source of data	Peer-reviewed article + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Treatment allocation was based on a computer-generated sequence of treatments randomly permuted in blocks of varying size. Concealment was obtained with the use of opaque envelopes. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	This was an open-label study; participants were aware of group allocation. There were no apparent deviations from the intended interventions. The authors conducted a per-protocol analysis. Two patients in 4 patients in the opioid group and

		2 patients in the opioid-free group were excluded from the final analysis due to protocol violations. The number of patients excluded from the analysis was not substantial (only 3%).
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data (pain or adverse events) may depend on its true value.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting; however, the two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score at 3 days, NRS (0-10)	Mean 2.74 (SD 2.04)*	Mean 2.62 (SD 1.90)*
Adverse events (any)	Incidence rate 12/96	Incidence rate 6/98
Vomiting	Incidence rate 1/96	Incidence rate 0/98
Nausea	Incidence rate 2/96	Incidence rate 2/98

*NRS scores were standardized to VAS scores as described in the Appendix (pp 156-157).

Casey 1997 (https://pubmed.ncbi.nlm.nih.gov/9327190/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare the efficacy and safety of etodolac and acetaminophen with codeine in controlling post-surgical pain in an open-label, randomized, parallel-group outpatient study. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 20; opioid-free group: 20. **Diagnosis (% of participants):** Not reported. **Surgery:** Vasectomy (100%). **Age:** Opioid group: mean 35 (SE 1); opioid-free group: mean 36 (SE 0.4). **Sex (female):** 0%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients voluntarily having a vasectomy for sterilization. **Exclusion criteria:** Not reported.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anesthesia (2% lidocaine). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 300 mg, every 6 hours as needed, PO + Codeine 30 mg, every 6 hours as needed, PO. *Duration:* 7 days. ***Opioid-free group***

	Medication: Etodolac 200 mg, every 6 hours as need, PO. *Duration:* 7 days.
Outcomes	**Primary outcome:** Unclear. **Timepoints:** Not applicable. **Secondary outcomes:** Patient satisfaction with study medication, analgesic consumption, adverse events (unclear), reasons for discontinuing medication. **Total length of follow up:** 7 days.
Country and setting	**Country:** Canada. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized-controlled trial, but no information about randomization nor concealment is reported. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants and carers were not blinded. Deviations that arose such as drug discontinuation and switching were likely due to trial context. This is consistent with what may have happened in practice. Analysis was 'per protocol', but only 1 patient was excluded due to protocol violation.
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting; however, the two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.

Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Patient satisfaction with study medication*		
Poor	Incidence rate 0%	Incidence rate 8.8%
Fair	Incidence rate 6.2%	Incidence rate 8.5%
Good	Incidence rate 66.5%	Incidence rate 45.7%
Excellent	Incidence rate 27.3%	Incidence rate 37.0%
Adverse events (any)	Incidence rate 0/20	Incidence rate 3/20

*Ordinal satisfaction scale was dichotomized to facilitate interpretation (dissatisfied = poor; not dissatisfied = fair, good, or excellent).

Chen 2009 (https://pubmed.ncbi.nlm.nih.gov/19769830/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare the efficacy and side effects of ibuprofen and acetaminophen with codeine when given postoperatively following cosmetic facial surgery and to assess whether bruising is worse or the incidence of hematoma is greater when ibuprofen is taken postoperatively. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 17; opioid-free group: 18. **Diagnosis (% of participants):** Not reported. **Surgery:** Cosmetic facial surgery (100%). **Age:** Not reported. **Sex (female):** Not reported. **Ethnicity:** Not reported. **Inclusion criteria:** Patients undergoing ambulatory cosmetic facial surgery. **Exclusion criteria:** Patients with allergies or intolerance to the test drugs, peptic ulcer disease, renal insufficiency, severe asthma, bleeding disorders, patients taking blood thinners.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 600 mg, every 6 hours around the clock, PO + Codeine 60 mg, every 6 hours around the clock, PO. *Duration:* 3 days.

	Opioid-free group *Medication:* Ibuprofen 400 mg, every 6 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcomes:** Pain score, visual analogue scale 0-10 cm, mean; bruising, visual analogue scale 0-10 cm, mean. **Timepoints:** Day 1, day 2, and day3. **Secondary outcomes:** Reason for changing medication. **Total length of follow up:** 3 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2006-2007.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	Patients were randomized into one of two study groups using a random number generator, but no information about concealment is reported. There is limited information regarding patient characteristics.
Risk of bias due to deviation from intended interventions.	High risk.	Participants and carers were blinded. It is unclear if the authors conducted an intention to treat or a per protocol analysis.
Risk of bias due to missing outcome data.	High risk.	Fourteen patients (out of 35) did not complete the survey. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data (pain) may depend on its true value. The authors did not document reasons for missing outcome data.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score 24h after surgery, VAS (0-10)	Mean 2.12*	Mean 2.37*
Pain score 48h after surgery, VAS (0-10)	Mean 2.14*	Mean 2.36*
Pain score 72h after surgery, VAS (0-10)	Mean 1.62*	Mean 1.59*

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Church 2006 (https://pubmed.ncbi.nlm.nih.gov/16585866/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To investigate the safety and efficacy of rofecoxib vs. hydrocodone/acetaminophen in outpatient functional endoscopic sinus surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 14; opioid-free group: 14. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: bilateral multisinus surgery (64%), unilateral multisinus surgery (21%), unilateral maxillary surgery (14%); opioid-free group: bilateral multisinus surgery (57%), unilateral multisinus surgery (29%), unilateral maxillary surgery (14%). **Age:** Mean 44.71. **Sex (female):** Opioid group: 36%; opioid-free group: 29%. **Ethnicity:** Not reported. **Inclusion criteria:** Age 18-89, undergoing functional endoscopic sinus surgery. **Exclusion criteria:** Allergy to the study drugs, peptic ulcer disease, liver disease, recent history of study medication use, chronic pain disorder, use of other analgesics.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** General anaesthesia. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 750 mg, every 6 hours around the clock, PO + Hydrocodone 7.5 mg, every 6 hours around the clock, PO + Acetaminophen 500 mg, every 12 hours as needed for breakthrough pain, PO.

	Duration: 5 days. ***Opioid-free group*** *Medication:* Rofecoxib 50 mg, once a day, PO + Acetaminophen 500 mg, every 12 hours as needed for breakthrough pain, PO. *Duration:* 5 days.
Outcomes	**Primary outcomes:** Pain score (worst), visual analogue scale 0-100 mm, mean (SE). **Timepoints:** Day 0, day 1, day 2, day 3, and day 4. **Secondary outcomes:** Time to stop analgesia, amount of rescue analgesia consumed, patient satisfaction, adverse events (confusion, constipation, difficulty urinating, difficulty breathing, drowsiness, diarrhoea, headache, nausea and/or vomiting, sleep problems). **Total length of follow up:** 3 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2006-2007.
Source of funding	None reported.
Source of data	Peer-reviewed article + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized-controlled trial, but no information about randomization nor concealment is reported. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants and carers were blinded by using indistinguishable drug capsules. Analysis was per protocol. 30% of patients were excluded from the analysis because of failure to take the medications as directed, incomplete surveys, or failure to return to clinic.
Risk of bias due to missing outcome data.	High risk.	30% of patients were excluded from the analysis because of incomplete surveys or failure to return to clinic. The exact rate of missing data is unclear. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value. The authors did not document reasons for missing outcome data.

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score on the day of surgery, VAS (0-100)	Mean 30.86 (SE 5.774)*	Mean 38.50 (SE 7.515)*
Pain score 1 day after surgery, VAS (0-100)	Mean 27.36 (SE 5.519)*	Mean 29.43 (SE 5.907)*
Pain score 2 day after surgery, VAS (0-100)	Mean 35.79 (SE 7.814)*	Mean 26.29 (SE 7.463)*
Pain score 3 day after surgery, VAS (0-100)	Mean 31.21 (SE 9.004)*	Mean 22.64 (SE 5.956)*
Pain score 4 day after surgery, VAS (0-100)	Mean 28.57 (SE 8.641)*	Mean 20.00 (SE 6.119)*
Patient satisfaction†		
Inadequate	Incidence rate 0%	Incidence rate 7.14%
Satisfactory	Incidence rate 50%	Incidence rate 50%
Excellent	Incidence rate 50%	Incidence rate 42.86%
Confusion	Incidence rate 0/14	Incidence rate 1/14
Constipation	Incidence rate 3/14	Incidence rate 3/14
Difficulty urinating	Incidence rate 1/14	Incidence rate 2/14
Difficulty breathing	Incidence rate 0/14	Incidence rate 2/14
Drowsiness	Incidence rate 4/14	Incidence rate 3/14
Diarrhoea	Incidence rate 2/14	Incidence rate 1/14
Headache	Incidence rate 8/14	Incidence rate 6/14
Nausea and/or vomiting	Incidence rate 1/14	Incidence rate 2/14
Sleep problems	Incidence rate 2/14	Incidence rate 4/14

*SD was calculated from the SE according to methods described in the Cochrane Handbook.[1]

†Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = inadequate; not dissatisfied = satisfactory or excellent).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Collins 1997 (https://pubmed.ncbi.nlm.nih.gov/9043007/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To assess the analgesic effect of tramadol in the relief of pain after dentoalveolar operations that involve the removal of bone and suturing. **Number of arms:** 4 (3 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1:1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group 1: 114; opioid group: 115; opioid group: 111; opioid-free group: 112. **Diagnosis (% of participants):** Not reported. **Surgery:** Dentoalveolar surgery (100%). **Age:** Not reported. **Sex (female):** Opioid group 1: 50%; opioid group: 45%; opioid group: 49%; opioid-free group: 43%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients over 18 years, undergoing impacted dentoalveolar surgery under local anaesthesia. **Exclusion criteria:** Pregnancy or lactation, haemophilia, history of seizure disorders, impairment of any organ system likely to prohibit the use of tramadol or paracetamol, the use of anticoagulants, analgesics (other than paracetamol) or central nervous system depressants, allergy to opioids or paracetamol, patients who misused drugs, had suicidal tendencies, were unwilling or unable to conform to the protocol, patients who received any investigational drug (including tramadol) within 30 days of the start of the study.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (lignocaine 2% + epinephrine 1:80,000) **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group 1***

	Medication: Tramadol 100 mg, every 6 hours around the clock, PO + Acetaminophen 500 mg, as needed for breakthrough pain, PO. *Duration:* 3 days. ***Opioid group 2*** *Medication:* Tramadol 50 mg, every 6 hours around the clock, PO + Acetaminophen 500 mg, as needed for breakthrough pain, PO. *Duration:* 3 days. ***Opioid group 3*** *Medication:* Tramadol 50 mg, every 12 hours around the clock, PO + Acetaminophen 500 mg, as needed for breakthrough pain, PO. *Duration:* 3 days. ***Opioid-free group*** *Medication:* Acetaminophen 500 mg, as needed, PO. *Duration:* 3 days.
Outcomes	**Primary outcomes:** Pain score, 5-point Likert scale, mean. **Timepoints:** Just after extraction, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 1 day, 2 days. **Secondary outcomes:** Amount of rescue analgesia consumed, sleep disturbance. **Total length of follow up:** 7 days.
Country and setting	**Country:** England. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Searle Pharmaceuticals grant.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	Patients were assigned sequential numbers in the order in which they were enrolled and received their allocated treatment according to a computer-generated randomization schedule prepared before the start of the study. No information about randomization nor concealment is reported.

		Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were blinded by using a double-dummy technique. No information is available regarding carer blinding. Analyses were 'per protocol': limited to patients who had taken at least one dose of study drug and had recorded at least five pain scores. There is no information regarding how many patients were excluded from the analysis.
Risk of bias due to missing outcome data.	High risk.	Based on the data presented, it can be inferred that rate of missing data was 17%. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value. The authors did not document reasons for missing outcome data.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid group 3***	**Opioid-free group**
Pain score just after extraction, Likert (1-5)	Mean 1.63†	Mean 1.66†	Mean 1.73†	Mean 1.83†
Pain score 1h after surgery, Likert (1-5)	Mean 2.16†	Mean 2.30†	Mean 2.18†	Mean 2.35†
Pain score 2h after surgery, Likert (1-5)	Mean 2.38†	Mean 2.56†	Mean 2.45†	Mean 2.79†
Pain score 3h after surgery, Likert (1-5)	Mean 2.43†	Mean 2.53†	Mean 2.34†	Mean 2.60†
Pain score 4h after surgery, Likert (1-5)	Mean 2.27†	Mean 2.39†	Mean 2.27†	Mean 2.47†
Pain score 5h after surgery, Likert (1-5)	Mean 2.21†	Mean 2.14†	Mean 2.10†	Mean 2.41†
Pain score 6h after surgery, Likert (1-5)	Mean 2.08†	Mean 2.09†	Mean 2.08†	Mean 2.37†
Pain score 7h after surgery, Likert (1-5)	Mean 1.93†	Mean 2.02†	Mean 1.91†	Mean 2.24†
Pain score 8h after surgery, Likert (1-5)	Mean 1.85†	Mean 1.87†	Mean 1.89†	Mean 2.22†
Pain score 1 day after surgery, Likert (1-5)	Median 2†	Median 2†	Median 2†	Median 2.28†
Pain score 2 days after surgery, Likert (1-5)	Median 1.33†	Median 1.5†	Median 1.63†	Median 1.75†
Sleep disturbance	Incidence rate 21%	Incidence rate 8%	Incidence rate 7%	Incidence rate 11%

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

†Likert scale scores were standardized to VAS scores as described in the Appendix (pp 156-157).

Comfort 2002 (https://pubmed.ncbi.nlm.nih.gov/12587769/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To evaluate the comparative efficacy of three commonly used analgesics (Panadeine, Diflunisal and Etodolac) in the control of pain after third molar surgery under local anaesthesia. **Number of arms:** 3 (1 opioid analgesia, 2 opioid-free analgesia). **Randomization ratio:** Not reported. **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 80; opioid-free group 1: 66; opioid-free group 80. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: median 25 (IQR 21-29); opioid-free group 1: median 26 (IQR 22-32); opioid-free group 2: median 26 (IQR 22-31). **Sex (female):** Opioid group: 66%; opioid-free group 1: 58%; opioid-free group 2: 63%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients awaiting removal of impacted mandibular third molars. **Exclusion criteria:** Any serious medical condition.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anesthesia (lidocaine 2%, epinephrine 1:80 000). **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group:*** Acetaminophen 500 mg, PO + Codeine 8 mg, PO. ***Opioid-free group 1:*** Diflunisal 250 mg, PO. ***Opioid-free group 2:*** Etodolac 200 mg, PO. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 500 mg, every 4-6 hours around the clock, PO + Codeine 8 mg, every 4-6 hours around the clock, PO. *Duration:* 1 day. ***Opioid-free group 1*** *Medication:* Diflunisal 250 mg, every 8-12 hours around the clock, PO. *Duration:* 1 day. ***Opioid-free group 2*** *Medication:* Etodolac 200 mg, every 6-8 hours around the clock, PO. *Duration:* 1 day.
Outcomes	**Primary outcomes:** Pain score, visual analogue scale 0-100 mm, mean (IQR). **Timepoints:** 4 hours, 8 hours, 12 hours, and 24 hours. **Secondary outcomes:** Use of rescue analgesia, adverse events (headache, vomiting, dizziness, skin rash). **Total length of follow up:** 1 day.
Country and setting	**Country:** Hong Kong SAR, China **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized-controlled trial, but no information about randomization nor concealment is reported. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	There is no information provided regarding blinding of patients and/or carers. There is no information regarding the analysis plan (intention to treat or per protocol).
Risk of bias due to missing outcome data.	High risk.	Rates of missing data are not reported by the authors. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).

Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. There was no information regarding blinding of patients, who were outcome assessors. Knowledge of group assignment could have influenced outcome reporting; however, the treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured any of the groups.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group 1***	**Opioid-free group 2***
Pain score 4 hours after surgery, VAS (0-100)	Mean 40.4 (IQR 25-79)†	Mean 34.2 (IQR 25-76)†	Mean 35.9 (IQR 25-72)†
Pain score 8 hours after surgery, VAS (0-100)	Mean 40.1†	Mean 26.7†	Mean 36.0†
Pain score 12 hours after surgery, VAS (0-100)	Mean 30.1†	Mean 23.0†	Mean 31.7†
Pain score 24 hours after surgery, VAS (0-100)	Mean 26.0†	Mean 17.4†	Mean 25.0†
Headache	Incidence rate 4/80	Incidence rate 0/66	Incidence rate 2/80
Vomiting	Incidence rate 4/80	Incidence rate 1/66	Incidence rate 2/80
Dizziness	Incidence rate 2/80	Incidence rate 2/66	Incidence rate 5/80
Skin rash	Incidence rate 0/80	Incidence rate 0/66	Incidence rate 0/80

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

†SD was calculated from the IQR provided according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Da Silva 2021 (https://pubmed.ncbi.nlm.nih.gov/32651644/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design (not adaptive). **Study objective:** To compare the acetaminophen administration efficacy or its combination with codeine for pain control in acute apical abscesses cases. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The authors stated that a sample size requirement of 19 patients per group was calculated based on the following parameters: 95% confidence level, 80% statistical power, mean and standard deviation from 1000 mg acetaminophen group of 6.0 ± 3.42, and mean and standard deviation from the associated analgesics group (acetaminophen 500 mg + codeine 30 mg) of 9.0 ± 3.30.
Participants	**N randomised:** Opioid group: 20; opioid-free group: 19. **Diagnosis (% of participants):** Acute apical abscess (100%). **Surgery:** Dental surgery (100%). **Age:** Opioid group: mean 44.3 (SD 13.5); opioid-free group: mean 42.6 (SD 15.5). **Sex (female):** Opioid group: 70%; opioid-free group: 63.2%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients > 18 years old, with an acute apical abscess with pulp necrosis origin, and moderate to severe pain (> 40 mm on VAS) **Exclusion criteria:** Allergy to study medication, pregnant or lactating, liver disease, opioid or NSAID chronic user, illicit drug users.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Unclear.
Interventions	**Intraoperative anaesthesia:** Local anesthesia (lidocaine 2%, epinephrine 1:100 000). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 1000 mg, every 6 hours around the clock, PO + Codeine 30 mg, every 6 hours around the clock, PO + Acetaminophen 500 mg, every 6 hours as needed for breakthrough pain, PO. *Duration:* 3 days. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 6 hours around the clock, PO + Acetaminophen 500 mg, every 6 hours as needed for breakthrough pain, PO. *Duration:* 3 days.
Outcomes	**Primary outcomes:** Pain score, visual analogue scale 0-10 cm, mean. **Timepoints:** Just after surgery, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours. **Secondary outcomes:** Use of rescue analgesia, adverse events (nausea, headache, drowsiness, vomiting, dizziness, other). **Total length of follow up:** 7 days.
Country and setting	**Country:** Brazil. **Number of centres:** Single centre. **Study period:** 2016-2017.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	The patient's allocation for one of the treatments was performed by employing a random number table that was generated by Random Allocation Software®. Operator and patient's masking were assured since medications were included in identical capsules by a professional who was not dealing with the patients. Capsules were placed in properly sealed white flasks and sequentially numbered from 1 to 20. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Participants and carers were blinded. Analysis was done according to intention to treat principle.
Risk of bias due to missing outcome data.	Low risk.	Only 1 patient had missing data (2.5%).

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score just after surgery, VAS (0-10)	Mean 82*	Mean 85*
Pain score 6h after surgery, VAS (0-10)	Mean 52*	Mean 45*
Pain score 12h after surgery, VAS (0-10)	Mean 36*	Mean 25*
Pain score 24h after surgery, VAS (0-10)	Mean 25*	Mean 24*
Pain score 48h after surgery, VAS (0-10)	Mean 18*	Mean 15*
Pain score 72h after surgery, VAS (0-10)	Mean 5*	Mean 0*
Nausea	Incidence rate 8/20	Incidence rate 2/19
Headache	Incidence rate 3/20	Incidence rate 4/19
Drowsiness	Incidence rate 7/20	Incidence rate 3/19
Vomiting	Incidence rate 2/20	Incidence rate 0/19
Dizziness	Incidence rate 3/20	Incidence rate 1/19

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Desjardins 2020 (https://pubmed.ncbi.nlm.nih.gov/32488263/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To evaluate the analgesic efficacy and safety of tramadol hydrochloride/diclofenac sodium fixed-dose combination 25 mg/25 mg (FDC 25/25) and 50 mg/50 mg (FDC 50/50) vs tramadol 50 mg (T50) and diclofenac 50 mg (D50) monotherapies in acute postoperative dental pain. **Number of arms:** 4 (3 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1:1:1 **Power (sample size calculation):** It was estimated that a total number of 720 subjects or 180 subjects per treatment group would be required to achieve an overall power of at least 85% to reject the null hypothesis of at least one of the four formal statistical tests in the primary analysis of the trial (one-sided t test, type I error of a/4 with a 1⁄4 2.5%). This assumed a common standard deviation of change from baseline values of 4 points and an expected treatment difference of at least 2 points on the primary efficacy end point (TOTPAR 4) in the comparisons between FDC 50/50 and D50 or T50, using a noninferiority margin of D 1⁄4 1.5 points.
Participants	**N randomised:** Opioid group 1: 206; opioid group 2: 205; opioid group 3: 208; opioid-free group: 207. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group 1: triple molar extraction (20.4%), quadruple molar extraction (79.6%); opioid group 2: triple molar extraction (20%), quadruple molar extraction (80%); opioid group 3: triple molar extraction (17.8%), quadruple molar extraction (82.2%); opioid-free group: triple molar extraction (20.8%), quadruple molar extraction (79.2%). **Age:** Opioid group 1: mean 23.8 (SD 4.88); opioid group 2: mean 24.0 (SD 5.76); opioid group 3: mean 22.9 (SD 4.58); opioid-free group: mean 23.6 (SD 6.47). **Sex (female):** Opioid group 1: 64%; opioid group 2: 66%; opioid group 3: 61%; opioid-free group: 65%. **Ethnicity:** Opioid group 1: Hispanic/Latino (100%), Mestizo (97.1%); opioid group 2: Hispanic/Latino (99.5%), Mestizo (96.6%); opioid group 3: Hispanic/Latino (100%), Mestizo (97.1%); opioid-free group: Hispanic/Latino (99.5%), Mestizo (98.1%) **Inclusion criteria:** Age 18-60, in good general health and required extraction of three or more third molars with two mandibular partial or full bony impacted third molars. **Exclusion criteria:** Subjects were excluded if they had molars close to the mandibular canal, required immediate dental procedures other than extraction of the third molars, had a history of seizures, known alcohol or drug abuse in the last six months, or hypersensitivity to any of the investigational medicinal products (IMPs) or the anaesthetic used during surgery or the rescue medication (ibuprofen, ketorolac). Also excluded were subjects who received >300 mg of lidocaine in total, a long-acting NSAID within 24 hours, or five times the elimination half- life of that NSAID (whichever was longer) before surgery, any systemic corticosteroid, any analgesic medication other than short-acting preoperative or intraoperative anaesthetic agents within 24 hours before taking IMPs, or an analgesic medication other than the IMPs immediately after the surgical procedure. Subjects who did not achieve pain intensity of >5 points on an 11-point numerical rating scale (NRS; score range 0–10) within four hours after the surgical procedure were ineligible for the study.

Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group 1*** *Medication:* Tramadol 50mg, every 8 hours around the clock, PO (2 doses at research site). ***Opioid group 2*** *Medication:* Diclofenac 25mg, every 8 hours around the clock, PO (2 doses at research site) + Tramadol 25mg, every 8 hours around the clock, PO (2 doses at research site). ***Opioid group 3*** *Medication:* Diclofenac 50mg, every 8 hours around the clock, PO (2 doses at research site) + Tramadol 50mg, every 8 hours around the clock, PO (2 doses at research site). ***Opioid-free group*** *Medication:* Diclofenac 50mg, every 8 hours around the clock, PO (2 doses at research site). **Post-discharge analgesia:** ***Opioid group 1*** *Medication:* Tramadol 50 mg, every 8 hours around the clock, PO. *Duration:* 1 day. ***Opioid group 2*** *Medication:* Diclofenac 25mg, every 8 hours around the clock, PO + Tramadol 25mg, every 8 hours around the clock, PO. *Duration:* 1 day. ***Opioid group 3*** *Medication:* Diclofenac 50mg, every 8 hours around the clock, PO + Tramadol 50mg, every 8 hours around the clock, PO. *Duration:* 1 day.

	Opioid-free group *Medication:* Diclofenac 50mg, every 8 hours around the clock, PO. *Duration:* 1 day.
Outcomes	**Primary outcome:** Pain relief over four hours after dose 1, visual rating scale (0-4). **Timepoints:** 4 hours after surgery. **Secondary outcomes:** Adverse events (any, nausea, vomiting, dizziness, hypotension, abdominal pain) **Total length of follow up:** 14 days.
Country and setting	**Country:** United States and Mexico. **Number of centres:** Multicentre. **Study period:** Not reported.
Source of funding	Grunenthal S.A.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Randomization across all eight research sites was performed centrally using an interactive response voice/web system and stratified according to pain intensity at baseline. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Patients and carers were blinded. Data were evaluated according to the intention to treat principle.
Risk of bias due to missing outcome data.	Low risk.	Rate of missing data was only 2.4%.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid group 3***	**Opioid-free group**
Overall adverse events	Incidence rate 105/206	Incidence rate 62/205	Incidence rate 96/208	Incidence rate 48/207

Nausea	Incidence rate 52/206	Incidence rate 15/205	Incidence rate 51/208	Incidence rate 7/207
Vomiting	Incidence rate 44/206	Incidence rate 12/205	Incidence rate 41/208	Incidence rate 3/207
Dizziness	Incidence rate 29/206	Incidence rate 11/205	Incidence rate 25/208	Incidence rate 6/207
Hypotension	Incidence rate 2/206	Incidence rate 1/205	Incidence rate 1/208	Incidence rate 0/207

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Dinis 2020 (https://pubmed.ncbi.nlm.nih.gov/31816306/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To determine whether NSAIDS alone can be prescribed after discharge from the postpartum ward without a significant change in pain scores and patient satisfaction in the postpartum period. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Sample size calculation was based on VAS pain score at 2-4 weeks, assuming a mean of 10mm and standard deviation (SD) of 20 mm in the opioid group. They prespecified an equivalence margin of -10 to 10 mm. Assuming a two-sided alpha level of 0.05 and 80% power to detect equivalence, a total of 138 participants would be needed. To account for a 25% expected attrition rate and crossover, a total of 170 participants were targeted.
Participants	**N randomised:** Opioid group: 85; opioid-free group: 85. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: primary c-section (51.8%), repeat c-section (47%), caesarean hysterectomy (1.2%); opioid-free group: primary c-section (50.6%), repeat c-section (47%), caesarean hysterectomy (2.4%). **Age:** Opioid group: mean 28 (SD 5.6); opioid-free group: mean 28.4 (SD 5.9). **Sex (female):** Opioid group: 100%; opioid-free group: 100%. **Ethnicity:** Opioid group: African American (58%), Asian (2%), Hispanic (34%), White (4%), Other (2%); opioid-free group: African American (42%), Asian (2%), Hispanic (40%), White (15%), Other (0%). **Inclusion criteria:** Age 18-50, English or Spanish speaker women, had a caesarean delivery. **Exclusion criteria:** Inability or refusal to provide informed consent, reported current or prior opioid or benzodiazepine use disorder, including urine drug screen positive for a non-prescribed opioid or benzodiazepine upon admission or during prenatal care, current treatment with methadone, buprenorphine or buprenorphine plus naloxone, known alcoholism disorder, severe renal or hepatic impairment, severe peptic ulcer disease, severe asthma (if patient has asthma but has previously tolerated NSAIDS, she will be allowed to participate), known CYP450/CY92D6 mutation conferring opioid ultra-rapid metabolizer status, allergy to any of the study drugs (anaphylaxis), incarcerated or institutionalized patients, inability to follow up as outpatient in our outpatient clinic, wound dehiscence or infection diagnosed prior to discharge from the hospital, wound vac placed prior to discharge from the hospital.
Procedure characteristics	**Surgical setting:** In-patient. **Surgery location:** Hospital operating room. **Surgical discharge:** Length of stay not reported. **Surgery classification:** Moderate.

	Surgery status: Not reported.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Ibuprofen 600 mg, every 6 hours as needed, PO + Hydrocodone 5-10 mg every 4 hours as needed, PO + Acetaminophen 325-650 mg, every 4 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Ibuprofen 600 mg, every 6 hours as needed, PO + Acetaminophen 325-650 mg, every 4 hours as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain score, visual analogue scale 0-100 mm, mean (SD). **Timepoints:** 2-4 weeks after discharge. **Secondary outcomes:** Patient satisfaction at 2-4 weeks postpartum, hospital readmission or emergency room visit, need for rescue opioid prescription, adverse events (unclear). **Total length of follow up:** 4 weeks.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2017-2018.
Source of funding	The University of Texas Health Science Center, Houston.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Randomization sequence was created by a nonclinical member of the research team, it had permuted blocks, and was stratified by repeat caesarean section. Patients were randomized via REDCap, based on a randomization list prepared by an independent researcher. Baseline characteristics were similar between groups.

Risk of bias due to deviation from intended interventions.	Low risk.	Participants and carer were not blinded to treatment allocation. No signs of deviations in interventions due to lack of blinding. Rates of non-adherence was consistent with what may have happened in practice. Intention-to-treat analysis was reported.
Risk of bias due to missing outcome data.	Some concerns.	VAS data was missing for 12% of patients. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events). Rates of missing data was relatively similar across groups (10 vs 14%).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Other data (e.g., complications, readmissions) were collected by a blinded research assistant. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score POD14-28, VAS (0-100)	Mean 15.9 (SD 20.4)	Mean 12.3 (SD 19.5)
Hospital readmission or emergency room visit	Incidence rate 7/76	Incidence rate 6/73
Patient satisfaction*		
Very dissatisfied	Incidence rate 4/85	Incidence rate 2/85
Somewhat dissatisfied	Incidence rate 3/85	Incidence rate 3/85
Neutral	Incidence rate 12/85	Incidence rate 11/85
Satisfied	Incidence rate 16/85	Incidence rate 23/85
Very satisfied	Incidence rate 46/85	Incidence rate 37/85
Adverse event (any)	Incidence rate 25/81	Incidence rate 14/76

*Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = very dissatisfied or somewhat dissatisfied; not dissatisfied = neutral, satisfied, or very satisfied).

Frants 2021 (https://pubmed.ncbi.nlm.nih.gov/33370050/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; non-inferiority design (not adaptive). **Study objective:** To compare effectiveness of opioids versus NSAIDs for postoperative analgesia in outpatient rhinoplasty. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported
Participants	**N randomised:** Opioid group: 29; opioid-free group: 41. **Diagnosis (% of participants):** Not reported. **Surgery:** Rhinoplasty (100%). **Age:** Opioid group: mean 32; opioid-free group: mean 32. **Sex (female):** Opioid group: 41%; opioid-free group: 46%. **Ethnicity:** Not reported. **Inclusion criteria:** Age 18-80, undergoing open or closed rhinoplasty for cosmetic or airway purposes. **Exclusion criteria:** Patients with autologous rib graft, concurrent endoscopic sinus surgery, paediatric patients undergoing rhinoplasty, contraindications to NSAIDs, and/or a baseline pain disorder.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Hydrocodone 5mg, every 4 hours as needed, PO + Acetaminophen 325mg, every 6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group***

	Medication: Ibuprofen 400 mg, as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** Postoperative days (POD) 0, 1, 7. **Secondary outcomes:** Days to medication cessation, adverse effects (unclear). **Total length of follow up:** 7 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	High risk.	Patients were then randomized to either the test arm or the control arm by means of a random number generator in Excel (Microsoft Corp., Redmond, Wash.), where those receiving a number between 0 and 0.5 would be placed in the test group and those receiving a number between 0.51 and 1 would be placed in the control group. There is no information on mechanisms used to conceal allocation. There are substantial differences between intervention group sizes
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants were not blinded. Carers were not blinded. Deviations arose because of the trial context such as drug discontinuation and switching. This is consistent with what may have happened in practice. Data were analysed according to intention to treat.
Risk of bias due to missing outcome data.	Low risk.	Rate of missing data was small: 4% (3/70).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Other data (e.g., complications, readmissions) were collected by a blinded research assistant. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.

Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score day of surgery, VAS (0-10)	Mean 3.14 (SD 1.75)	Mean 2.54 (SD 1.57)
Pain score 1 day after surgery, VAS (0-10)	Mean 2.46 (SD 1.90)	Mean 1.84 (SD 1.29)
Pain score 7 days after surgery, VAS (0-10)	Mean 3.14 (SD 2.12)	Mean 3.29 (SD 2.14)
Adverse event (any)	Incidence rate 0/29	Incidence rate 0/41

Garibaldi 2002 (https://pubmed.ncbi.nlm.nih.gov/12190134/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To analyse the combination of oral ketorolac 10 mg with varying amounts of codeine phosphate, and the postoperative pain relief that developed from this combination. **Number of arms:** 5 (4 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** Not reported. **Power (sample size calculation):** Not reported.
Participants	**N randomised:** 67 **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Range 18-32 **Sex (female):** 49% **Ethnicity:** Not reported. **Inclusion criteria:** Patients over 18 years, with bilateral third molar mandibular impactions. **Exclusion criteria:** Fibrinolytic alveolitis, allergic manifestations to aspirin or other NSAIDs, hypersensitivity to codeine or its derivatives, dry socket, taking other medication during the study, full bony impactions.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (lidocaine 2%, epinephrine 1:100 000) + conscious sedation (midazolam 2.5mg IV, meperidine 25 mg IV). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group 1*** *Medication:* Ketorolac 10 mg, every 6 hours as needed, PO + Codeine 7.5 mg, every 6 hours as needed, PO. *Duration:* 6 days.

	Opioid group 2 *Medication:* Ketorolac 10 mg, every 6 hours as needed, PO + Codeine 15 mg, every 6 hours as needed, PO. *Duration:* 6 days. ***Opioid group 3*** *Medication:* Ketorolac 10 mg, every 6 hours as needed, PO + Codeine 30 mg, every 6 hours as needed, PO. *Duration:* 6 days. ***Opioid group 4*** *Medication:* Codeine 30 mg, every 6 hours as needed, PO. *Duration:* 6 days. ***Opioid-free group*** *Medication:* Ketorolac 10 mg, every 6 hours as needed, PO. *Duration:* 6 days.
Outcomes	**Primary outcomes:** Pain score, numerical rating scale. **Timepoints:** Not reported. **Secondary outcomes:** Cessation of primary analgesia, adverse events (unspecified) **Total length of follow up:** 7 days.
Country and setting	**Country:** Untied States. **Number of centres:** Single centre. **Study period:** 2016-2017.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	The method for choosing this number was through a simple blind draw. A total of 100 numbered chips were placed in a drum. There were 20 chips each with the numbers 1, 2, 3, 4, or 5 printed on them. Patients were randomized in a preoperative consultation. According to the authors, a licensed, labelling pharmacist who formulated the study drugs and one experimenter, not involved with obtaining the informed consent, knew the contents of the packets and the patients' assignments,

		and were involved with breaking the study codes. Unclear if this was enough to ensure concealment of allocation. Very limited patient characteristics are provided in this study.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were blinded to group allocation. All capsules were identical in colour, shape, size, and appearance to prevent any patient or investigator bias. The authors conducted a per protocol analysis but did not report how many patients were excluded due to lack of adherence.
Risk of bias due to missing outcome data.	High risk.	33% of the patients recruited were not included in the analysis. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid group 3***	**Opioid group 4***	**Opioid-free group**
Adverse event (any)	Incidence rate 21%	Incidence rate 25%	Incidence rate 35%	Incidence rate 66%	Incidence rate 10%

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Gimbel 2001 (https://pubmed.ncbi.nlm.nih.gov/11293556/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To assess the single- and multiple-dose analgesic efficacy and tolerability of celecoxib in the treatment of acute pain after orthopaedic surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported
Participants	**N randomised:** Opioid group: 181; opioid-free group: 185. **Diagnosis (% of participants):** Not reported. **Surgery:** Orthopaedic surgery with open manipulation of bone with periosteal elevation (100%). **Age:** Opioid group: mean 44.4 (SD 16.1); opioid-free group: mean 46.6 (SD 15.2). **Sex (female):** Opioid group: 63%; opioid-free group: 58%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, undergone uncomplicated orthopaedic surgery that required open manipulation of bone with periosteal elevation, baseline pain intensity score of ~45 mm on a 100~mm visual analogue scale, in satisfactory health (investigator assessment). **Exclusion criteria:** Undergone total hip or knee replacement, scheduled for an additional surgical procedure that might produce greater surgical trauma than the orthopaedic procedure alone, cognitive impairment that would preclude compliance with the protocol, inability to tolerate oral medication, diagnosis of or treatment for oesophageal, gastric, or duodenal ulceration, history of cancer or uncontrolled chronic disease, abnormalities in aspartate transaminase, alanine transaminase, blood urea nitrogen, or creatinine levels ~1.5 times the upper limit of the reference range, history of hypersensitivity to any NSAID, COX-2- specific inhibitor, sulfonamide, opiate, or analgesic that has cross-sensitivity with the medications used in these studies.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group***

	*Medication: H*ydrocodone 10 mg, PO + Acetaminophen 1000 mg, PO. ***Opioid-free group*** *Medication:* Celecoxib 200 mg, PO. **Post-discharge analgesia:** ***Opioid group*** *Medication: H*ydrocodone 10 mg, every 8 hours as needed, PO + Acetaminophen 1000 mg, every 8 hours as needed. PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Celecoxib 200 mg, every 8 hours as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Maximum pain score, visual analogue scale 0-10 cm, mean. **Timepoints:** Postoperative day (POD) 1, 2, 3, 4. **Secondary outcomes:** Adverse events (overall, nausea, headache, somnolence, vomiting, dizziness, indigestion, dry mouth, pruritus, constipation), pain interference, rescue analgesia requirement, analgesic dosages. **Total length of follow up:** 4 days.
Country and setting	**Country:** United States. **Number of centres:** Multicentre. **Study period:** 1998.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized-controlled trial, but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics are not reported of the outpatient phase of the trial.
Risk of bias due to deviation from intended interventions.	Low risk.	The study is described as a double-blinded trial. It is assumed that participants were blinded. It is assumed that carers and people delivering the interventions were blinded. The authors describe the use of a 'modified intention to treat analysis',

		excluding patients who did not take the first medication dose or missed assessments in the single-dose phase. This did not seem to affect the multiple-dose phase.
Risk of bias due to missing outcome data.	Low risk.	Only 1 patient was lost to follow-up in the multi-dose phase.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Outcome assessors were apparently blinded to group allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score day 1 after discharge, VAS (0-10)	Mean 2.10*	Mean 1.75*
Pain score day 2 after discharge, VAS (0-10)	Mean 1.80*	Mean 1.40*
Pain score day 3 after discharge, VAS (0-10)	Mean 1.82*	Mean 1.30*
Pain score day 4 after discharge, VAS (0-10)	Mean 1.60*	Mean 1.20*
Pain interference with general activity, APSQ (0-10)	Mean 5.1†	Mean 4.0†
Nausea	Incidence rate 53/181	Incidence rate 22/185
Headache	Incidence rate 23/181	Incidence rate 20/185
Somnolence	Incidence rate 30/181	Incidence rate 15/185
Vomiting	Incidence rate 17/181	Incidence rate 10/185
Dizziness	Incidence rate 31/181	Incidence rate 7/185
Indigestion	Incidence rate 1/181	Incidence rate 7/185
Dry mouth	Incidence rate 5/181	Incidence rate 2/185
Pruritus	Incidence rate 6/181	Incidence rate 2/185
Constipation	Incidence rate 6/181	Incidence rate 0/185

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

†Pain interference was standardized to PROMIS-PI scores as described in the appendix (pp 156-157).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Han 1998 (https://www.koreamed.org/SearchBasic.php?RID=2104794**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To evaluate the efficacy and side effects of Myprodol. **Number of arms:** 3 (2 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1:1 **Power (sample size calculation):** Not reported
Participants	**N randomised:** Opioid group 1: 20; opioid group 2: 20; opioid-free group: 20. **Diagnosis (% of participants):** Opioid group 1: chronic periodontitis (60%), dental caries (30%), tooth crack (5%), loss of tooth (5%); opioid group 2: chronic periodontitis (70%), dental caries (30%), tooth crack (0%), loss of tooth (0%); opioid-free group: chronic periodontitis (65%), dental caries (25%), tooth crack (0%), loss of tooth (10%). **Surgery:** Opioid group 1: open flap curettage (20%), regenerative surgery (25%), ridge augmentation (5%), implant first surgery (10%), root resection (0%), bicuspidization (5%), crown lengthening (35%); opioid group 2: open flap curettage (35%), regenerative surgery (20%), ridge augmentation (0%), implant first surgery (0%), root resection (15%), bicuspidization (0%), crown lengthening (30%); opioid-free group: open flap curettage (55%), regenerative surgery (5%), ridge augmentation (5%), implant first surgery (5%), root resection (0%), bicuspidization (5%), crown lengthening (25%). **Age:** Opioid group 1: mean 43.8 (SD 10.5); opioid group 2: mean 44.6 (SD 12); opioid-free group: mean 48.5 (SD 11.5). **Sex (female):** Opioid group 1: 50%; opioid group 2: 50%; opioid-free group: 45%. **Ethnicity:** Not reported. **Inclusion criteria:** Dental surgery with local anaesthesia for periodontal disease **Exclusion criteria:** Asthma, gastrointestinal peptic ulcer, anticoagulant therapy, haemorrhagic tendency or history, lung disease, thyroid or adrenal dysfunction.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (unclear regimen). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:**

	Opioid group 1 *Medication:* Codeine 10 mg, every 6 hours around the clock, PO + Ibuprofen 200 mg, every 6 hours around the clock, PO + Acetaminophen 250 mg, every 6 hours around the clock, PO. ***Opioid group 2*** *Medication:* Codeine 20 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group*** *Medication:* Ibuprofen 400 mg, every 6 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean. **Timepoints:** Postoperative day (POD) 1, 2, 3. **Secondary outcomes:** Patient satisfaction, adverse events (nausea, constipation, dizziness). **Total length of follow up:** 3 days.
Country and setting	**Country:** South Korea. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	High risk.	The study is described as a randomized-controlled trial, but no information about randomization is reported. No information is provided regarding concealment of allocation. Rates of procedures seemed unbalanced across groups.
Risk of bias due to deviation from intended interventions.	High risk.	The study is described as a double-blinded trial. It is assumed that participants were blinded. It is assumed that carers and people delivering the interventions were blinded. There is no information as to whether the analysis was 'per protocol' or 'intention-to-treat'.
Risk of bias due to missing outcome data.	High risk.	1 patient had missing data for satisfaction scores. There is no information regarding rates of missing data for pain. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Outcome assessors were apparently blinded to group allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid-free group**
Pain score day 1 after surgery, VAS (0-10)	Mean 4.02†	Mean 5.63†	Mean 5.12†
Pain score day 2 after surgery, VAS (0-10)	Mean 1.95†	Mean 3.06†	Mean 2.52†
Pain score day 3 after surgery, VAS (0-10)	Mean 0.99†	Mean 2.11†	Mean 0.99†
Nausea	Incidence rate 0/20	Incidence rate 6/20	Incidence rate 0/20
Dizziness	Incidence rate 1/20	Incidence rate 4/20	Incidence rate 0/20
Constipation	Incidence rate 0/20	Incidence rate 4/20	Incidence rate 0/20
Patient satisfaction‡			
Satisfied	Incidence rate 45%	Incidence rate 45%	Incidence rate 75%
Extremely satisfied	Incidence rate 30%	Incidence rate 30%	Incidence rate 10%
No response	Incidence rate 0%	Incidence rate 0%	Incidence rate 5%

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

†SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

‡Ordinal satisfaction scale was dichotomized to facilitate interpretation (not dissatisfied = neutral, satisfied, or very satisfied).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Helmerhorst 2017 (https://pubmed.ncbi.nlm.nih.gov/29135664/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; non-inferiority design (not adaptive). **Study objective:** To determine whether prescription of step 1 pain medication (acetaminophen) is noninferior to step 2 pain medication (acetaminophen and tramadol) after operative treatment of an extremity fracture. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** A 2.0-point noninferiority margin for the satisfaction score was used for sample size calculation. It was estimated that 23 subjects per group would yield a power of 0.90 with an alpha significance level of 0.02525 (2-group noninferiority t test). To account for a possible loss of 10% to 15%, they targeted a sample of 26 subjects in each group.
Participants	**N randomised:** Opioid group: 25; opioid-free group: 27. **Diagnosis (% of participants):** Opioid group: hand/wrist/foot/ankle/clavicle fracture (60.0%%), shoulder/elbow/hip/humerus/tibia/femur fracture (40.0%); opioid-free group: hand/wrist/foot/ankle/clavicle fracture (59.3%), shoulder/elbow/hip/humerus/tibia/femur fracture (40.7%). **Surgery:** Isolated extremity fracture surgery (100%). **Age:** Opioid group: mean 42 (SD 19); opioid-free group: mean 45 (SD 18). **Sex (female):** Opioid group: 40%; opioid-free group: 52%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, undergoing surgery for a single extremity fracture. **Exclusion criteria:** Pregnancy or possible pregnancy, breastfeeding, drug allergies, multi-trauma, pelvic fracture, stress fracture, pathological fracture, other substantial injuries outside the skeletal system, liver or renal dysfunction, diagnosed constipation, inability to complete the questionnaires, chronic analgesic use.
Procedure characteristics	**Surgical setting:** In-patient. **Surgery location:** Hospital operating room. **Surgical discharge:** In-patient (0-4 days). **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Acetaminophen, diclofenac, oxycodone as needed. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 1000 mg, every 6 hours as needed, PO + Tramadol 50 mg, every 8 hours as needed, PO + Diclofenac 50 mg, every 8 hours as needed for breakthrough pain, PO + Oxycodone (unclear dose), as needed for breakthrough pain. *Duration:* Acetaminophen and Tramadol 2 weeks, Diclofenac 5 days. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 6 hours as needed, PO + Diclofenac 50 mg, every 8 hours as needed for breakthrough pain, PO. *Duration:* Acetaminophen 2 weeks, Diclofenac 5 days.
Outcomes	**Primary outcome:** Self-reported satisfaction with pain relief, visual analogue scale, 0-10, mean. **Timepoints:** Postoperative day (POD) 14. **Secondary outcomes:** Anxiety in response to nociception, pain intensity level, overall worst pain intensity level, mean pain intensity level, acceptable pain intensity level, adverse events (vomiting, nausea, constipation, dizziness, drowsiness, diarrhoea, overall). **Total length of follow up:** 14 days.
Country and setting	**Country:** Netherlands **Number of centres:** Single centre. **Study period:** 2012-2013.
Source of funding	Stichting Merel.
Source of data	Peer-reviewed article + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	All subjects were randomly assigned by computer random number generation to either a step 1 regimen or a step 2 regimen, with a 1:1 allocation ratio. No information on allocation concealment. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Because of funding limitations, they were not able to blind patients. There is no mention of blinding of carers. No signs of deviations in interventions due to lack of blinding. Intention-to-treat analysis reported.
Risk of bias due to missing outcome data.	Low risk.	Only 2 patients per group missed the follow-up assessment.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be pre-specified and appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes, and patients were not blinded. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active

		interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Patient satisfaction, VAS (0-10)*	Mean 8.5 (SD 2.1)	Mean 8.3 (SD 2.3)
Worst pain 14 days after surgery, VAS (0-10)	Mean 5.5, 95%CI (4.68-6.32)†	Mean 6.9, 95%CI (6.18-7.62)†
Vomiting	Incidence rate 0/25	Incidence rate 0/27
Nausea	Incidence rate 4/25	Incidence rate 2/27
Constipation	Incidence rate 2/25	Incidence rate 0/27
Dizziness	Incidence rate 4/25	Incidence rate 0/27
Drowsiness	Incidence rate 1/25	Incidence rate 0/27
Diarrhoea	Incidence rate 1/25	Incidence rate 0/27
Adverse event (any)	Incidence rate 10/25	Incidence rate 2/27

*Patient satisfaction data were dichotomized to facilitate interpretation (dissatisfied <5/10; not dissatisfied ≥5/10).

†Mean and 95%CI data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Ilyas 2019 (https://pubmed.ncbi.nlm.nih.gov/30810754/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial, non-inferiority design (not adaptive). **Study objective:** To evaluate 3 common oral analgesics—oxycodone (OXY), ibuprofen (IBU), and acetaminophen (ACE)—for pain management following carpal tunnel release (CTR) and trigger finger release (TFR) surgery. **Number of arms:** 3 (1 opioid analgesia, 2 opioid-free analgesia). **Randomization ratio:** 1:1:1 **Power (sample size calculation):** To detect a 1-capsule difference in consumption and/or a 0.5-unit difference in the 11-point numeric rating scale for pain, the authors estimated that 60 patients per group (180 total) would be necessary using a beta of 80%.
Participants	**N randomised:** Opioid group: 62; opioid-free group 1: 64; opioid-free group 2: 62. **Diagnosis (% of participants):** Opioid group: carpal tunnel syndrome (61%), trigger finger (39%); opioid-free group 1: carpal tunnel syndrome (53%), trigger finger (47%); opioid-free group 2: carpal tunnel syndrome (65%), trigger finger (35%). **Surgery:** Opioid group: carpal tunnel release (61%), trigger finger release (39%); opioid-free group 1: carpal tunnel release (53%), trigger finger release (47%); opioid-free group 2: carpal tunnel release (53%), trigger finger release (47%). **Age:** Opioid group: mean 59.6, range (29-84); opioid-free group 1: mean 62.1, range (19-94); opioid-free group 2: mean 59.6, range (32-88). **Sex (female):** Opioid group: 58%; opioid-free group 1: 59%; opioid-free group 2: 55%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, scheduled to have a primary, unilateral trigger finger release or carpal tunnel release surgery. **Exclusion criteria:** Required bilateral surgical procedures, simultaneous operations involving bone and/or soft tissues, require the use of sedation and/or general anaesthesia during surgery, history of allergies and/or medical contraindications [lidocaine, epinephrine, or any of the distributed analgesics (OXY, IBU, or ACE)], preoperative exposure to opioids, not speaking English, pregnancy.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (unclear regimen).

	Inpatient analgesia (after surgery, prior to discharge): Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Oxycodone 5mg, every 6 hours as needed, PO. *Duration:* 5 days. ***Opioid-free group 1*** *Medication:* Ibuprofen 600mg, every 6 hours as needed, PO. *Duration:* 5 days. ***Opioid-free group 2*** *Medication:* Acetaminophen 500mg, every 6 hours as needed, PO. *Duration:* 5 days.
Outcomes	**Primary outcome:** Mean daily worse pain score, visual analogue scale 0-10 cm, mean for all 5 days presented; patient satisfaction. **Timepoints:** Postoperative day (1-5). **Secondary outcomes:** Adverse events (nausea, pruritus, constipation, diarrhoea, dizziness), primary analgesia consumption. **Total length of follow up:** 14 days.
Country and setting	**Country:** United States **Number of centres:** Single centre. **Study period:** 2017-2018.
Source of funding	American Foundation for Surgery of the Hand.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Randomization was generated via a computerized random number generator. A compounding pharmacy prepared all 3 medications, with each serial-numbered prescription bottle containing 10 capsules of one of the chosen analgesics. Capsules were indistinguishable from one another. All formulated medications were stored in a locked cabinet in the research suite. The allocated medications were distributed by the unblinded research coordinator, who provided them to the blinded

		physician for dispersal to the blinded patient on the day of surgery. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants were blinded to group allocations. Carers were blinded to group allocations. The authors describe the use of an 'intention-to-treat analysis'; however, 8 patients were excluded because they required stronger pain medications (unclear if data previous to trial deviation was analysed). Rates of exclusion due to trial deviation was relatively low (7%).
Risk of bias due to missing outcome data.	Low risk.	According to the authors, all patients completed the study.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Outcome assessors were apparently blinded to group allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group 1***	**Opioid-free group 2***
Nausea	Incidence rate 7/62	Incidence rate 0/64	Incidence rate 0/62
Pruritis	Incidence rate 1/62	Incidence rate 0/64	Incidence rate 0/62
Constipation	Incidence rate 1/62	Incidence rate 0/64	Incidence rate 0/62
Dizziness	Incidence rate 0/62	Incidence rate 1/64	Incidence rate 0/62
Diarrhoea	Incidence rate 0/62	Incidence rate 0/64	Incidence rate 1/62
Patient satisfaction[†]			
Strongly agree	Incidence rate 43.5%	Incidence rate 40.6%	Incidence rate 41.9%
Agree	Incidence rate 25.8%	Incidence rate 26.6%	Incidence rate 27.4%
Neutral	Incidence rate 8.1%	Incidence rate 14.1%	Incidence rate 12.9%
Disagree	Incidence rate 11.3%	Incidence rate 4.7%	Incidence rate 1.6%
Strongly disagree	Incidence rate 0%	Incidence rate 3.1%	Incidence rate 4.8%
No data	Incidence rate 11.3%	Incidence rate 10.9%	Incidence rate 11.3%

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[†]Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = strongly disagree or disagree; not dissatisfied = neutral, agree, or strongly agree).

Jildeh 2021 (A) (https://pubmed.ncbi.nlm.nih.gov/34391876/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial, equivalency design (not adaptive). **Study objective:** To compare postoperative pain and patient satisfaction in patients undergoing primary arthroscopic labral surgery managed with either a nonopioid alternative pain regimen or a traditional opioid pain regimen. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1. **Power (sample size calculation):** For β level = 0.80, α level = 0.05, effect size of 2.4 mm, and standard deviation of 2.8 mm, the minimum number of 23 patients was targeted per cohort to evaluate the primary outcome. A sample size of 60 (30 per cohort) was selected at allow for incomplete data collection.
Participants	**N randomised:** Opioid group: 24; opioid-free group: 24. **Diagnosis (% of participants):** Opioid group: ALPSA, GLAD, HAGL (20.8%)/SLAP Tear (29.2%), Bony Bankart Lesion (16.7%)/Hill Sachs Lesion (16.7%)/Reverse Hill Sachs Lesion (0%); opioid-free group: ALPSA, GLAD, HAGL (16.6%)/SLAP Tear (33.3%), Bony Bankart Lesion (16.7%)/Hill Sachs Lesion (25%)/Reverse Hill Sachs Lesion (8.3%). **Surgery:** Primary arthroscopic labral repair (100%). **Age:** Opioid-group: mean 26.4 (SD 8.2); opioid-free group: mean 25.4 (SD 9.2). **Sex (female):** Opioid group: 21%; opioid-free group: 21%. **Ethnicity:** Opioid group: White (50%), African American (33.3%), other (8.3%), unknown (8.3%); opioid-free group: White (39.1%), African American (39.1%), other 8.3%, unknown 16.6%). **Inclusion criteria:** Age >15, undergoing primary arthroscopic labral repair. **Exclusion criteria:** A previous history of peptic ulcer disease, recent or current pregnancy, substance abuse, intolerance or allergy to study medication, renal impairment or dysfunction, use of blood thinner medication, gastrointestinal bleeding, same-joint surgery within the previous year, and use of opioids three months prior to surgery.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Local analgesia (30 mL 0.50% ropivacaine + 1 mL epinephrine + 1 mL ketorolac in the subcutaneous tissues prior to closure).

	Inpatient analgesia (after surgery, prior to discharge): Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Hydrocodone 5-10 mg, every 4-6 hours as needed, PO + Acetaminophen 325-650 mg, every 4-6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Ketorolac 10 mg, as needed, PO + Gabapentin 300 mg, as needed, PO + Acetaminophen 1000 mg, ass needed, PO. *Duration:* 14 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** 10 days. **Secondary outcomes:** Pain interference. **Total length of follow up:** 10 days.
Country and setting	**Country:** United States **Number of centres:** Single centre. **Study period:** 2019-2020.
Source of funding	None reported.
Source of data	Peer-reviewed article + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	Patients consented for participation were randomly assigned preoperatively to either an opioid or a multimodal non-opioid pain regimen with a 1:1 allocation ratio using adaptive randomization computer software (Adaptive Randomization, MD Anderson Cancer Center, Houston TX). Randomization was conducted using adaptive randomization computer software, but it's unclear how the concealment of allocation occurred. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were not blinded. Carers were not blinded. The authors do not report on protocol deviations. It's unclear if the analysis was according to intention to treat or per protocol.

Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e, pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 4.9*	Mean 4.1*
Pain score 2 days after discharge, VAS (0-10)	Mean 4.3*	Mean 4.0*
Pain score 3 days after discharge, VAS (0-10)	Mean 4.0*	Mean 3.0*
Pain score 4 days after discharge, VAS (0-10)	Mean 3.9*	Mean 2.5*
Pain score 5 days after discharge, VAS (0-10)	Mean 3.4*	Mean 2.1*
Pain score 6 days after discharge, VAS (0-10)	Mean 3.0*	Mean 2.5*
Pain score 7 days after discharge, VAS (0-10)	Mean 2.6*	Mean 2.0*
Pain score 8 days after discharge, VAS (0-10)	Mean 2.7*	Mean 1.8*
Pain score 9 days after discharge, VAS (0-10)	Mean 2.2*	Mean 1.8*
Pain score 10 days after discharge, VAS (0-10)	Mean 2.5*	Mean 1.9*
Pain interference, PROMIS PI	Mean 62.7 (SD 6.8)	Mean 54.2 (SD 9.6)

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias study.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Jildeh 2021 (B) (https://pubmed.ncbi.nlm.nih.gov/33713756/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial, equivalency design (not adaptive). **Study objective:** To assess the effectiveness of a nonopioid pain regimen in controlling postoperative pain as compared with a traditional opioid pain control following primary meniscectomy or meniscal repair. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** For a power of 80% (β level = .80, α level = .05), the authors estimated that a minimum of 25 patients per group (n = 50) was necessary to properly evaluate the primary hypothesis.
Participants	**N randomised:** Opioid group: 30; opioid-free group: 31. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: meniscus repair (3%), meniscus excision (97%), chondroplasty (67%), loose body removal (0%), microfracture (0%); opioid-free group: meniscus repair (3%), meniscus excision (97%), chondroplasty (61%), loose body removal (6%), microfracture (3%). **Age:** Opioid-group: mean 48.8 (SD 14.1); opioid-free group: mean 41.3 (SD 16.4). **Sex (female):** Opioid group: 27%; opioid-free group: 29%. **Ethnicity:** Opioid group: White (57%), African American (20%), Hispanic (3%), Asian (3%), other (10%), unknown (7%); opioid-free group: White (52%), African American (16%), Hispanic (0%), Asian (6%), other 16%, unknown 10%). **Inclusion criteria:** Age >16, undergoing primary arthroscopic meniscectomy or meniscal repair. **Exclusion criteria:** Had a significant history of substance abuse, peptic ulcer disease, recent or current pregnancy, intolerance or allergy to any study medication, renal impairment or dysfunction, same-joint surgery for any reason within the previous year, use of blood thinner medication, gastrointestinal bleeding, use of opioid medication within 3 months of surgery, or if they were undergoing revision surgery.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Local analgesia (30 mL 0.50% ropivacaine + 1 mL epinephrine + 1 mL ketorolac in the subcutaneous tissues prior to closure). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:**

	Opioid group *Medication:* Hydrocodone 5-10 mg, every 4-6 hours as needed, PO + Acetaminophen 325-650 mg, every 4-6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Ketorolac 10 mg, as needed, PO + Gabapentin 300 mg, as needed, PO + Acetaminophen 1000 mg, ass needed, PO. *Duration:* 14 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** 10 days. **Secondary outcomes:** Pain interference. **Total length of follow up:** 10 days.
Country and setting	**Country:** United States **Number of centres:** Single centre. **Study period:** 2019-2020.
Source of funding	None reported.
Source of data	Peer-reviewed article + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	This was a randomized controlled trial, but its unclear how the randomization sequence was generated. Randomization was conducted using adaptive randomization computer software. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants were not blinded. Carers were not blinded. Both groups complied with the proposed intervention. The analysis was apparently per intention to treat (there were no protocol deviations).
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could

		have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 2.8 (SD 0.8)	Mean 2.7*
Pain score 2 days after discharge, VAS (0-10)	Mean 3.2 (SD 0.6)	Mean 2.8*
Pain score 3 days after discharge, VAS (0-10)	Mean 2.9 (SD 0.4)	Mean 2.4*
Pain score 4 days after discharge, VAS (0-10)	Mean 2.5 (SD 0.1)	Mean 1.7*
Pain score 5 days after discharge, VAS (0-10)	Mean 2.3 (SD 0.2)	Mean 1.7*
Pain score 6 days after discharge, VAS (0-10)	Mean 2.3 (SD 0.2)	Mean 1.7*
Pain score 7 days after discharge, VAS (0-10)	Mean 2.2 (SD 0.2)	Mean 1.6*
Pain score 8 days after discharge, VAS (0-10)	Mean 2.4 (SD 0.2)	Mean 1.5*
Pain score 9 days after discharge, VAS (0-10)	Mean 2.9 (SD 0.1)	Mean 1.4*
Pain score 10 days after discharge, VAS (0-10)	Mean 2.3 (SD 0.1)	Mean 1.3*
Pain interference, PROMIS PI	Mean 59.8 (SD 6.8)	Mean 54.9 (SD 9.6)

*SD was imputed based on the highest SD from the same trial.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Kim 2005 (https://www.kjorl.org/journal/view.php?number=2163**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial, unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To evaluate the effectiveness of Myprodol codeine combination analgesics, on the pain control and time to return to normal daily activities. **Number of arms:** 3 (2 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group 1: 30; opioid group 2: 30; opioid-free group: 30. **Diagnosis (% of participants):** Not reported. **Surgery:** Tonsillectomy (100%). **Age:** Opioid group 1: mean 29.6 (Range 19-49); opioid-group 2: mean 26.6 (Range 17-34); opioid-free group: mean 31.2 (Range 18-48). **Sex (female):** Opioid group 1: 53%; opioid-group 2: 60%; opioid-free group: 50%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >15, undergoing tonsillectomy. **Exclusion criteria:** Other comorbid health conditions, prolonged hospital stay, re-admission after discharge, other diseases during follow-up period.
Procedure characteristics	**Surgical setting:** In-patient surgery. **Surgery location:** Hospital operating room. **Surgical discharge:** In-patient (2 days). **Surgery classification:** Minor. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** General anaesthesia (unclear regimen). **Inpatient analgesia (after surgery, prior to discharge):** beta-Cyclodextrin piroxicam 20 mg, daily, PO + Diclofenac 75 mg, every 12 hours around the clock, IM. **Post-discharge analgesia:** ***Opioid group 1*** *Medication:* Acetaminophen 250 mg, every 8 hours around the clock, PO + Ibuprofen 20 mg, every 8 hours around the clock + Codeine 10 mg, every 8 hours around the clock, PO.

	Duration: 12 days. ***Opioid group 2*** *Medication:* Dihydrocodeine 20 mg, every 12 hours around the clock, PO. *Duration:* 12 days. ***Opioid-free group*** *Medication:* Piroxicam 20mg, every day, PO. *Duration:* 12 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10, mean (SD). **Timepoints:** 1, 7, 14 after discharge at waking, breakfast, lunch, and dinner. **Secondary outcomes:** Time to return to normal daily activities, adverse events (nausea, constipation, sleep problems). **Total length of follow up:** 21 days.
Country and setting	**Country:** South Korea **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics seemed similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	There is no information regarding blinding of participants. There is no information regarding blinding of carers. There is no information regarding deviations from the intended intervention. There is no information as to whether the analysis was 'per protocol' or 'intention-to-treat'.
Risk of bias due to missing outcome data.	High risk.	There is no information regarding rates of missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes; it is unclear if patients were blinded. Knowledge of group assignment could have

		influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid-free group**
Pain score after waking up day 1, VAS (0-10)	Mean 5.3 (SD 3.0)	Mean 7.6 (SD 1.9)	Mean 6.4 (SD 2.4)
Pain score at breakfast day 1, VAS (0-10)	Mean 7.5 (SD 2.3)	Mean 7.4 (SD 1.8)	Mean 7.9 (SD 1.1)
Pain score at lunch day 1, VAS (0-10)	Mean 7.0 (SD 2.2)	Mean 6.4 (SD 1.8)	Mean 7.7 (SD 0.9)
Pain score at dinner day 1, VAS (0-10)	Mean 7.0 (SD 2.1)	Mean 6.3 (SD 1.9)	Mean 7.4 (SD 1.5)
Pain score after waking up day 7, VAS (0-10)	Mean 3.6 (SD 1.7)	Mean 6.4 (SD 2.7)	Mean 5.0 (SD 1.5)
Pain score at breakfast day 7, VAS (0-10)	Mean 4.9 (SD 1.4)	Mean 6.7 (SD 2.4)	Mean 6.2 (SD 1.7)
Pain score at lunch day 7, VAS (0-10)	Mean 4.6 (SD 1.2)	Mean 5.7 (SD 2.5)	Mean 5.7 (SD 1.9)
Pain score at dinner day 7, VAS (0-10)	Mean 4.7 (SD 1.5)	Mean 5.5 (SD 2.7)	Mean 5.9 (SD 1.5)
Pain score after waking up day 14, VAS (0-10)	Mean 1.3 (SD 2.4)	Mean 4.8 (SD 2.1)	Mean 2.7 (SD 2.1)
Pain score at breakfast day 14, VAS (0-10)	Mean 1.9 (SD 2.2)	Mean 4.8 (SD 2.0)	Mean 3.9 (SD 2.0)
Pain score at lunch day 14, VAS (0-10)	Mean 1.7 (SD 2.0)	Mean 4.3 (SD 2.2)	Mean 3.7 (SD 2.0)
Pain score at dinner day 14, VAS (0-10)	Mean 1.3 (SD 2.2)	Mean 4.5 (SD 2.1)	Mean 3.3 (SD 1.9)
Nausea	Incidence rate 0/30	Incidence rate 2/30	Incidence rate 0/30
Constipation	Incidence rate 2/30	Incidence rate 0/30	Incidence rate 2/30
Nights with awakenings	Incidence rate 0/30	Incidence rate 3/30	Incidence rate 0/30
Skin rash	Incidence rate 1/30	Incidence rate 0/30	Incidence rate 0/30

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Kim 2019 (https://pubmed.ncbi.nlm.nih.gov/30585803/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To compare the efficacy and safety of celecoxib and oxycodone for acute pain management after lumbar decompressive surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 47; opioid-free group: 46. **Diagnosis (% of participants):** Symptomatic lumbar stenotic condition (100%). **Surgery:** Single-level lumbar decompressive surgery (100%). **Age:** Opioid group: mean 62.9 (SD 11.0); opioid-free group: mean 63.5 (SD 10.9). **Sex (female):** Opioid group: 62%; opioid-free group: 54%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, single-level lumbar stenotic condition confirmed by magnetic resonance imaging (MRI), failed conservative treatment of >6 weeks. **Exclusion criteria:** Recurrent disc herniation, a recent history (<1 month) of neuraxial blockade, preoperative use of opioids, contraindication of NSAIDs or opioids, history of other clinical pain conditions such as fibromyalgia, herpes zoster, or rheumatoid arthritis, cauda equina syndrome.
Procedure characteristics	**Surgical setting:** In-patient surgery. **Surgery location:** Hospital operating room. **Surgical discharge:** In-patient (7 days). **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group:*** Celecoxib 200mg daily for 2 days, Pregabalin 75mg twice a day for 2 days, Acetaminophen 500mg twice a day for 2 days, extended-release Oxycodone twice a day for 2 days, extended-release Oxycodone 10mg twice a day until discharge.

	Opioid-free group: Celecoxib 200mg daily for 2 days, Pregabalin 75mg twice a day for 2 days, Acetaminophen 500mg twice a day for 2 days, extended-release Oxycodone twice a day for 2 days, Celecoxib 200mg daily until discharge. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Extended-release Oxycodone 10mg, every 12 hours around the clock, PO. *Duration:* Until postoperative day 14. ***Opioid-free group*** *Medication:* Celecoxib 200mg, every day, PO. *Duration:* Until postoperative day 14.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD); Oswestry Back Pain Disability Index (ODI), mean (SD). **Timepoints:** Postoperative days 2, 3, 7, and 14. **Secondary outcomes:** Adverse effects (bleeding, indigestion, constipation, dry mouth, hypotension, nausea/vomiting, drowsiness). **Total length of follow up:** 1 month.
Country and setting	**Country:** Korea **Number of centres:** Single centre. **Study period:** 2011-2016.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. The authors report that patients were randomized preoperatively by sealed envelope, but no further information is provided regarding concealment of allocation. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	The clinician and patients were not blinded. No signs of deviations in interventions due to lack of blinding. Dropouts for unclear reasons were balanced between groups

		(3 vs 2). There is no information as to whether the analysis was 'per protocol' or 'intention-to-treat'.
Risk of bias due to missing outcome data.	Low risk.	According to the authors, only 1 patient was lost to follow up.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were not blinded. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 4.34 (SD 1.67)	Mean 4.35 (SD 1.35)
Pain score 7 days after discharge, VAS (0-10)	Mean 3.91 (SD 1.68)	Mean 4.04 (SD 1.41)
Bleeding	Incidence rate 0/47	Incidence rate 0/46
Indigestion	Incidence rate 6/47	Incidence rate 5/46
Constipation	Incidence rate 8/47	Incidence rate 1/46
Dry mouth	Incidence rate 6/47	Incidence rate 2/46
Hypotension	Incidence rate 0/47	Incidence rate 0/46
Dizziness	Incidence rate 6/47	Incidence rate 2/46
Nausea/vomiting	Incidence rate 8/47	Incidence rate 1/46
Drowsiness	Incidence rate 5/47	Incidence rate 2/46

La Monaca 2021 (https://pubmed.ncbi.nlm.nih.gov/34922726/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare analgesic effects of preoperative administration of paracetamol 500 milligram plus codeine 30 milligram in single-tablet and effervescent formulation to ibuprofen 400 milligram, and placebo in the management of moderate to severe postoperative pain after mandibular third molar surgery. **Number of arms:** 3 (2 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1:1. **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group 1: 34; opioid group 2: 34; opioid-free group: 38. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Mean 20.53 (SD 3.57). **Sex (female):** 66%. **Ethnicity:** Not reported. **Inclusion criteria:** Age 15-29, healthy status (ASA class I), non-smoker, not pregnant or breastfeeding, no medication consumption in the past 21 days, good oral hygiene, bony impaction of one mandibular third molars, the presence of the first and second molars, compliance to cooperate with the research protocol. **Exclusion criteria:** Chronic systemic disease, medications with potential interaction to paracetamol-codeine or ibuprofen, a history of intolerance or hypersensitivity to the study drugs, any pre-existing pain and acute inflammatory or infectious conditions, inability to understand or perform the study procedure.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group 1*** *Medication:* Paracetamol 500 mg, as needed, PO + Codeine 30 mg, as needed, PO.

	Duration: 1 day. ***Opioid group 2*** *Medication:* Paracetamol 500 mg, as needed, PO + Codeine 30 mg, as needed, PO. *Duration:* 1 day. ***Opioid-free group*** *Medication:* Ibuprofen 400 mg, as needed, PO. *Duration:* 1 day.
Outcomes	**Primary outcome:** Pain scores (worst), numerical rating scale 0-10, mean (SD). **Timepoints:** Day of surgery, 1 day after surgery, and 2 days after surgery. **Secondary outcomes:** Adverse events (unclear). **Total length of follow up:** 3 days.
Country and setting	**Country:** Italy **Number of centres:** Single centre. **Study period:** 2018-2020.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Before the start of the study, analgesic treatments were assigned using a list of random numbers generated using CLINSTAT software (Martin Bland, York, UK). The concealed allocation was performed with consecutively numbered sealed opaque envelopes. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Patients, surgeon, data collector and biometrician were unaware of the analgesic treatment (triple blind design). It's unclear if all the medications given to patients looked the same. The authors do not mention if the analysis was per intention to treat or per protocol. Data regarding treatment compliance is not presented.
Risk of bias due to missing outcome data.	High risk.	12% of patients were excluded due to incomplete pain diaries. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events). There were differences between groups in the proportions of missing outcome data (more frequent in the opioid groups).

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were blinded to group allocation.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid-free group**
Pain score 0 days after discharge, NRS (0-10)	Mean 3.18 (SD 1.17)†	Mean 5.76 (SD 2.53)†	Mean 3.61 (SD 2.51)†
Pain score 1 day after discharge, NRS (0-10)	Mean 2.22 (SD 1.88)†	Mean 3.41 (SD 1.75)†	Mean 3.57 (SD 2.49)†
Pain score 2 days after discharge, NRS (0-10)	Mean 1.81 (SD 1.77)†	Mean 2.07 (SD 2.31)†	Mean 3.16 (SD 2.41)†
Adverse events (unclear)	Incidence rate 0/34	Incidence rate 0/34	Incidence rate 0/38

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

†NRS scores were standardized to VAS scores as described in the Appendix (pp 156-157).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Li 2005 (https://pubmed.ncbi.nlm.nih.gov/17162863/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To evaluate the efficacy and safety of tramadol for controlling post-operative ocular pain from laser assisted subepithelial keratomileusis. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 33; opioid-free group: 31. **Diagnosis (% of participants):** Not reported. **Surgery:** Laser assisted subepithelial keratomileusis (100%). **Age:** Opioid group: mean 28.5 (SD 6.6); opioid-free group: mean 31.1 (SD 8.0). **Sex (female):** Opioid group: 70%; opioid-free group: 65%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18. **Exclusion criteria:** Other acute or chronic eye diseases, severe heart, liver, lung or renal dysfunction, pregnant or lactating women.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Diclofenac 1 drop, every 6 hours around the clock, PO + Tramadol 100 mg, every 12 hours around the clock, PO. *Duration:* 3 days.

	Opioid-free group *Medication:* Diclofenac 1 drop, every 6 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, numerical rating scale 0-4, mean (SD). **Timepoints:** Postoperative day (POD) 1, 4, and 7. **Secondary outcomes:** Eyelid edema, conjunctival congestion, adverse event (nausea, vomiting, dizziness, photophobia, lacrimation, foreign body sensation). **Total length of follow up:** 7 days.
Country and setting	**Country:** China **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	Author's judgement	Support for judgement
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized controlled trial but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics were not reported with between-group comparison.
Risk of bias due to deviation from intended interventions.	High risk.	There is no information regarding blinding of participants and carers. There is no information regarding deviations from the intended intervention. There is no information as to whether the analysis was 'per protocol' or 'intention-to-treat'.
Risk of bias due to missing outcome data.	High risk.	There is no information regarding rates of missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes; it is unclear if patients were blinded. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score 1 day after surgery, NRS (0-4)	Mean 0.48 (SD 0.67)*	Mean 1.70 (SD 0.69)*
Pain score 4 days after surgery, NRS (0-4)	Mean 0.18 (SD 0.39)*	Mean 0.65 (SD 0.55)*
Pain score 7 days after surgery, NRS (0-4)	Mean 0 (SD 0)*	Mean 0 (SD 0)*
Nausea, dizziness, vomiting	Incidence rate 4/33	Incidence rate 0/31

*NRS scores were standardized to VAS scores as described in the Appendix (pp 156-157).

Lownie 1992 (https://pubmed.ncbi.nlm.nih.gov/9511622/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To compare the efficacy of a combination anti-inflammatory analgesic, Myprodol, with Ponstan in the alleviation of dental pain following the removal of impacted or unerupted third molar teeth. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 25; opioid-free group: 27. **Diagnosis (% of participants):** Impacted or unerupted third molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: mean 22.0; opioid-free group: mean 23.0. **Sex (female):** Opioid group: 60%; opioid-free group: 37%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >16, requiring surgical removal of 2-4 wisdom teeth (third molars). **Exclusion criteria:** Pregnant patients, patients with hypersensitivity to anti-inflammatory and analgesic medication, peptic ulceration, asthma, hepatic disease, renal disease. Patients on concomitant analgesic therapy.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Diclofenac sodium 75mg/3ml single injection. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Ibuprofen 400mg, every 8 hours around the clock, PO + Acetaminophen 500mg, every 8 hours around the clock, PO + Codeine 20mg, every 8 hours around the clock, PO.

	Duration: 5 days. ***Opioid-free group*** *Medication:* Mefenamic acid 500mg, every 8 hours around the clock, PO. *Duration:* 5 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean. **Timepoints:** Just after extraction, 1 hour after surgery, day 1 after surgery, day 2 after surgery, day 3 after surgery, day 4 after surgery, and day 5 after surgery. **Secondary outcomes:** Time to and duration of pain relief, patient satisfaction with medication. **Total length of follow up:** 5 days.
Country and setting	**Country:** South Africa **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Adcock Ingram Pharmaceuticals Limited.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics seemed were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	The study is described as a double-blinded trial. It is assumed that participants were blinded. It is assumed that carers and people delivering the interventions were blinded. Capsules were identical and packages as well. Analysis seemed to be 'per protocol' as one patient was excluded for non-adherence.
Risk of bias due to missing outcome data.	High risk.	There is no information regarding rates of missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Outcome assessors were apparently blinded to group allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score just after extraction, VAS (0-10)	Mean 5.3*	Mean 5.1*
Pain score 1 hour after surgery, VAS (0-10)	Mean 1.8*	Mean 2.5*
Pain score 1 day after surgery, VAS (0-10)	Mean 1.4*	Mean 2.4*
Pain score 2 days after surgery, VAS (0-10)	Mean 1.7*	Mean 2.9*
Pain score 3 days after surgery, VAS (0-10)	Mean 2.3*	Mean 2.9*
Pain score 4 days after surgery, VAS (0-10)	Mean 1.5*	Mean 2.1*
Pain score 5 days after surgery, VAS (0-10)	Mean 2.5*	Mean 2.1*
Patient satisfaction†		
Poor	Incidence rate 0%	Incidence rate 4%
Fair	Incidence rate 4.5%	Incidence rate 20%
Good	Incidence rate 40.9%	Incidence rate 40%
Excellent	Incidence rate 54.5%	Incidence rate 36%

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

†Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = poor; not dissatisfied = fair, good, or excellent).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Lysell 1992 (https://pubmed.ncbi.nlm.nih.gov/1455326/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare two analgesics commonly used in oral surgery: ibuprofen and paracetamol/codeine combination after third molar surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 60; opioid-free group: 60. **Diagnosis (% of participants):** Impacted or unerupted third molar (100%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: median 25.5; opioid-free group: median 26.5. **Sex (female):** Opioid group: 48%; opioid-free group: 48%. **Ethnicity:** Not reported. **Inclusion criteria:** Age 18-45, required surgical removal of mandibular third molar, healthy, and not using other drugs except oral contraceptives. **Exclusion criteria:** Patients who used steroids in the last month and/or had a medical condition contraindicating the use of any the active agents in Ibumentin or Citodon.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (xylocaine 2% and epinephrine 12.5 ug/ml, 3.6-5.4ml). **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group*** *Medication*: Acetaminophen 1000mg, PO + Codeine 60mg, PO. ***Opioid-free group*** *Medication*: Ibuprofen 600mg, PO. **Post-discharge analgesia:**

	Opioid group *Medication:* Acetaminophen 500mg, every 8 hours around the clock, PO + Codeine 30mg (Citodon) every 8 hours around the clock, PO. *Duration:* 7 days. ***Opioid-free group*** *Medication:* Ibuprofen 600mg, every 8 hours around the clock, PO. *Duration:* 6 days.
Outcomes	**Primary outcome:** Pain scores (worst), visual analogue scale 0-100 mm, median. **Timepoints:** Just after extraction, 2 hours after surgery, 6 hours after surgery, day 1 after surgery (morning, bedtime), day 2 after surgery (morning, bedtime), day 3 after surgery (morning, bedtime), day 4 after surgery (morning, bedtime), day 5 after surgery (morning, bedtime), and day 6 after surgery (morning, bedtime). **Secondary outcomes:** Swelling score, trismus score, CNS-associated adverse events. **Total length of follow up:** 6 days.
Country and setting	**Country:** Sweden **Number of centres:** Multi-centre **Study period:** Not reported.
Source of funding	Not reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were not blinded to the intervention. According to the authors, carers and observers were blinded. No signs of deviations in interventions due to lack of blinding. Rates of non-adherence was consistent with what may have happened in practice. Analysis was 'per protocol' with several patients excluded due to non-adherence. According to the authors, 17 (12%) patients were excluded for non-adherence. This may have impacted study results.
Risk of bias due to missing outcome data.	Low risk.	According to the authors, only one patient was lost to follow up.

Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes; patients were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score at end of surgery, VAS (0-100)	Median 4*	Median 3*
Pain score, 2h after surgery, VAS (0-100)	Median 37*	Median 13*
Pain score, 6h after surgery, VAS (0-100)	Median 26*	Median 10*
Pain score, day 1 after surgery (morning), VAS (0-100)	Median 13*	Median 8*
Pain score, day 1 after surgery (bedtime), VAS (0-100)	Median 18*	Median 14*
Pain score, day 2 after surgery (morning), VAS (0-100)	Median 12*	Median 14*
Pain score, day 2 after surgery (bedtime), VAS (0-100)	Median 15*	Median 14*
Pain score, day 3 after surgery (morning), VAS (0-100)	Median 9*	Median 10*
Pain score, day 3 after surgery (bedtime), VAS (0-100)	Median 7*	Median 10*
Pain score, day 4 after surgery (morning), VAS (0-100)	Median 6*	Median 8*
Pain score, day 4 after surgery (bedtime), VAS (0-100)	Median 6*	Median 7*
Pain score, day 5 after surgery (morning), VAS (0-100)	Median 5*	Median 7*
Pain score, day 5 after surgery (bedtime), VAS (0-100)	Median 3.5*	Median 6.5*
Pain score, day 6 after surgery (morning), VAS (0-100)	Median 3*	Median 5.5*
Pain score, day 6 after surgery (bedtime), VAS (0-100)	Median 2*	Median 6.5*

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Mitchell 2008 (https://pubmed.ncbi.nlm.nih.gov/18308218/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; non-inferiority design (not adaptive). **Study objective:** To compare the efficacy of acetaminophen, codeine, and caffeine (Tylenol No. 3) with acetaminophen and ibuprofen for management of pain after outpatient general surgery procedures. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The sample size was calculated based on the primary outcomes of overall mean daily and maximum pain intensity, as measured by VAS. The authors chose a threshold of 5 mm to ensure that small differences in efficacy could be identified statistically. A sample size of 64 in each group was estimated to have 80% power to detect a difference in means of 5 mm assuming a common standard deviation of 10 mm using a 2-group student's t-test with a 0.05 two-sided significance level. Assuming losses from follow-up and failure to comply with study protocol of 15%, 147 patients were targeted.
Participants	**N randomised:** Opioid group: 74; opioid-free group: 72. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: cholecystectomy (47%), inguinal hernia (34%), umbilical hernia (14%), ventral hernia (5%); opioid-free group: cholecystectomy (49%), inguinal hernia (31%), umbilical hernia (17%), ventral hernia (4%). **Age:** Opioid group: median 46 (IQR 33-55); opioid-free group: median 50 (IQR 38-56). **Sex (female):** Opioid group: 55%; opioid-free group: 53%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients aged 17 to 65 years, undergoing elective outpatient unilateral inguinal hernia repair, umbilical hernia repair, laparoscopic cholecystectomy, or small incisional hernias (5 cm). **Exclusion criteria:** Pre-existing pain condition requiring analgesic, fibromyalgia, recent upper gastrointestinal bleeding, coagulopathy (primary or medication related), serious renal impairment or liver disease, pregnancy, patients with active symptomatic peptic ulcer disease, patients with self-described allergies to acetaminophen, aspirin, any NSAID, or codeine, patients who consented to the study but who required unexpected admission, including those requiring admission because of operative complications.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** General anaesthesia (regimen unclear).

	Inpatient analgesia (after surgery, prior to discharge): Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 300 mg, every 6 hours as needed, PO + Caffeine 15 mg, every 6 hours as needed, PO + Codeine 30 mg, every 6 hours as needed, PO. *Duration:* 7 days. ***Opioid-free group*** *Medication:* Acetaminophen 325 mg, every 6 hours as needed, PO + Ibuprofen 400 mg, every 6 hours as needed, PO. *Duration:* 7 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-100 mm, mean (SD). **Timepoints:** Day 1 after discharge, day 2 after discharge, day 3 after discharge, day 4 after discharge, day 5 after discharge, day 6 after discharge, and day 7 after discharge. **Secondary outcomes:** Time to stopping analgesia, adverse events (any, constipation, nausea, upset stomach), patient satisfaction. **Total length of follow up:** 7 days.
Country and setting	**Country:** Canada. **Number of centres:** Single centre. **Study period:** 2005.
Source of funding	Supported by Capital District Health Authority grant. MacNeil Pharmaceuticals made an unrestricted research grant to the Dalhousie University Department of Surgery; they were not involved in the study design, methodology, data collection, or analysis. MacNeil Pharmaceuticals were not made aware of the results of the study until it was submitted for peer-review presentation.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2**)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Stratified block randomization, using tables of random numbers, was used to ensure equivalent numbers of patients in each treatment group for each of the four procedures. Patients were randomized in groups of 10 and randomization was conducted using a sealed envelope method. The randomization code was concealed from study investigators, nurses, and patients and was kept in sealed envelopes in a secure location until the end of the study.

		Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Patients and carers were blinded. Data were evaluated according to intention to treat.
Risk of bias due to missing outcome data.	Low risk.	According to the authors, only 4% of patients were lost to follow up.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, day 1 after surgery, VAS (0-100)	Mean 39.7 (SD 22.4)	Mean 37.1 (SD 22.0)
Pain score, day 2 after surgery, VAS (0-100)	Mean 44.4 (SD 21.6)	Mean 35.6 (SD 21.6)
Pain score, day 3 after surgery, VAS (0-100)	Mean 36.6 (SD 19.0)	Mean 30.6 (SD 19.8)
Pain score, day 4 after surgery, VAS (0-100)	Mean 29.6 (SD 17.1)	Mean 27.2 (SD 17.1)
Pain score, day 5 after surgery, VAS (0-100)	Mean 27.5 (SD 17.4)	Mean 26.0 (SD 15.3)
Pain score, day 6 after surgery, VAS (0-100)	Mean 24.2 (SD 19.1)	Mean 25.7 (SD 18.4)
Pain score, day 7 after surgery, VAS (0-100)	Mean 24.3 (SD 16.8)	Mean 21.2 (SD 17.6)
Adverse events (any)	Incidence rate 41/71	Incidence rate 28/69
Constipation	Incidence rate 23/71	Incidence rate 17/69
Nausea	Incidence rate 11/71	Incidence rate 5/69
Upset stomach	Incidence rate 6/71	Incidence rate 4/69
Patient satisfaction (dichotomous)	Incidence rate 44/71	Incidence rate 57/69

Mitchell 2012 (https://pubmed.ncbi.nlm.nih.gov/22713999/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare the efficacy of a nonnarcotic approach (acetaminophen and ibuprofen) to T3 after outpatient breast surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The sample size was calculated based on the primary outcomes of overall mean daily and maximum pain intensity, as measured by VAS. The authors chose a threshold of 5 mm to ensure that small differences in efficacy could be identified statistically. A sample size of 64 in each group was estimated to have 80% power to detect a difference in means of 5 mm assuming a common standard deviation of 10 mm using a 2-group student's t-test with a 0.05 two-sided significance level. Assuming losses from follow-up and failure to comply with study protocol of 15%, 147 patients were targeted.
Participants	**N randomised:** Opioid group: 70; opioid-free group: 71. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: lumpectomy (80%), mastectomy (20%); opioid-free group: lumpectomy (79%), mastectomy (21%). **Age:** Opioid group: median 52 (IQR 47-58); opioid-free group: median 52 (IQR 44-61). **Sex (female):** 100%. **Ethnicity:** Not reported. **Inclusion criteria:** Age 18–70 years, undergoing elective lumpectomy or mastectomy, with or without concomitant axillary surgery. **Exclusion criteria:** Pre-existing pain condition requiring analgesia, fibromyalgia, recent upper gastrointestinal bleeding, coagulopathy (primary or medication related), renal impairment, liver disease, and pregnancy, active symptomatic peptic ulcer disease, self-described allergies to acetaminophen, aspirin, any NSAID, patients who consented to the study but who required unexpected admission, including those requiring admission resulting from operative complications.
Procedure characteristics	**Surgical setting:** In-patient. **Surgery location:** Hospital operating room. **Surgical discharge:** Overnight stay. **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** General anaesthesia (regimen unclear).

	Inpatient analgesia (after surgery, prior to discharge): Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 600 mg, every 6 hours as needed, PO + Caffeine 30 mg, every 6 hours as needed, PO + Codeine 60 mg, every 6 hours as needed, PO. *Duration:* 7 days. ***Opioid-free group*** *Medication:* Acetaminophen 650 mg, every 6 hours as needed, PO + Ibuprofen 400 mg, every 6 hours as needed, PO. *Duration:* 7 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-100 mm, mean (SD). **Timepoints:** Day 1 after discharge, day 2 after discharge, day 3 after discharge, day 4 after discharge, day 5 after discharge, day 6 after discharge, and day 7 after discharge. **Secondary outcomes:** Time to stopping analgesia, adverse events (any, constipation, nausea, bleeding), patient satisfaction. **Total length of follow up:** 7 days.
Country and setting	**Country:** Canada. **Number of centres:** Single centre. **Study period:** 2006-2008.
Source of funding	Supported by Capital District Health Authority grant. MacNeil Pharmaceuticals made an unrestricted research grant to the Dalhousie University Department of Surgery; they were not involved in the study design, methodology, data collection, or analysis. MacNeil Pharmaceuticals were not made aware of the results of the study until it was submitted for peer-review presentation.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2**)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Stratified block randomization using tables of random numbers, stratified according to breast surgery type (mastectomy or lumpectomy) and axillary surgery (any or none), was used to ensure equivalent numbers of patients in each treatment group for each of the four procedures. Patients were randomized in groups of 10, and randomization was conducted by a sealed envelope method. The randomization code was concealed from study investigators, nurses, and patients and was kept in sealed envelopes in a secure location until the end of the study.

		Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Patients and carers were blinded. Data were analysed according to intention to treat.
Risk of bias due to missing outcome data.	Low risk.	The authors report that there were no losses of follow-up.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice were appropriate, and the same measurement strategy was used in both groups. Outcome assessors were blinded to the intervention received.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, day 1 after discharge, VAS (0-100)	Mean 20.4 (SD 17.4)	Mean 19.6 (SD 18.2)
Pain score, day 2 after discharge, VAS (0-100)	Mean 17.5 (SD 16.8)	Mean 17.3 (SD 17.4)
Pain score, day 3 after discharge, VAS (0-100)	Mean 17.1 (SD 17.0)	Mean 15.3 (SD 15.9)
Pain score, day 4 after discharge, VAS (0-100)	Mean 14.8 (SD 16.5)	Mean 14.7 (SD 16.4)
Pain score, day 5 after discharge, VAS (0-100)	Mean 12.2 (SD 12.9)	Mean 15.6 (SD 17.9)
Pain score, day 6 after discharge, VAS (0-100)	Mean 12.3 (SD 14.9)	Mean 10.7 (SD 14.6)
Adverse events (any)	Incidence rate 29/70	Incidence rate 30/71
Constipation	Incidence rate 15/70	Incidence rate 10/71
Nausea	Incidence rate 15/70	Incidence rate 7/71
Bleeding	Incidence rate 3/70	Incidence rate 2/71
Patient satisfaction (dichotomous)	Incidence rate 62/70	Incidence rate 65/71

Papoian 2020 (https://pubmed.ncbi.nlm.nih.gov/32127178/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To evaluate the efficacy of nonopioid-based, postoperative analgesia after thyroidectomy. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Sample size was calculated to detect a 1-point difference in the Visual Analog Scale (VAS) pain (2-sided alpha of 5% and beta of 20%). A total of 41 subjects were required in each study arm. With a dropout or loss to follow-up of 20%, each study arm would require 50 patients.
Participants	**N randomised:** Opioid group: 46; opioid-free group: 49. **Diagnosis (%):** Opioid group: nodule (28%), cancer (15%), graves (13%), goiter (43%); opioid-free group: nodule (37%), cancer (18%), graves (12%), goiter (33%). **Surgery:** Opioid group: total thyroidectomy (96%), lobectomy (4%); opioid-free group: total thyroidectomy (94%), lobectomy (6%). **Age:** Opioid group: mean 53; opioid-free group: mean 55. **Sex (% female):** Opioid group: 41%; opioid-free group: 34%. **Ethnicity:** Not reported **Inclusion criteria:** Adult patients over the age 18 undergoing thyroidectomy. **Exclusion criteria:** Current use of opioid pain medications, having used opioid pain medications within 30 days of enrolment, chronic kidney disease, liver disease, other medical reason for which patients cannot tolerate a NSAID or acetaminophen (e.g., allergy, gastrointestinal bleed due to NSAID), the need for a more extensive operation than a thyroid lobectomy or total thyroidectomy with or without central lymph node dissection (e.g., median sternotomy or modified radical neck dissection).
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (1:1 of 0.5% bupivacaine: 1% lidocaine with epinephrine). **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group***

	Medication: Acetaminophen 650 mg, every 4 hours as needed, PO + Oxycodone 5-10 mg, every 4 hours as needed, PO. ***Opioid-free group*** *Medication*: Acetaminophen 650 mg, every 8 hours as needed, PO + Ibuprofen 800 mg every 8 hours as needed, PO. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Oxycodone 5-10 mg, every 4 to 6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Acetaminophen 650 mg, every 8 hours as needed, PO + Ibuprofen 800, every 8 hours as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** 6 hours after discharge, day 1 after discharge, and more than 7 days after discharge. **Secondary outcomes:** Amount of opioid use. **Total length of follow up:** > 7 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2018-2019.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	A pre-generated table with block randomization assignments (block sizes of 2, 4, and 6) was formed by the coinvestigator at the start of the study by use of the service www.randomization.com. Patient assignments were concealed in sequential envelopes by a coinvestigator and were not known by the recruiter until the patient was enrolled into the study and the sequential envelope was unsealed (unclear if envelopes were opaque). Unclear when randomization was conducted. Baseline characteristics were similar between groups.

Risk of bias due to deviation from intended interventions.	Some concerns.	Participants and carers were not blinded. Deviations arose because of the trial context such as drug discontinuation and switching. This is consistent with what may have happened in practice. Analyses followed the intention to treat principle.
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Other data (e.g., complications, ED visits, readmissions) were collected by a blinded research assistant. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, 6 hours after discharge, VAS (0-100)	Mean 3.0 (SD 3.0)	Mean 2.8 (SD 2.1)
Pain score, day 1 after discharge, VAS (0-100)	Mean 2.4 (SD 2.5)	Mean 1.6 (SD 2.2)
Pain score, > day 7 after discharge, VAS (0-100)	Mean 0.1 (SD 0.6)	Mean 0.2 (SD 0.8)

Petrikovets 2019 (https://pubmed.ncbi.nlm.nih.gov/31201808/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To determine whether, icepacks, Tylenol, and Toradol has improved pain control compared with the standard postoperative pain regimen in patients undergoing inpatient vaginal pelvic reconstructive surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The authors estimated that 27 patients in each arm would be needed to achieve 90% power to detect a mean difference of approximately 25mm on a 100mm VAS scale for a significance level of 0.05. This difference was selected based on articles stating that a VAS pain score difference between 20mm to 30mm is significant for most patients. They targeted the enrolment of 33 patients in each arm to account for loss to follow-up.
Participants	**N randomised:** Opioid group: 33; opioid-free group: 30. **Diagnosis (% of participants):** Opioid group: Pelvic organ prolapse (100%), Stress urinary incontinence (39.4%), abnormal uterine bleeding (9.1%); opioid-free group: Pelvic organ prolapse (96.7%), Stress urinary incontinence (46.7%), abnormal uterine bleeding (3.3%), cervical dysplasia (3.3%). **Surgery:** Opioid group: Vaginal hysterectomy (55%), trachelectomy (1%), sacrospinous ligament fixation (18%), uterosacral ligament suspension (58%), colocleisis (9%), retropubic midurethral sling (42%), anterior colporrhaphy (30%), posterior colporrhaphy (45%), perineorrhaphy (49%), McCall culdoplasty (49%), bilateral salpingectomy (49%), bilateral salpingoophorectomy (3%), cystoscopy (97%); Opioid-free group: Vaginal hysterectomy (66.7%), sacrospinous ligament fixation (23%), uterosacral ligament suspension (63%), colocleisis (7%), retropubic midurethral sling (53%), anterior colporrhaphy (27%), posterior colporrhaphy (33%), perineorrhaphy (40%), McCall culdoplasty (43%), bilateral salpingectomy (50%), bilateral salpingoophorectomy (13%), cystoscopy (100%). **Age:** Opioid group: Mean 59.8 (SD 12.7); opioid-free group: Mean 61.8 (SD 10.1). **Sex (female):** 100%. **Ethnicity:** Opioid group: White (85%), African American (15%), Hispanic (0%); opioid-free group: White (67%), African American (23%), Hispanic (10%). **Inclusion criteria:** Patients at least 18 years of age, English speakers, able to read and understand VAS, admitted overnight after vaginal pelvic reconstructive surgery. **Exclusion criteria:** History of chronic pelvic pain, history of illicit drug use, liver disease, renal disease, cardiac disease, dementia, allergy to any of the study medications, NSAID intolerance, currently using daily analgesics or sedatives, had a planned or unplanned abdominal or laparoscopic procedure.
Procedure characteristics	**Surgical setting:** In-patient. **Surgery location:** Hospital operating room. **Surgical discharge:** Overnight stay.

	Surgery classification: Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** General anaesthesia (regimen not specified) + Ketorolac 30 mg IV. **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group*** *Medication*: Ibuprofen 600 mg, every 4 hours as needed, PO + Acetaminophen 325-650 mg, every 4-6 hours as needed, PO + Oxycodone 5-10 mg, every 4-6 hours as needed, PO + Hydromorphone 0.2 mg, every 3 hours as needed for breakthrough pain, IV. ***Opioid-free group*** *Medication*: Ice packs for 20 min, every 2 hours around the clock + Acetaminophen 1000 mg, every 6 hours around the clock, PO + Ketorolac 30 mg, every 6 hours around the clock, IV + Hydromorphone 0.2 mg, every 3 hours as needed for breakthrough pain, IV. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Ibuprofen 600 mg, every 8 hours as needed, PO + Acetaminophen 325 mg, every 4-6 hours as needed, PO + Oxycodone 5 mg, every 4-6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 6 hours as needed, PO + Ketorolac 10 mg, every 6 hours as needed, PO. *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, median (IQR). **Timepoints:** After discharge in the morning and day 3 after discharge. **Secondary outcomes:** Quality of recovery, patient satisfaction, narcotic use, adverse events (itching, shortness of breath), and emergency department visits. **Total length of follow up:** 5 days.
Country and setting	**Country:** United States. **Number of centres:** Multi-centre. **Study period:** 2017-2018
Source of funding	Not reported.

Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	A statistician developed the 1:1 mixed block randomization sequence using a random number generator; only the statistician was aware of the sequence. Patients were randomized at the end of surgery using sequentially numbered opaque sealed envelopes. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were not blinded to the allocated intervention. Carers were not blinded to the allocated intervention. Two patients withdrew consent because of the trial arm they were allocated to (non-opioid); but for patients who received the intervention there were no signs of deviations in interventions due to lack of blinding. It is unclear whether the analysis was per protocol or according to intention-to-treat.
Risk of bias due to missing outcome data.	High risk.	The authors state that missing data was minimal, but do not report rates of missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events). The authors do not report reasons for not retuning questionnaires, or between-group comparison in rates of missing data.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Other data (e.g., complications, ED visits, readmissions) were collected by a blinded research assistant. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, after discharge in the morning, VAS (0-10)	Median 4 (IQR 2-5)	Median 2 (IQR 1-2)
Pain score, day 3 after discharge, VAS (0-10)	Median 3 (IQR 1.5-5)	Median 2 (IQR 0-3)
Patient satisfaction	Median 9 (IQR 8-10)	Median 10 (IQR 8-10)
Itching	Incidence rate 6.1%	Incidence rate 0%
Shortness of breath	Incidence rate 0%	Incidence rate 0%

Emergency department visit	Incidence rate 0%	Incidence rate 3.4%
Quality of recovery (QoR-40)	Median 184 (IQR 166-192)*	Median 187 (IQR 178-190)*

*Quality of recovery was standardised to QoR-9 scores as described in the appendix (pp 156-157).

Raeder 2001 (https://pubmed.ncbi.nlm.nih.gov/11375827/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare ibuprofen with codeine/acetaminophen for pain control during the first 72 h after ambulatory surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 53; Opioid-free group: 51. **Diagnosis (% of participants):** Not reported. **Surgery:** Hernia repair, haemorrhoidectomy, varicose vein excision. **Age:** Not reported. **Sex (female):** Not reported. **Ethnicity:** Not reported. **Inclusion criteria:** Adult patients scheduled for elective hernia repair, haemorrhoidectomy, or varicose vein resection. **Exclusion criteria:** History of allergic reactions or side effects with aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs; opioid-containing oral analgesic use.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** IV midazolam + General anesthesia (fentanyl + propofol). Maintenance with oxygen + alfentanil + Ketorolac 30mg IV + Lidocaine 10mg/mL IV + Acetaminophen 1000mg PR. **Inpatient analgesia (after surgery, prior to discharge):** Fentanyl 0.5 ug/kg IV. **Post-discharge analgesia:** ***Opioid group*** *Medication*: Acetaminophen 800 mg, every 8 hours around the clock, PO + Codeine 60 mg, every 8 hours around the clock, PO.

	Duration: 3 days. ***Opioid-free group*** *Medication:* Ibuprofen 800 mg, every 8 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores (worst), visual analogue scale 0-10 cm, mean (SD). **Timepoints:** day 1 after surgery and day 3 after surgery. **Secondary outcomes:** Adverse events (nausea, constipation). **Total length of follow up:** 3 days.
Country and setting	**Country:** Norway **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Research grant from Weiders Pharmaceuticals, Norway
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization or concealment of allocation is reported. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	The study is described as a double-blinded trial. It is assumed that participants, carers, and people delivering the interventions were blinded. There is no information as to whether the analysis was 'per protocol' or 'intention-to-treat'.
Risk of bias due to missing outcome data.	Some concerns.	12 patients (10%) did not return the questionnaires. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events). The authors do not report reasons for not retuning questionnaires. Rates of missing data were similar between groups (7 vs 5).
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded to treatment allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score, day 1 after surgery, VAS (0-10)	Mean 5.2 (SD 3.0)	Mean 5.4 (SD 2.5)
Pain score, day 3 after surgery, VAS (0-10)	Mean 4.8 (SD 2.8)	Mean 4.7 (SD 2.7)
Nausea	Incidence rate 43%	Incidence rate 35%
Constipation	Incidence rate 70%	Incidence rate 32%

Samieirad 2017 (https://pubmed.ncbi.nlm.nih.gov/28864284/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare caffeine containing versus codeine-containing analgesics in relation to their anti-inflammatory and analgesic effects after dental implant surgeries. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 40; opioid-free group: 40. **Diagnosis (% of participants):** Edentulism (100%). **Surgery:** Single implants (100%). **Age:** Opioid group: mean 41.5 (SD 5.3); opioid-free group: mean 40.5 (SD 4.8). **Sex (female):** Opioid group: 50%; Opioid-free group: 50%. **Ethnicity:** Not reported. **Inclusion criteria:** Systemically healthy, ASA Class I or II, age range 35-55. **Exclusion criteria:** Serious medical or mental condition, risk of infectious endocarditis, acute local infection, bleeding disorder, known sensitivity to NSAIDs, codeine, caffeine, and/or acetaminophen, pregnancy or lactation, history of asthma, history of drug, or alcohol abuse, taking an investigational drug, making a blood donation within the previous months.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication*: Acetaminophen 300 mg, every 6 hours around the clock, PO + Codeine 20 mg, every 6 hours around the clock, PO.

	Duration: 3 days. ***Opioid-free group*** *Medication:* Acetaminophen 300 mg, every 6 hours around the clock, PO + Caffeine 20 mg, every 6 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** Just after surgery, 3 hours after surgery, 6 hours after surgery, 12 hours after surgery, 24 hours after surgery, 48 hours after surgery, 72 hours after surgery, and 1 week after surgery. **Secondary outcomes:** Swelling. **Total length of follow up:** 7 days.
Country and setting	**Country:** Iran. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Research Counselor of Mashhad University of Medical Sciences (Grant No: 123/95).
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	In line with Consort guidelines, random codes were applied according to the number of patients and drugs, and each patient was randomly categorized with a code. Then, according to that code, a drug package was delivered by the student. This procedure was executed randomly; therefore, neither the patient nor the surgeon and statistician were aware of the pharmaceutical packages involved, and the student was the only informed person (triple-blind, randomized clinical trial). In the results, it is specified that randomization was computer-generated. The packing involved putting ten acetaminophen caffeine tablets in 40 packages, and ten acetaminophen-codeine tablets in another 40 packages with the same form and appearance. All the packages were labelled and numbered randomly. Prior to the surgery each patient was given a package. The randomization code was concealed from the study investigators, nurses, and patients, and kept in a secure location until the end of the study. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants and carers were blinded to group allocation. A per protocol analysis was conducted: patients who required other medications were excluded. Only two patients were excluded because of 'self-medication'.
Risk of bias due to missing outcome data.	Low risk.	Only 2 patients did not return the evaluation sheets (2%).

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded to treatment allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, 30 min after surgery, VAS (0-10)	Mean 0.56 (SD 0.616)	Mean 0.44 (SD 0.616)
Pain score, 3h after surgery, VAS (0-10)	Mean 4 (SD 1.572)	Mean 5.61 (SD 1.243)
Pain score, 6h after surgery, VAS (0-10)	Mean 4.39 (SD 1.614)	Mean 6.06 (SD 1.259)
Pain score, 12h after surgery, VAS (0-10)	Mean 3.22 (SD 1.003)	Mean 5.17 (SD 1.757)
Pain score, 24h after surgery, VAS (0-10)	Mean 2.39 (SD 1.037)	Mean 2.94 (SD 0.735)
Pain score, 48h after surgery, VAS (0-10)	Mean 0.78 (SD 1.166)	Mean 0.94 (SD 0.416)
Pain score, 72h after surgery, VAS (0-10)	Mean 0.28 (SD 0.575)	Mean 0.67 (SD 0.686)
Pain score, 1 week after surgery, VAS (0-10)	Mean 0 (SD 0)	Mean 0.17 (SD 0.383)

Shah 2008 (https://www.semanticscholar.org/paper/COMPARISON-OF-ANALGESIC-EFFICACY-OF-TRAMADOL-WITH-Shah-Zaeem/03081533b12ded300e34d745044626bb41b46d6a**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To find a safe and effective analgesic alternative to non-steroidal anti-inflammatory drugs (NSAIDs) for patients undergoing dento-alveolar surgery who could not tolerate NSAIDs. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 30; opioid-free group: 29. **Diagnosis (% of participants):** Not reported. **Surgery:** Dento-alveolar surgery (100%). **Age:** Opioid group: mean 34.6; opioid-free group: mean 34.4. **Sex (female):** Opioid group: 50%; opioid-free group: 45%. **Ethnicity:** Not reported. **Inclusion criteria:** Underwent surgical removal of one of their impacted mandibular third molars. **Exclusion criteria:** Receiving any potent analgesic; history of asthma, peptic ulcer, chronic opiate abuse; contraindication to NSAIDs or opiates.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (regimen unclear). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Tramadol 50 mg, every 8 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group***

	Medication: Diclofenac 50 mg, every 8 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, median. **Timepoints:** 6 hours after surgery, 12 hours after surgery, 24 hours after surgery, 48 hours after surgery, and 72 hours after surgery. **Secondary outcomes:** Adverse events (any, nausea, indigestion). **Total length of follow up:** 3 days.
Country and setting	**Country:** Pakistan. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	Author's judgement	Support for judgement
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized trial but no information about randomization nor concealment of allocation is reported. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	The authors described that patients were blinded. The trial is described as 'double-blind'. We assume that carers were blinded. There is no information as to whether the analysis was per protocol or according to intention to treat.
Risk of bias due to missing outcome data.	Low risk.	According to the authors, data from only one patient was missing.
Risk of bias in measurement of the outcome.	Low.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded to treatment allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	Opioid group	Opioid-free group
Pain score, 6h after surgery, VAS (0-10)	Median 5*	Median 5*
Pain score, 12h after surgery, VAS (0-10)	Median 3*	Median 4*

Pain score, 24h after surgery, VAS (0-10)	Median 3*	Median 4*
Pain score, 48h after surgery, VAS (0-10)	Median 1*	Median 1*
Pain score, 72h after surgery, VAS (0-10)	Median 1*	Median 1*
Adverse events (overall)	Incidence rate 2/30	Incidence rate 1/29
Nausea	Incidence rate 2/30	Incidence rate 0/29
Dyspepsia	Incidence rate 0/30	Incidence rate 1/29

*Median data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Spagnoli 2011 (https://pubmed.ncbi.nlm.nih.gov/21471550/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To compare the efficacy and effectiveness between an analgesic combination of tramadol/paracetamol (37.5+325 mg), and paracetamol monotherapy (1000 mg) for acute postoperative pain after hand and foot surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1. **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 57; opioid-free group 57. **Diagnosis (% of participants):** Opioid group: carpal tunnel syndrome (35%), Guyon canal syndrome (5%), Dupuytren disease (7%), de Quervain's tenosynovitis (5%), hallux valgus (9%), claw-finger (7%), mallet-finger (11%), tarsal tunnel syndrome (5%), distal necrosis (7%), trauma (9%). opioid-free group: carpal tunnel syndrome (30%), Guyon canal syndrome (5%), Dupuytren disease (7%), de Quervain's tenosynovitis (5%), hallux valgus (12%), claw-finger (7%), mallet-finger (11%), tarsal tunnel syndrome (5%), distal necrosis (5%), trauma (12%). **Surgery:** Hand and foot surgery (100%). **Age:** Opioid group: mean 56.69; opioid-free group: mean 56.81. **Sex (female):** Opioid group: 60%; opioid-free group: 56%. **Ethnicity:** Not reported. **Inclusion criteria:** Diagnosis of carpal tunnel syndrome, Guyon canal syndrome, Dupuytren disease, De Quervain's tenosynovitis, hallux valgus, claw-finger and mallet-finger of the hand or foot, tarsal tunnel syndrome, necrosis of the distal phalanx by scleroderma, or hand trauma; ASA class I, II, III **Exclusion criteria**: Alcoholism; drug dependency; psychiatric disease; pregnancy and lactation; history of allergy; hypersensitivity to tramadol or paracetamol; ASA IV.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Brachial plexus block (2% lidocaine, 10 mL). **Inpatient analgesia (after surgery, prior to discharge):**

	Opioid group: *Medication*: Acetaminophen 325 mg, one dose, PO + Tramadol 37.5 mg, one dose, PO. ***Opioid-free group*** *Medication*: Acetaminophen 1000 mg, one dose, PO. **Post-discharge analgesia:** ***Opioid group*** *Medication*: Acetaminophen 325 mg, every 12 hours around the clock, PO + Tramadol 37.5 mg, every 12 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group*** *Medication*: Acetaminophen 1000 mg, every 12 hours around the clock, PO. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-4 cm, mean. **Timepoints:** 6 hours after surgery, 12 hours after surgery, 24 hours after surgery, 48 hours after surgery, 72 hours after surgery, and 7 days after surgery. **Secondary outcomes:** Adverse events (nausea/vomiting, itching, headache, dizziness, serious adverse events). **Total length of follow up:** 7 days.
Country and setting	**Country:** Italy. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. The authors state that medication bottles were labeled with a code, but no further information is provided regarding concealment of allocation. Demographic characteristics were similar between groups.

Risk of bias due to deviation from intended interventions.	High risk.	The study was deemed single blind. It's reasonable to assume that patients were blinded to allocation. Carers seemed to be aware of the intervention. There were no signs of deviations in interventions due to lack of blinding. There is no information as to whether the analysis was per protocol or according to intention to treat.
Risk of bias due to missing outcome data.	High risk.	There is no information regarding rates of missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e, pain or adverse events).
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded to treatment allocation.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, 6h after surgery, VAS (0-4)	Mean 0.40*	Mean 1.92*
Pain score, 12h after surgery, VAS (0-4)	Mean 0.05*	Mean 0.63*
Pain score, 24h after surgery, VAS (0-4)	Mean 0*	Mean 0.36*
Pain score, 72h after surgery, VAS (0-4)	Mean 0*	Mean 0*
Pain score, 1 week after surgery, VAS (0-4)	Mean 0*	Mean 0*
PONV	Incidence rate 2/57	Incidence rate 1/57
Itching	Incidence rate 1/57	Incidence rate 1/57
Headache	Incidence rate 0/57	Incidence rate 0/57
Dizziness	Incidence rate 0/57	Incidence rate 0/57

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Stessel 2014 (https://pubmed.ncbi.nlm.nih.gov/25516773/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare the efficacy of paracetamol/controlled release (CR) oxycodone and paracetamol/naproxen for treatment of acute postoperative pain at home after ambulatory surgery. **Number of arms:** 3 (2 opioid-based; 1 opioid-free). **Randomization ratio:** 1:1:1 **Power (sample size calculation):** The statistical power analysis was based on a calculation using an SD of 22 for the postoperative VAS scores. To detect a difference of 15 with a power of 0.80 and α=0.05, 35 patients in each group were deemed to be required.
Participants	**N randomised:** Opioid group 1: 35; opioid group 2: 35; opioid-free group 35. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group 1: laparoscopic inguinal hernia repair (17%), open inguinal hernia repair (6%), arthroscopy (77%); opioid group 2: laparoscopic inguinal hernia repair (14%), open inguinal hernia repair (9%), arthroscopy (77%); opioid-free group: laparoscopic inguinal hernia repair (17%), open inguinal hernia repair (6%), arthroscopy (77%). **Age:** Opioid group 1: mean 45.1 (SD 14.2); opioid-group 2: mean 48.5 (SD 10.2); opioid-free group: mean 45.2 (SD 14.2). **Sex (% female):** Opioid group 1: 26%; opioid group 2: 23%; opioid-free group: 31%. **Ethnicity:** Not reported. **Inclusion criteria:** Scheduled for painful ambulatory surgery (i.e., knee arthroscopy and unilateral open or laparoscopic inguinal hernia repair); aged 18 to 70 years; ASA I or II. **Exclusion criteria:** Cognitive impairment, preoperative pharmacologic pain treatment, allergy to or a contraindication for taking the study medication, porphyria, pregnancy or lactation, history of severe renal, hepatic, pulmonary, or cardiac failure, current symptoms or history of gastrointestinal bleeding, ileus, chronic obstipation, history of substance abuse; use of medication with a suppressive effect on the central nervous system.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.

Interventions	**Intraoperative anaesthesia:** Spinal anaesthesia (hyperbaric bupivacaine 10-15mg, 0.5% or plain lidocaine 60-80mg, 2%); or general anaesthesia (propofol 1.5–2 mg/kg iv and sufentanil 0.1–0.3µg/kg); or spinal anaesthesia to general anaesthesia. **Inpatient analgesia (after surgery, prior to discharge):** Piritramide 0.1 mg/kg IV bolus. **Post-discharge analgesia:** ***Opioid group 1*** *Medication*: Acetaminophen 1000 mg, every 6 hours around the clock, PO + Oxycodone 10 mg, every 12 hours around the clock, PO. *Duration:* 2 days. ***Opioid group 2*** *Medication*: Acetaminophen 1000 mg, every 6 hours around the clock, PO + Oxycodone 10 mg, every 12 hours around the clock, PO. *Duration:* 2 days. ***Opioid-free group*** *Medication:* Acetaminophen 1000 mg, every 6 hours around the clock, PO + Naproxen 500 mg every 12 hours around the clock, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain scores (movement), visual analogue scale 0-100 mm, median (IQR). **Timepoints:** 24 hours after surgery, 30 hours after surgery, 36 hours after surgery, 48 hours after surgery, 54 hours after surgery, and 60 hours after surgery. **Secondary outcomes:** Patient satisfaction, adverse events (fatigue, nausea, vomiting, micturition problems, constipation, pruritus), clinic visit. **Total length of follow up:** Not reported.
Country and setting	**Country:** Netherlands. **Number of centres:** Single centre. **Study period:** 2007-2009.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**

Risk of bias arising from the randomization process.	Some concerns.	Patients were randomized according to a computer-generated list. No information is provided regarding concealment of allocation. Demographic characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Patients and carers were not blinded to group allocation. There are no signs of deviations in interventions due to lack of blinding. Intention-to-treat analysis was reported.
Risk of bias due to missing outcome data.	Low risk.	Only four (4%) patients did not return the pain diary.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were not blinded to treatment allocation. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group 1**	**Opioid group 2**	**Opioid-free group**
Pain score, 24h after surgery, VAS (0-100)	Median 30 (IQR 10-58)*	Median 20 (IQR 6-51)*	Median 26 (IQR 2-52)*
Pain score, 30h after surgery, VAS (0-100)	Median 23 (IQR 8-45)*	Median 18 (IQR 5-39)*	Median 26 (IQR 3-44)*
Pain score, 36h after surgery, VAS (0-100)	Median 24 (IQR 8-42)*	Median 12 (IQR 3-33)*	Median 19 (IQR 2-34)*
Pain score, 48h after surgery, VAS (0-100)	Median 15 (IQR 6-33)*	Median 14 (IQR 2-39)*	Median 11 (IQR 1-27)*
Pain score, 54h after surgery, VAS (0-100)	Median 11 (IQR 8-33)*	Median 8 (IQR 2-23)*	Median 8 (IQR 2-20)*
Pain score, 60h after surgery, VAS (0-100)	Median 15 (IQR 7-38)*	Median 8 (IQR 2-19)*	Median 6 (IQR 2-16)*
Pain satisfaction, Likert scale (0-10)[†]	Mean 8.1 (SD 1.5)	Mean 8.6 (SD 1.1)	Mean 8.3 (SD 1.7)
Nausea	Incidence 7/35	Incidence 8/35	Incidence 5/35
Vomiting	Incidence 0/35	Incidence 1/35	Incidence 0/35
Micturition problems	Incidence 0/35	Incidence 1/35	Incidence 0/35
Constipation	Incidence 4/35	Incidence 11/35	Incidence 12/35
Pruritus	Incidence 3/35	Incidence 8/35	Incidence 7/35
Clinic visit	Incidence 0/35	Incidence 0/35	Incidence 3/35

*Median and IQR data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]
†Patient satisfaction data were dichotomized to facilitate interpretation (dissatisfied <5/10; not dissatisfied ≥510).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Torabinejad 1994 (https://pubmed.ncbi.nlm.nih.gov/7996111/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial, design unclear. **Study objective:** To compare the effectiveness of nine medications and a placebo in controlling pain following obturation. **Number of arms:** 10 (1 opioid analgesia, 9 opioid-free analgesia). **Randomization ratio:** 1:1:1:1:1:1:1:1:1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 29; opioid-free group 1: 43; opioid-free group 2: 45; opioid-free group 3: 48; opioid-free group 4: 39; opioid-free group 5: 46; opioid-free group 6: 33; opioid-free group 7: 49; opioid-free group 8: 38; opioid-free group 9: 41. **Diagnosis (% of participants):** Not reported. **Surgery:** Root canal obturation (100%). **Age:** Not reported. **Sex (female):** Not reported. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, undergoing root canal obturation. **Exclusion criteria:** History of allergy to medications used in this study, severe pain and/or swelling who need additional treatment procedures, on anti-inflammatory, antibiotic, or sedative medications, required concurrent use of other drugs that might have increased or reduced the effects of the test medications, were unable or unwilling, root canal therapy was completed in one visit.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (regimen unclear). **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group*** *Medication:* Acetaminophen 325 mg, single dose, PO + Codeine 60 mg, single dose, PO. ***Opioid-free group 1***

Medication: Aspirin 650 mg, every 6 hours, as needed, PO.

Opioid-free group 2

Medication: Acetaminophen 650 mg, single dose, PO.

Opioid-free group 3

Medication: Ibuprofen 400 mg, single dose, PO.

Opioid-free group 4

Medication: Ketoprofen 50 mg, single dose, PO.

Opioid-free group 5

Medication: Penicillin 500 mg, single dose, PO.

Opioid-free group 6

Medication: Erythromycin 2x250 mg, single dose, PO.

Opioid-free group 7

Medication: Penicillin 500 mg, single dose, PO + Ibuprofen 400 mg, single dose, PO.

Opioid-free group 8

Medication: Methylprednisolone 2 mg, single dose, PO + Penicillin 500 mg, single dose, PO.

Opioid-free group 9

Medication: Placebo.

Post-discharge analgesia:

Opioid group

Medication: Acetaminophen 325 mg, every 6 hours around the clock, PO + Codeine 60 mg, every 6 hours around the clock, PO.

Duration: 3 days.

Opioid-free group 1

Medication: Aspirin 650 mg, every 6 hours around the clock, PO.

Duration: 3 days.

Opioid-free group 2

Medication: Acetaminophen 650 mg, every 6 hours around the clock, PO.

Duration: 3 days.

	Opioid-free group 3 *Medication:* Ibuprofen 400 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 4*** *Medication:* Ketoprofen 50 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 5 (excluded from meta-analysis; no pain medication)*** *Medication:* Penicillin 500 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 6 (excluded from meta-analysis; no pain medication)*** *Medication:* Erythromycin 2x250 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 7*** *Medication:* Penicillin 500 mg, every 6 hours around the clock, PO + Ibuprofen 400 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 8*** *Medication:* Methylprednisolone 2 mg, every 6 hours around the clock, PO + Penicillin 500 mg, every 6 hours around the clock, PO. *Duration:* 3 days. ***Opioid-free group 9 (excluded from meta-analysis; no pain medication)*** *Medication:* Placebo. *Duration:* 3 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-9 cm, mean. **Timepoints:** Just after surgery, 6 hours after surgery, 12 hours after surgery, 18 hours after surgery, 24 hours after surgery, 30 hours after surgery, and 36 hours after surgery. **Secondary outcomes:** Not reported. **Total length of follow up:** 3 days.
Country and setting	**Country:** United States.

Number of centres: Single centre.

Study period: Not reported.

Source of funding	Not reported
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization nor concealment of allocation. Demographic characteristics were not reported.
Risk of bias due to deviation from intended interventions.	Some concerns.	The authors mention that capsules were identical, so it can be assumed that patients were blinded. There is no information regarding blinding of carers. There are no signs of deviations in interventions due to lack of blinding. There is no information regarding deviations from the intended intervention. There is no information as to whether the analysis was per protocol or according to intention-to-treat.
Risk of bias due to missing outcome data.	Some concerns.	38 patients were excluded (dropped-out) from the study. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes; it is unclear if patients were blinded. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group 1***	**Opioid-free group 2***	**Opioid-free group 3***	**Opioid-free group 4***	**Opioid-free group 7***	**Opioid-free group 8***
Pain score, just after surgery, VAS (0-9)	Mean 0.68†	Mean 0.42†	Mean 0.68†	Mean 0.52†	Mean 0.5†	Mean 0.36†	Mean 0.4†
Pain score, 6h after surgery, VAS (0-9)	Mean 1.4†	Mean 0.96†	Mean 1.4†	Mean 0.9†	Mean 0.92†	Mean 1.06†	Mean 1.18†
Pain score, 12h after surgery, VAS (0-9)	Mean 1.32†	Mean 0.8†	Mean 1.24†	Mean 1.0†	Mean 0.8†	Mean 0.74†	Mean 0.78†

Pain score, 18h after surgery, VAS (0-9)	Mean 1.04†	Mean 0.76†	Mean 1.04†	Mean 0.8†	Mean 0.92†	Mean 0.54†	Mean 0.6†
Pain score, 24h after surgery, VAS (0-9)	Mean 0.9†	Mean 0.4†	Mean 0.92†	Mean 0.7†	Mean 0.56†	Mean 0.6†	Mean 0.52†
Pain score, 30h after surgery, VAS (0-9)	Mean 0.74†	Mean 0.34†	Mean 0.92†	Mean 0.62†	Mean 0.58†	Mean 0.36†	Mean 0.36†
Pain score, 36h after surgery, VAS (0-9)	Mean 0.44†	Mean 0.28†	Mean 0.84†	Mean 0.32†	Mean 0.44†	Mean 0.36†	Mean 0.36†

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

†SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Vallecillo 2021 (https://pubmed.ncbi.nlm.nih.gov/34922724/**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare the analgesic effectiveness, swelling, and adverse events after impacted third molar surgery following multimodal therapy with 75mgtramadol hydrochloride plus 25mg dexketoprofen or monotherapy with 400mg ibuprofen. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** The sample was determined with a confidence level of 95% and a power of 90%. A sample size was calculated to detect a 2-point difference on the pain scale with a standard deviation of 2.5 based on previous studies, resulting in a targeted sample size of 68 patients.
Participants	**N randomised:** Opioid group: 36; opioid-free group: 34. **Diagnosis (% of participants):** Opioid group: lower left third molar (55.6%), lower right third molar (44.4%), periosteal tear (28.6%); opioid-free group: lower left third molar (47.1%), lower right third molar (52.9%), periosteal tear (26.5%). **Surgery:** 3rd molar extraction (100%). **Age:** Opioid group: 30.6% age <20, 30.6% age 20-24, 13.9% age 25-29, 25% age >30; opioid-free group: 20.6% age <20, 38.2% age 20-24, 23.5% age 25-29, 17.6% age >30. **Sex (% female):** Opioid group:63.9%; opioid-free group: 50%. **Ethnicity:** Not reported. **Inclusion criteria:** Adults (>18 years), volunteer patients of the Master of Oral Surgery and Implantology demanding an extraction of a third lower molar; ASA I. **Exclusion criteria:** Pregnant or breastfeeding period (for the risk of undergoing such an intervention and for the non-recommendation to take the medication used in the study during breastfeeding), patients with some systemic pathology that may alter the results of the study or that the study medication may interfere with the patient's base medication, patients with known allergies to any of the study medications, patients who have taken antibiotics or analgesics 24 hours before the surgery, patients with pericoronitis days before surgery.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (4 % articaine with 1: 100,000 epinephrine).

	Inpatient analgesia (after surgery, prior to discharge): Acetaminophen 1000 mg, once as needed for breakthrough pain, PO. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Dexketoprofen 25 mg, every 8 hours around the clock, PO + Tramadol 75 mg, every 8 hours around the clock, PO. *Duration:* 2 days. ***Opioid-free group*** *Medication*: Ibuprofen 400 mg, every 8 hours around the clock, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (95% CI). **Timepoints:** Just after extraction, 1 hour after surgery, 2 hours after surgery, 4 hours after surgery, 6 hours after surgery, 8 hours after surgery, 12 hours after surgery, 24 hours after surgery, 36 hours after surgery, and 48 hours after surgery. **Secondary outcomes:** Number of tablets taken, adverse events (overall, nausea, headache, drowsiness, vomiting, trembling, indigestion, diarrhoea, bleeding, confusion), patient satisfaction. **Total length of follow up:** 2 days.
Country and setting	**Country:** Spain. **Number of centres:** Single centre. **Study period:** 2019.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Patients were consecutively admitted in the study following a scheme of balanced randomization every 8 patients (4 patients per group) using a computer-generated randomization sequence, up to have 72 patients (block randomization with known block sizes). The assignments were stored in numbered sealed envelopes and opened after surgery by a clinician not involved in the perioperative evaluation to provide medication to patients. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	All data were gathered by the main researcher, who was blinded to the group assignment. Also, none of the patients or surgeons were aware of the treatment

		condition. The analysis was likely per protocol as 1 patient was excluded for non-compliance.
Risk of bias due to missing outcome data.	Low risk.	Only 2 patients (3%) were lost to follow up.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were blinded to group allocation.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, 0h after surgery, VAS (0-10)	Mean 0.72*	Mean 0.85, 95%CI (0.2-1.51)*
Pain score, 1h after surgery, VAS (0-10)	Mean 1.17, 95%CI (0.57-1.76)*	Mean 1.74, 95%CI (0.89-2.58)*
Pain score, 2h after surgery, VAS (0-10)	Mean 1.53, 95%CI (0.89-2.17)*	Mean 2.12, 95%CI (1.4-2.84)*
Pain score, 4h after surgery, VAS (0-10)	Mean 2.56, 95%CI (1.87-3.24)*	Mean 2.94, 95%CI (1.4-2.84)*
Pain score, 6h after surgery, VAS (0-10)	Mean 2.69, 95%CI (1.95-3.43)*	Mean 3.71, 95%CI (2.66-4.76)*
Pain score, 8h after surgery, VAS (0-10)	Mean 2.86, 95%CI (1.98-3.74)*	Mean 3.88, 95%CI (2.9-4.86)*
Pain score, 12h after surgery, VAS (0-10)	Mean 2.42, 95%CI (1.52-3.31)*	Mean 3.26, 95%CI (2.33-4.2)*
Pain score, 24h after surgery, VAS (0-10)	Mean 2.78, 95%CI (1.72-3.84)*	Mean 3.15, 95%CI (2.21-4.08)*
Pain score, 36h after surgery, VAS (0-10)	Mean 2.61, 95%CI (1.64-3.58)*	Mean 3.03, 95%CI (2.16-3.9)*
Pain score, 48h after surgery, VAS (0-10)	Mean 2.78, 95%CI (1.84-3.72)*	Mean 2.41, 95%CI (1.61-3.21)*
Adverse events (overall)	Incidence rate 15/36	Incidence rate 3/34
Nausea	Incidence rate 7/36	Incidence rate 0/34
Headache	Incidence rate 3/36	Incidence rate 0/34
Drowsiness	Incidence rate 3/36	Incidence rate 1/34
Vomiting	Incidence rate 9/36	Incidence rate 0/34
Indigestion	Incidence rate 0/36	Incidence rate 0/34
Diarrhoea	Incidence rate 0/36	Incidence rate 0/34
Bleeding	Incidence rate 0/36	Incidence rate 1/34

Confusion	Incidence rate 1/36	Incidence rate 0/34
Patient satisfaction†	Incidence rate 0/36	Incidence rate 1/34
Poor	Incidence rate 1/36	Incidence rate 0/34
Acceptable	Incidence rate 6/36	Incidence rate 9/34
Good	Incidence rate 18/36	Incidence rate 14/34
Very good	Incidence rate 11/36	Incidence rate 11/34

*Mean and 95%CI data were transformed into mean and SD according to methods described in the Cochrane Handbook.[1]

†Ordinal scales were dichotomized to facilitate interpretation (dissatisfied = poor; not dissatisfied = acceptable, good, or very good).

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Walton 1990 (https://pubmed.ncbi.nlm.nih.gov/2245092/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To compare the efficacy of ibuprofen with that of an ibuprofen-codeine combination for pain relief following oral surgery. **Number of arms:** 2 (1 opioid analgesia; 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 48; opioid-free group: 49. **Diagnosis (% of participants):** Impacted 3rd molar (100%). **Surgery**: 3rd molar extraction (100%). **Age:** Opioid group: mean 24 (SD 5.6); opioid-free group: mean 24.4 (SD 5.1). **Sex (female):** Not reported. **Ethnicity:** Not reported. **Inclusion criteria:** Patients between 16 and 65, undergoing removal of an impacted lower third molar. **Exclusion criteria:** Not reported.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local Anesthesia (lignocaine 1.5ml, 2%) + Nerve block (epinephrine 1:800000) + Buccal infiltration (epinephrine 1ml). **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Ibuprofen 600 mg, every day, PO + Codeine 40 mg, every day, PO + Acetaminophen 500 mg, every 4 hours as needed for breakthrough pain, PO. *Duration:* 2 days. ***Opioid-free group***

	Medication: Ibuprofen 600 mg, every day, PO + Acetaminophen 500 mg, every 4 hours as needed for breakthrough pain, PO. *Duration:* 2 days.
Outcomes	**Primary outcome:** Pain scores, verbal rating scale 0-10, mean. **Timepoints:** Same day as surgery (noon), same day as surgery (6:00 pm), same day as surgery (midnight), day 1 after surgery (6:00 am), day 1 after surgery (noon), day 1 after surgery (6:00 pm), day 1 after surgery (midnight), day 2 after surgery (6:00 am), day 2 after surgery (noon), day 2 after surgery (6:00 pm), and day 2 after surgery (midnight). **Secondary outcomes:** Amount of rescue analgesia consumed, adverse events (any). **Total length of follow up:** 3 days.
Country and setting	**Country:** United Kingdom. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	None reported.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The study is described as a randomized- trial but no information about randomization is reported. No information is provided regarding concealment of allocation. Demographic characteristics were not reported with between-group comparison.
Risk of bias due to deviation from intended interventions.	Some concerns.	The study is described as a double-blinded trial. It is assumed that participants and carers were blinded. There is no information as to whether the analysis was per protocol or according to intention to treat.
Risk of bias due to missing outcome data.	Low risk.	According to the authors, only 2 patients (2%) were lost to follow up.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**

Pain score, same day as surgery (noon), VRS (0-10)	Mean 0.56*	Mean 0.78*
Pain score, same day as surgery (6:00 pm), VRS (0-10)	Mean 0.88*	Mean 1.1*
Pain score, same day as surgery (midnight), VRS (0-10)	Mean 0.71*	Mean 0.75*
Pain score, day 1 after surgery (6:00 am), VRS (0-10)	Mean 0.52*	Mean 0.46*
Pain score, day 1 after surgery (noon), VRS (0-10)	Mean 0.62*	Mean 0.68*
Pain score, day 1 after surgery (6:00 pm), VRS (0-10)	Mean 0.56*	Mean 0.67*
Pain score, day 1 after surgery (midnight), VRS (0-10)	Mean 0.76*	Mean 0.83*
Pain score, day 2 after surgery (6:00 am), VRS (0-10)	Mean 0.58*	Mean 0.46*
Pain score, day 2 after surgery (noon), VRS (0-10)	Mean 0.54*	Mean 0.59*
Pain score, day 2 after surgery (6:00 pm), VRS (0-10)	Mean 0.60*	Mean 0.57*
Pain score, day 2 after surgery (midnight), VRS (0-10)	Mean 0.62*	Mean 0.47*
Adverse event (any)	Incidence rate 13/48	Incidence rate 3/49

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Weinheimer 2019 (https://pubmed.ncbi.nlm.nih.gov/30502019/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; superiority design (not adaptive). **Study objective:** To compare the efficacy of opioid versus nonopioid analgesic regimens after elective, soft tissue hand surgery. **Number of arms:** 2 (1 opioid analgesia; 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Sample size was calculated based on the primary outcome of mean daily pain intensity measured by VAS. The authors chose a difference of 10 mm in VAS as their threshold. A sample size of 16 in each group had an 80% power to detect a difference in means of 10 mm assuming a common SD of 10 mm by a 2-group Student t test with a 0.05, 2-sided significance level. The study targeted a sample of 30 patients in each group to have an improved chance to identify differences in our secondary outcomes.
Participants	**N randomised:** Opioid group: 30; opioid-free group: 30. **Diagnosis (% of participants):** Opioid group: carpal tunnel syndrome (70%), trigger finger (20%), ganglion cyst (10%); opioid-free group: carpal tunnel syndrome (37%), trigger finger (33%), ganglion cyst (17%), other (13%). **Surgery:** Opioid group: carpal tunnel release (70%), trigger finger release (20%), ganglion cyst excision (10%), de Quervain's syndrome release (0%); opioid-free group: carpal tunnel release (37%), trigger finger release (33%), ganglion cyst excision (17%), de Quervain's syndrome release (13%). **Age:** Opioid group: mean 53 (range 18-75); opioid-free group mean 52 (range 18-86). **Sex (% female):** Opioid group: 57%; opioid-free group 60%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients older than 21 years, undergoing elective soft tissue hand surgery (carpal tunnel release, trigger finger release, first dorsal compartment release, ganglion cyst excision, or combination thereof), expressed understanding of the study protocol. **Exclusion criteria:** Known allergy to a study medication, chronic opioid use or dependency, chronic pain requiring systemic analgesia including nonsteroidal anti-inflammatory drugs, fibromyalgia, recent upper gastrointestinal bleeding, coagulopathy (primary or medication-related), renal impairment, liver disease.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.

Interventions	**Intraoperative anaesthesia:** Local anaesthesia (lidocaine 1% + bupivacaine 0.5% OR bupivacaine 0.5% OR lidocaine 1%) OR general anaesthesia. **Inpatient analgesia (after surgery, prior to discharge):** Ketorolac, as needed (unclear dose and route). **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen 325 mg, every 4 hours as needed, PO + Hydrocodone 5 mg, every 4 hours as needed, PO + Oxycodone 5mg, every 4 hours as needed, PO (requires additional contact). *Duration:* 7 days. ***Opioid-free group*** *Medication:* Acetaminophen 500 mg, every 4 hours as needed, PO + Ibuprofen 400 mg, every 4 hours as needed, PO + Oxycodone 5mg, every 4 hours as needed, PO (requires additional contact). *Duration:* 7 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-100 mm, mean. **Timepoints:** Same day as surgery, day 1 after surgery, day 2 after surgery, day 3 after surgery, day 4 after surgery, day 5 after surgery, and day 6 after surgery. **Secondary outcomes:** Time to pain relief, adverse event (overall, drowsiness, constipation, pruritus). **Total length of follow up:** 14 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Grant support from The Penn State Clinical and Translational Research Institute, Pennsylvania State University CTSA, NIH/NCATS Grant Number UL1 TR000127 and UL1 TR002014, and Orthopedic Research Initiation Grant 2014.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	High risk.	The study is described as a randomized- trial but limited information about randomization is reported: 'randomization was performed electronically'. No information is provided regarding concealment of allocation. There was a higher proportion of patients having potentially more painful procedures (carpal tunnel release) in the opioid group.

Risk of bias due to deviation from intended interventions.	High risk.	The study is described as a double-blinded trial. It is assumed that participants and carers were blinded. The analysis was conducted per protocol as the authors excluded patients who did not comply with the medications. Up to 5 patients (7%) were excluded due to non-compliance with medications or non-completion of diaries. We cannot exclude that the exclusion of non-compliant patients may have affected study results.
Risk of bias due to missing outcome data.	Low risk.	Up to 5 patients (7%) were excluded due to non-compliance with medications or non-completion of diaries. The exact amount of missing data is unclear but can be assumed to be less than 7%.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes and patients were blinded.
Risk of bias in selection of the reported results.	Some concerns.	*A priori* study protocol not identified.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, same day as surgery, VAS (0-100)	Mean 24*	Mean 22*
Pain score, day 1 after surgery, VAS (0-100)	Mean 30*	Mean 22*
Pain score, day 2 after surgery, VAS (0-100)	Mean 22*	Mean 16*
Pain score, day 3 after surgery, VAS (0-100)	Mean 19*	Mean 13*
Pain score, day 4 after surgery, VAS (0-100)	Mean 17*	Mean 14*
Pain score, day 5 after surgery, VAS (0-100)	Mean 14*	Mean 14*
Pain score, day 6 after surgery, VAS (0-100)	Mean 13*	Mean 13*
Adverse event (overall)	Incidence rate 7/30	Incidence rate 1/30
Drowsiness	Incidence rate 4/30	Incidence rate 1/30
Constipation	Incidence rate 3/30	Incidence rate 0/30
Pruritus	Incidence rate 1/30	Incidence rate 0/30

*SD was imputed based on the highest SD from the largest trial with the lowest risk of bias.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Zuniga 2019 (https://pubmed.ncbi.nlm.nih.gov/30657996/)

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To evaluate the prevention of opioid-induced nausea and vomiting (OINV) and the relief of moderate to severe acute pain by CL-108, a novel drug combining a low-dose antiemetic (rapid-release promethazine 12.5mg) with hydrocodone 7.5mg/acetaminophen 325mg (HC/APAP) was used. **Number of arms:** 3 (2 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 4:4:1. **Power (sample size calculation):** A sample size of 810 patients was planned in order to yield >90% power to test each co-primary end point at the 0.05 level of significance, with 360 subjects each in the CL-108 and HC/APAP groups and 90 subjects in the placebo group. A sample size of 109 subjects per group was estimated to provide 90% power to detect at least a 20% difference in the occurrence rate of OINV. A sample size of 288 in the CL-108 group and 72 in the placebo group was estimated to provide 90% power to detect a difference of 3 in the SPID24, assuming a common standard deviation of 7.
Participants	**N randomised:** Opioid group 1: 205; opioid group 2: 211; opioid-free group 50. **Diagnosis (% of participants):** Opioid group 1: impacted third molar (100%), partial bony impaction (38.5%), full bony impaction (61.5%); opioid group 2: impacted third molar (100%), partial bony impaction (45.5%), full bony impaction (54.5%); opioid-free group: impacted third molar (100%), partial bony impaction (41.3%), full bony impaction (58.7%). **Surgery**: 3rd molar extraction (100%). **Age:** Opioid group 1: mean 22.3 (SD 4.78); opioid group 2: mean 22.6 (SD 5.31); opioid-free group: mean 22.2 (SD 4.88). **Sex (% female):** Opioid group 1: 73%; opioid group 2: 74%; opioid-free group: 64%. **Ethnicity:** Opioid group 1: Hispanic/Latino (19.5%), non-Hispanic/Latino (80.5%); opioid group 2: Hispanic/Latino (23.2%), non-Hispanic/Latino (76.8%); opioid-free group: Hispanic/Latino (12%), non-Hispanic/Latino (88%). **Inclusion criteria:** Patients 18 years of age or older, at least two impacted third molar teeth, at least one mandibular molar tooth with >50% bony impaction. **Exclusion criteria:** Serious medical condition or infection, history of allergy or hypersensitivity to opioids, promethazine, acetaminophen, or nonsteroidal anti-inflammatory drugs, use of contraindicated or confounding medication in the 24 hours before screening, refused to not smoke during the study.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Outpatient clinic. **Surgical discharge:** Same day. **Surgery classification:** Minor.

	Surgery status: Not reported.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (3% mepivacaine and lidocaine with epinephrine 1:100,000) + Midazolam. **Inpatient analgesia (after surgery, prior to discharge):** ***Opioid group 1*** *Medication*: Acetaminophen 325 mg, one dose, PO + Hydrocodone 7.5 mg, one dose, PO. ***Opioid group 2*** *Medication*: Acetaminophen 325 mg, one dose, PO + Hydrocodone 7.5 mg, one dose, PO + Promethazine 12.5 mg, one dose, PO. ***Opioid-free group*** *Medication:* None. **Post-discharge analgesia:** ***Opioid group 1*** *Medication*: Acetaminophen 325 mg, every 6 hours as needed, PO + Hydrocodone 7.5 mg, every 6 hours as needed, PO. *Duration:* 5 days. ***Opioid group 2*** *Medication*: Acetaminophen 325 mg, every 6 hours as needed, PO + Hydrocodone 7.5 mg, every 6 hours as needed, PO + Promethazine 12.5 mg, every 6 hours as needed, PO. *Duration:* 5 days. ***Opioid-free group*** *Medication*: Ibuprofen 400 mg, every 6 hours as needed, PO. *Duration:* 5 days.
Outcomes	**Primary outcome:** Adverse events (nausea/vomiting). Only compares opioid groups without opioid-free group. **Timepoints:** 7 days. **Secondary outcomes:** Adverse events (confusion, constipation, difficulty concentrating, difficulty urinating, drowsiness, dry mouth, pruritus, headache). **Total length of follow up:** 7 days.
Country and setting	**Country:** United States.

Number of centres: Multicentre

Study period: Not reported.

Source of funding	The study was funded by Olas Pharma, Inc.
Source of data	Peer-reviewed article.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	The allocation sequence was computer generated. From the design of the study and the fact that a computer-generated randomization was used as well as a double-blind design, it's likely that the allocation was concealed. There might be imbalances regarding PI-CAT and x-ray results.
Risk of bias due to deviation from intended interventions.	Low risk.	The study was designed as a double-blinded study, according to the authors. The authors used an intention to treat analysis.
Risk of bias due to missing outcome data.	Low risk.	Less than 2% of patients discontinued the study.
Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be pre-specified and appropriate. The same measurement strategy was used in both groups. The study focused on patient reported outcomes, and patients and assessors were apparently blinded.
Risk of bias in selection of the reported results.	Some concerns.	A protocol was identified online; however, it contained no information on analysis plan.

Results

Outcome	**Opioid group 1***	**Opioid group 2***	**Opioid-free group**
Confusion	Incidence rate 4/205	Incidence rate 8/208	Incidence rate 0/48
Constipation	Incidence rate 5/205	Incidence rate 6/208	Incidence rate 0/48
Difficulty concentrating	Incidence rate 7/205	Incidence rate 11/208	Incidence rate 1/48
Difficulty urinating	Incidence rate 3/205	Incidence rate 3/208	Incidence rate 0/48
Drowsiness	Incidence rate 37/205	Incidence rate 38/208	Incidence rate 5/48
Dry mouth	Incidence rate 8/205	Incidence rate 11/208	Incidence rate 3/48
Pruritus	Incidence rate 12/205	Incidence rate 8/208	Incidence rate 0/48
Headache	Incidence rate 12/205	Incidence rate 9/208	Incidence rate 5/48

*Data from multiple treatment arms were aggregated according to methods described in the Cochrane Handbook.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

NCT02647788 2019 (https://clinicaltrials.gov/ct2/show/NCT02647788**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; equivalency design (not adaptive). **Study objective:** To find out if taking acetaminophen with ibuprofen, a non-opioid regimen, provides the same type of pain relief after hand surgery compared to acetaminophen and codeine, an opioid regimen. **Number of arms:** 2 (1 opioid analgesia; 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** A sample size of 63 in each group was estimated to have a 80 % power to detect a difference in means of 5 mm assuming a common standard deviation of 10 mm by a two-group Student's t test with a 0.05 two-sided significance level. Assuming a 30% lost to follow-up and failure to comply with study protocol, a sample of 145 patients (63 patients in each group) were targeted.
Participants	**N randomised:** Opioid group: 70; opioid-free group: 70. **Diagnosis (% of participants):** Carpal tunnel or trigger finger (100%). **Surgery:** Carpal tunnel release or trigger finger release (100%). **Age:** Opioid group: mean 59 (SD 13); opioid-free group mean 60 (SD 12). **Sex (% female):** Opioid group: 67%; opioid-free group 69%. **Ethnicity:** Not reported. **Inclusion criteria:** Patients undergoing ambulatory hand surgery for carpal tunnel and trigger finger, under local anaesthesia with or without sedation. **Exclusion criteria:** ASA> 2, coagulopathy, renal disease, liver disease, history of recent gastro-intestinal bleeding, pregnancy, diagnosis of chronic pain currently taking opioid pain medication or with a history of drug abuse, patients with a self-described allergy to ASA, acetaminophen, NSAIDs and codeine, all patients receiving a brachial plexus block for anaesthesia and/or analgesia
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Local anaesthesia (unclear regimen) +/- sedation. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 300 mg, every 6 hours as needed, PO + Codeine 30 mg, every 6 hours as needed, PO. *Duration:* 6-8 days. ***Opioid-free group*** *Medication:* Acetaminophen 650 mg, every 6 hours as needed, PO + Ibuprofen 400 mg, every 6 hours as needed, PO. *Duration:* 6-8 days.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** Day 1 after surgery, day 2 after surgery, day 3 after surgery, day 4 after surgery, day 5 after surgery, day 6 after surgery, and day 7 after surgery. **Secondary outcomes:** Quality of recovery, primary analgesia consumption, adverse events (any, nausea, constipation, pruritus, dizziness, drowsiness). **Total length of follow up:** 8 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** Not reported.
Source of funding	Penn Presbyterian Medical Center Bach Fund Award.
Source of data	Trial registry + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Stratified block randomization using tables of random numbers, stratified according to hand surgery type (carpal tunnel, trigger finger). Randomization will be performed by the Investigational Drug Service (IDS) using computer-generated tables. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	The Investigational Drug Service prepared the medication for both treatment groups, which were indistinguishable to the study team or to study participants. The statistical analysis followed intention to treat.
Risk of bias due to missing outcome data.	Some concerns.	~21% of patients didn't complete follow-up. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events). The proportion and reasons for missing data are similar between groups.

Risk of bias in measurement of the outcome.	Low risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Outcome assessors were blind to group allocation.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, day 1 after surgery, VAS (0-10)	Mean 3.51 (SD 2.69)	Mean 2.90 (SD 2.22)
Pain score, day 2 after surgery, VAS (0-10)	Mean 2.40 (SD 2.52)	Mean 2.36 (SD 2.31)
Pain score, day 3 after surgery, VAS (0-10)	Mean 2.26 (SD 2.38)	Mean 1.69 (SD 2.00)
Pain score, day 4 after surgery, VAS (0-10)	Mean 1.93 (SD 2.01)	Mean 1.47 (SD 1.82)
Pain score, day 5 after surgery, VAS (0-10)	Mean 1.48 (SD 1.48)	Mean 1.23 (SD 1.61)
Pain score, day 6 after surgery, VAS (0-10)	Mean 1.35 (SD 1.37)	Mean 1.29 (SD 1.49)
Pain score, day 7 after surgery, VAS (0-10)	Mean 1.01 (SD 1.21)	Mean 1.17 (SD 1.38)
Quality of recovery, QoR-9	Mean 16.65 (SD 1.91)	Mean 16.91 (SD 1.38)
Adverse event (any)	Incidence rate 30/70	Incidence rate 32/70
Nausea	Incidence rate 7/70	Incidence rate 8/70
Constipation	Incidence rate 12/70	Incidence rate 8/70
Pruritus	Incidence rate 11/70	Incidence rate 12/70
Dizziness	Incidence rate 2/70	Incidence rate 3/70
Drowsiness	Incidence rate 10/70	Incidence rate 22/70

NCT03605914 2021 (https://clinicaltrials.gov/ct2/show/NCT03605914**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; non-inferiority design (not adaptive). **Study objective:** To compare overall pain score (10 cm visual analogue scale) at 24 hours post-surgery between patients receiving diclofenac sodium to those receiving acetaminophen hydrocodone following ESS and/or septoplasty. Secondary objectives were to compare average, most severe, and least severe 24-hour pain score at 48 hours, 72 hours, and 120 hours post-surgery between patients receiving diclofenac sodium to those receiving acetaminophen-hydrocodone following ESS. Additional secondary objectives were to determine the rate of bleeding complications in patients receiving diclofenac sodium to those receiving acetaminophen-hydrocodone following ESS as well as noting the rates of constipation and nausea/vomiting in each group. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Sample calculations were performed for a non-inferiority limit of 15mm on the 100mm VAS score, 90% power, alpha of 0.025, with an estimated standard deviation of 22.8. 41 patients were calculated to be required in each group for a total patient count of 82. Due to a roughly anticipated 10% dropout (failure to complete survey at 24 hours), the authors planned to recruit a total of 100 patients.
Participants	**N randomised:** Opioid group: 57; opioid-free group: 43. **Diagnosis (% of participants):** Not reported. **Surgery:** Sinus surgery (100%). **Age:** Opioid group: mean 43; opioid-free group: mean 45.4. **Sex (female):** Opioid group: 39.5%; opioid-free group: 35.1%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, English speaking adults who are candidates for endoscopic sinus surgery as determined by medical necessity by the treating rhinologist. **Exclusion criteria:** Allergy to either NSAIDs or opioids, contraindication to NSAIDs (ex. gastritis, chronic kidney disease), surgical plan exceeding basic endoscopic sinus surgery, use of anti-coagulation, the presence of any pain disorder, the current usage of any analgesic medication, history of opioid addiction, pregnancy, history of chronic pain or fibromyalgia, current daily use of NSAIDs, acetaminophen, opioids, or other analgesics (pregabalin, tramadol, etc.).
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Minor. **Surgery status:** Not reported.

Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen, PO (unclear dose and regimen) + Hydrocodone, PO (unclear dose and regimen). *Duration:* Not reported. ***Opioid-free group*** *Medication:* Diclofenac, PO (unclear dose and regimen). *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-100 mm, mean (SD). **Timepoints:** 24 hours after surgery, 48 hours after surgery, 72 hours after surgery, and 120 hours after surgery. **Secondary outcomes:** Adverse events (bleeding, mortality). **Total length of follow up:** 5 days.
Country and setting	**Country:** United States. **Number of centres:** Single centre. **Study period:** 2018-2020.
Source of funding	Not reported.
Source of data	Trial registry + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	The authors planned to randomize patients by computer-generated sequencing in conjunction with a standard envelope system. The authors planned to randomize patients by computer-generated sequencing in conjunction with a standard envelope system. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	It is unclear if participants and/or carers were blinded. No information is provided regarding deviations from the intervention protocol. It is unclear if the analysis was conducted following intention to treat or per protocol approach.
Risk of bias due to missing outcome data.	High risk.	Rates of missing data in the assessment time points ranged from 41-46%. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse

		events). Reasons for missing data are not reported. Rates of missing data were similar between groups.
Risk of bias in measurement of the outcome.	High risk.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Unclear if outcome assessors were blinded to group allocation.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score, day 24h after surgery, VAS (0-100)	Mean 40.7 (SD 29.2)	Mean 30.2 (SD 25.3)
Pain score, day 48h after surgery, VAS (0-100)	Mean 28.3 (SD 23.4)	Mean 24.2 (SD 25.1)
Pain score, day 72h after surgery, VAS (0-100)	Mean 27.9 (SD 21.9)	Mean 22.9 (SD 20.4)
Pain score, day 120h after surgery, VAS (0-100)	Mean 18.9 (SD 18.8)	Mean 17.2 (SD 20.3)
Bleeding	Incidence rate 0/24	Incidence rate 0/30

NCT03818919 2021 (https://clinicaltrials.gov/ct2/show/NCT03818919**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To compare postoperative pain control in patients in two treatment arms of rotator cuff repair: a treatment group given a nonopioid pain control regimen, and a standard of care control group given standard opioid pain control regimen. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 27; opioid-free group: 17. **Diagnosis (% of participants):** Not reported. **Surgery:** Rotator cuff repair (100%). **Age:** Opioid group: mean 55.9 (SD 7.2); opioid-free group: mean 53.7 (SD 9.1). **Sex (female):** Opioid group: 40.7%; opioid-free group: 47.1%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, scheduled for a primary or revision rotator cuff repair. **Exclusion criteria:** Patients with a medical history of known allergies or intolerance to allergies or intolerance to Celebrex, Tylenol, Neurontin, dexamethasone, tramadol, substantial alcohol or drug abuse, and pregnancy, history of narcotics within 6 months of surgery, renal impairment, peptic ulcer disease, GI bleeding. Secondary exclusion criterion is an intact rotator cuff.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group*** *Medication:* Acetaminophen, PO (unclear dose and regimen) + Hydrocodone, PO (unclear dose and regimen).

	Duration: Not reported. ***Opioid-free group*** *Medication:* Celecoxib, PO (unclear dose and regimen) + Ketorolac, PO (unclear dose and regimen) + Gabapentin, PO (unclear dose and regimen) + Acetaminophen, PO (unclear dose and regimen). *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** Day 1 after surgery, day 2 after surgery, day 3 after surgery, day 4 after surgery, day 5 after surgery, day 6 after surgery, day 7 after surgery, day 8 after surgery, day 9 after surgery, and day 10 after surgery. **Secondary outcomes:** Pain interference. **Total length of follow up:** 10 days.
Country and setting	**Country:** United States **Number of centres:** Single centre. **Study period:** 2019-2020.
Source of funding	Not reported.
Source of data	Trial registry + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	Patients consented for participation were randomly assigned preoperatively to either an opioid or a multimodal non-opioid pain regimen with a 1:1 allocation ratio using adaptive randomization computer software (Adaptive Randomization, MD Anderson Cancer Center, Houston TX). Randomization was conducted using adaptive randomization computer software. Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	High risk.	Participants were not blinded. Carers were not blinded. In the immediate postoperative period 4 patients who randomized into the non-opioid group requested opioid analgesics due to concern of future pain. A total of 27 patients in the opioid group and 17 patients in the nonopioid group were included in the final analysis. Authors only conducted a per protocol analysis. Only patients in the non-opioid group crossed over to the other group. Deviations were unbalanced and crossed-over patients may have been the ones with worse outcomes.
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).

Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 5.7 (SD 2.2)	Mean 3.7 (SD 2.2)
Pain score 2 days after discharge, VAS (0-10)	Mean 4.7*	Mean 3.2*
Pain score 3 days after discharge, VAS (0-10)	Mean 4.4*	Mean 2.8*
Pain score 4 days after discharge, VAS (0-10)	Mean 4.4 (SD 2.7)	Mean 2.4 (SD 2.2)
Pain score 5 days after discharge, VAS (0-10)	Mean 3.5*	Mean 2.3*
Pain score 6 days after discharge, VAS (0-10)	Mean 3.1*	Mean 2.0*
Pain score 7 days after discharge, VAS (0-10)	Mean 3.1*	Mean 2.2*
Pain score 8 days after discharge, VAS (0-10)	Mean 3.0*	Mean 2.1*
Pain score 9 days after discharge, VAS (0-10)	Mean 2.7*	Mean 3.0*
Pain score 10 days after discharge, VAS (0-10)	Mean 3.0*	Mean 2.4*
Pain interference, PROMIS PI	Mean 60.0 (SD 9.3)	Mean 59.3 (SD 8.5)

*SD was imputed based on the highest SD from the same trial.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

NCT03818932 2021 (https://clinicaltrials.gov/ct2/show/NCT03818932**)**

Methods	**Study design:** Full-scale (definitive) randomized controlled trial; unclear if superiority, non-inferiority, or equivalence design. **Study objective:** To compare postoperative pain control in patients in two treatment arms of anterior cruciate ligament reconstruction: a treatment group given a nonopioid pain control regimen, and a standard of care control group given standard opioid pain control regimen. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** Not reported.
Participants	**N randomised:** Opioid group: 28; opioid-free group: 34. **Diagnosis (% of participants):** Not reported. **Surgery:** Anterior cruciate ligament reconstruction (100%). **Age:** Opioid group: mean 27.4 (SD 12.4); opioid-free group: mean 27.2 (SD 13.1). **Sex (female):** Opioid group: 46%; opioid-free group: 44%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, scheduled for a primary or revision anterior cruciate ligament reconstruction. **Exclusion criteria:** Patients with a medical history of known allergies or intolerance to allergies or intolerance to Celebrex, Tylenol, Neurontin, dexamethasone, tramadol, substantial alcohol or drug abuse, and pregnancy, history of narcotics within 6 months of surgery, renal impairment, peptic ulcer disease, GI bleeding. Secondary exclusion criterion is an intact anterior cruciate ligament reconstruction.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Not reported.
Interventions	**Intraoperative anaesthesia:** Nerve block (femoral or adductor canal) + Local anaesthesia (ropivacaine 0.5%, 30 mL + ketorolac 1 mL + epinephrine 1 mL. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:** ***Opioid group***

	Medication: Acetaminophen 325-650 mg, every 4-6 hours as needed, PO + Hydrocodone 5-10 mg, every 4-6 hours as needed, PO. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Celecoxib, PO (unclear dose and regimen) + Ketorolac, PO (unclear dose and regimen) + Gabapentin, PO (unclear dose and regimen) + Acetaminophen, PO (unclear dose and regimen). *Duration:* Not reported.
Outcomes	**Primary outcome:** Pain scores, visual analogue scale 0-10 cm, mean (SD). **Timepoints:** Day 1 after surgery, day 2 after surgery, day 3 after surgery, day 4 after surgery, day 5 after surgery, day 6 after surgery, day 7 after surgery, day 8 after surgery, day 9 after surgery, and day 10 after surgery. **Secondary outcomes:** Pain interference, adverse events (constipation, nausea, diarrhoea, upset stomach, drowsiness, confusion). **Total length of follow up:** 10 days.
Country and setting	**Country:** United States **Number of centres:** Single centre. **Study period:** 2019-2020.
Source of funding	Not reported.
Source of data	Trial registry + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: *https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2****)***

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Some concerns.	Patients consented for participation were randomly assigned preoperatively to either an opioid or a multimodal non-opioid pain regimen with a 1:1 allocation ratio using adaptive randomization computer software (Adaptive Randomization, MD Anderson Cancer Center, Houston TX). Randomization was conducted using adaptive randomization computer software, but it's unclear how the randomization was conducted (remote/central service, opaque envelopes?). Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Low risk.	Participants were not blinded. Carers were not blinded. The authors reported no deviations from the protocol. The analysis was apparently according to intention to treat (there were no protocol deviations).
Risk of bias due to missing outcome data.	High risk.	The authors provide no information about missing data. No sensitivity analyses or imputations were conducted to estimate the impact of missing data. Missingness of outcome data may depend on its true value (i.e., pain or adverse events).

Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 4.7*	Mean 3.9*
Pain score 2 days after discharge, VAS (0-10)	Mean 5.5*	Mean 4.8*
Pain score 3 days after discharge, VAS (0-10)	Mean 4.6*	Mean 3.5*
Pain score 4 days after discharge, VAS (0-10)	Mean 4.1*	Mean 3.1*
Pain score 5 days after discharge, VAS (0-10)	Mean 4.2*	Mean 3.8*
Pain score 6 days after discharge, VAS (0-10)	Mean 4.7*	Mean 3.9*
Pain score 7 days after discharge, VAS (0-10)	Mean 4.8*	Mean 3.8*
Pain score 8 days after discharge, VAS (0-10)	Mean 4.7*	Mean 3.1*
Pain score 9 days after discharge, VAS (0-10)	Mean 4.9*	Mean 2.0*
Pain score 10 days after discharge, VAS (0-10)	Mean 4.7*	Mean 2.4*
Pain interference, PROMIS PI	Mean 66.3 (SD 8.2)	Mean 61.4 (SD 8.8)
Constipation	Incidence rate 13/20	Incidence rate 12/22
Nausea	Incidence rate 10/18	Incidence rate 9/21
Diarrhoea	Incidence rate 2/13	Incidence rate 2/19
Upset stomach	Incidence rate 8/16	Incidence rate 9/21
Drowsiness	Incidence rate 12/18	Incidence rate 18/25
Confusion	Incidence rate 4/14	Incidence rate 12/22

*SD was imputed based on the highest SD from the same trial.[1]

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

NCT04254679 2021 (https://clinicaltrials.gov/ct2/show/NCT04254679**)**

Methods	**Study design:** Pilot randomized controlled trial; feasibility design. **Study objective:** To investigate the feasibility of conducting a full-scale RCT to assess the comparative-effectiveness of opioid analgesia (OA) versus opioid-free analgesia (OFA) after outpatient general surgery. **Number of arms:** 2 (1 opioid analgesia, 1 opioid-free analgesia). **Randomization ratio:** 1:1 **Power (sample size calculation):** This pilot trial was not confirmatory; therefore, a formal sample size calculation was not conducted. In accordance with previous recommendations that at least 70 measured participants are required for estimating standard deviations of continuous measures for future sample size calculations, the authors aimed to recruit and obtain outcome data from 80 patients (40 per group), allowing for a ~15% attrition rate. This sample size is also in line with recommendations regarding the minimal number of participants required to identify feasibility issues.
Participants	**N randomised:** Opioid group: 39; opioid-free group: 37. **Diagnosis (% of participants):** Not reported. **Surgery:** Opioid group: abdominal (51%), breast (49%); opioid-free group: abdominal (54%), breast 46%). **Age:** Opioid group: mean 54 (SD 15); opioid-free group: mean 57 (SD 14). **Sex (female):** Opioid group: 61%; opioid-free group: 70%. **Ethnicity:** Not reported. **Inclusion criteria:** Age >18, undergoing outpatient general surgery [abdominal (i.e., cholecystectomies, hernia repairs) or breast (i.e., lumpectomies, partial and complete mastectomies, axillary node dissection) procedures]. **Exclusion criteria:** Intraoperative or early postoperative complications (i.e., diagnosed in the Post-Anesthesia Care Unit (PACU)) that require postoperative hospital stay, contraindications to any of the drugs used in the trial, difficult to be reached after surgery, inability to provide written informed consent.
Procedure characteristics	**Surgical setting:** Ambulatory. **Surgery location:** Hospital operating room. **Surgical discharge:** Same day. **Surgery classification:** Moderate. **Surgery status:** Elective.
Interventions	**Intraoperative anaesthesia:** Not reported. **Inpatient analgesia (after surgery, prior to discharge):** Not reported. **Post-discharge analgesia:**

	Opioid group *Medication:* Around-the-clock non-opioid analgesics (Acetaminophen +/- NSAIDs) + Opioid tablets 'as needed' for breakthrough pain. *Duration:* Not reported. ***Opioid-free group*** *Medication:* Around-the-clock non-opioid analgesics (Acetaminophen +/- NSAIDs) + Rescue analgesia by increasing doses and/or adding non-opioid drugs. *Duration:* Not reported.
Outcomes	**Primary outcome:** Feasibility of recruitment, randomization, and follow up. **Timepoints:** Not applicable. **Secondary outcomes:** Pain score, time to stop analgesia, adverse events (overall, nausea, vomiting, pruritus, drowsiness, dizziness, difficulty concentrating, difficulty urinating, confusion), patient satisfaction, healthcare utilization (overall, emergency department visit, readmission, outpatient clinic visit), pain interference.
Country and setting	**Country:** Canada. **Number of centres:** Single centre. **Study period:** 2020. **Total length of follow up:** 30 days.
Source of funding	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)
Source of data	Trial registry + Additional data were obtained by contacting the authors.

Risk of bias (assessed according to: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2)

Bias	**Author's judgement**	**Support for judgement**
Risk of bias arising from the randomization process.	Low risk.	Randomization was based on a random allocation sequence generated electronically (via www.sealedenvelope.com) and uploaded onto REDCap (http://project-redcap.org/) by an external researcher not involved in the trial. Randomization used a remote method; Treatment allocations were concealed until patients were deemed ready to be discharged from the OR to the post-anaesthesia care unit (PACU). Baseline characteristics were similar between groups.
Risk of bias due to deviation from intended interventions.	Some concerns.	Participants were not blinded. Carers were not blinded. Deviations arose because of the trial context such as drug discontinuation and switching. This is consistent with what may have happened in practice. Comparison of postoperative outcomes between OA and OFA groups followed the intention to treat principle.

Risk of bias due to missing outcome data.	Low risk.	Seventy-three patients completed the 30-day follow-up (96%); rate of missing questionnaires was 1% and, among patients who submitted questionnaire responses, the rate of missing items was 0.1%.
Risk of bias in measurement of the outcome.	Some concerns.	The outcome measures of choice seemed to be appropriate. The same measurement strategy was used in both groups. Patients, the outcome assessors of self-reported data, were not blinded to group allocation. Other data (e.g., complications, ED visits, readmissions) were collected by a blinded research assistant. Knowledge of group assignment could have influenced outcome reporting (e.g., pain). The two treatments are active interventions. If knowledge of the intervention had an impact on outcomes, it could have favoured either group.
Risk of bias in selection of the reported results.	Low risk.	An a priori protocol is available online. Outcome measures are consistent with those reported in the manuscript. Analysis intentions are available and consistent with the analysis reported.

Results

Outcome	**Opioid group**	**Opioid-free group**
Pain score 1 day after discharge, VAS (0-10)	Mean 2.8 (SD 2.2)	Mean 3.0 (SD 1.7)
Pain score 2 days after discharge, VAS (0-10)	Mean 2.7 (SD 2.3)	Mean 2.6 (SD 2.1)
Pain score 3 days after discharge, VAS (0-10)	Mean 2.1 (SD 2.0)	Mean 1.7 (SD 1.8)
Pain score 4 days after discharge, VAS (0-10)	Mean 1.6 (SD 1.7)	Mean 1.4 (SD 1.7)
Pain score 5 days after discharge, VAS (0-10)	Mean 1.3 (SD 1.7)	Mean 1.1 (SD 1.3)
Pain score 6 days after discharge, VAS (0-10)	Mean 1.2 (SD 1.5)	Mean 1.1 (SD 1.4)
Pain score 7 days after discharge, VAS (0-10)	Mean 1.1 (SD 1.6)	Mean 0.9 (SD 1.2)
Pain score 2 weeks after discharge, VAS (0-10)	Mean 0.9 (SD 1.4)	Mean 0.4 (SD 0.8)
Pain score 3 weeks after discharge, VAS (0-10)	Mean 0.5 (SD 1.0)	Mean 0.4 (SD 0.8)
Pain score 4 weeks after discharge, VAS (0-10)	Mean 0.5 (SD 1.3)	Mean 0.3 (SD 0.8)
Pain interference, PROMIS PI	Mean 55.7 (SD 8.3)	Mean 55.5 (SD 9.1)
Adverse events (overall)	Incidence rate 18/39	Incidence rate 15/37
Nausea	Incidence rate 9/39	Incidence rate 8/37
Vomit	Incidence rate 6/39	Incidence rate 1/37
Pruritus	Incidence rate 15/39	Incidence rate 15/37
Drowsiness	Incidence rate 14/39	Incidence rate 13/37
Dizziness	Incidence rate 8/39	Incidence rate 7/37

Difficulty concentrating	Incidence rate 8/39	Incidence rate 11/37
Difficulty urinating	Incidence rate 4/39	Incidence rate 4/37
Confusion	Incidence rate 2/39	Incidence rate 3/37
Patient satisfaction (dichotomous)	Incidence rate 37/39	Incidence rate 34/37
Healthcare utilization (overall)	Incidence rate 6/39	Incidence rate 1/37
Emergency department visit	Incidence rate 5/39	Incidence rate 0/37
Readmission	Incidence rate 1/39	Incidence rate 1/37
Outpatient clinic visit	Incidence rate 2/39	Incidence rate 0/37

Risk of bias assessment of the eligible randomized clinical trials

Risk of bias assessment for pain at post-discharge day 0

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Walton (1990)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Torabinejad (1994)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Collins (1997)	Some concerns	High	High	Low	Some concerns	High
Breivik (1998)	Low	High	High	Low	Some concerns	High
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Best (2017)	Low	Low	Low	Low	Some concerns	Some concerns
Samieirad (2017)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
Papoian (2020)	Low	Some concerns	High	Some concerns	Low	High

Brady (2021)	High	Some concerns	High	Some concerns	Low	High
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Frants (2021)	High	Some concerns	Low	Some concerns	Low	High
La Monaca (2021)	Low	High	High	Low	Low	High
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns

Risk of bias assessment for pain at post-discharge day 1 (co-primary outcome)

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Walton (1990)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Torabinejad (1994)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Collins (1997)	Some concerns	High	High	Low	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Raeder (2001)	Some concerns	High	Some concerns	Low	Some concerns	High
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Li (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Chen (2009)	Some concerns	High	High	Low	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Best (2017)	Low	Low	Low	Low	Some concerns	Some concerns
Samieirad (2017)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Papoian (2020)	Low	Some concerns	High	Some concerns	Low	High
Brady (2021)	High	Some concerns	High	Some concerns	Low	High
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Frants (2021)	High	Some concerns	Low	Some concerns	Low	High
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
La Monaca (2021)	Low	High	High	Low	Low	High
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High
NCT03605914 (2021)	Low	High	High	High	Low	High

Risk of bias assessment for pain at post-discharge day 2

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Walton (1990)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Torabinejad (1994)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Collins (1997)	Some concerns	High	High	Low	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Chen (2009)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Best (2017)	Low	Low	Low	Low	Some concerns	Some concerns
Samieirad (2017)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns

Brady (2021)	High	Some concerns	High	Some concerns	Low	High
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
La Monaca (2021)	Low	High	High	Low	Low	High
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High
NCT03605914 (2021)	Low	High	High	High	Low	High

Risk of bias assessment for pain at post-discharge day 3

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Walton (1990)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Raeder (2001)	Some concerns	High	Some concerns	Low	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Chen (2009)	Some concerns	High	High	Low	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Bugada (2015)	Low	Some concerns	High	Some concerns	Low	High
Samieirad (2017)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
Brady (2021)	High	Some concerns	High	Some concerns	Low	High

Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High
NCT03605914 (2021)	Low	High	High	High	Low	High

Risk of bias assessment for pain at post-discharge days 4-7*

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Li (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Samieirad (2017)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Brady (2021)	High	Some concerns	High	Some concerns	Low	High
Frants (2021)	High	Some concerns	Low	Some concerns	Low	High
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns

NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High
NCT03605914 (2021)	Low	High	High	High	Low	High

* Median post-discharge days until assessment = 7 (range 4 – 7).

Risk of bias assessment for pain at post-discharge days 8-30*

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Papoian (2020)	Low	Some concerns	High	Some concerns	Low	High
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High

* Median post-discharge days until assessment = 12 (range 10 – 28)

Risk of bias assessment for nausea

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Breivik (1998)	Low	High	High	Low	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Raeder (2001)	Some concerns	High	Some concerns	Low	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Brown (2013)	Low	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Bugada (2015)	Low	Some concerns	High	Some concerns	Low	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Desjardins (2020)	Low	Low	Low	Low	Some concerns	Some concerns
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns

NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for overall adverse events

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Walton (1990)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Casey (1997)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Breivik (1998)	Low	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Li (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Bugada (2015)	Low	Some concerns	High	Some concerns	Low	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Desjardins (2020)	Low	Low	Low	Low	Some concerns	Some concerns
Brady (2021)	High	Some concerns	High	Some concerns	Low	High
Frants (2021)	High	Some concerns	Low	Some concerns	Low	High
La Monaca (2021)	Low	High	High	Low	Low	High
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns

NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for constipation

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Raeder (2001)	Some concerns	High	Some concerns	Low	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for dizziness

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Breivik (1998)	Low	High	High	Low	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Brown (2013)	Low	High	High	Low	Some concerns	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Desjardins (2020)	Low	Low	Low	Low	Some concerns	Some concerns
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
NCT02647788 (2019)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
NCT04254679 (2021)	Low	Low	Some concerns	Some concerns	Low	Some concerns

Risk of bias assessment for drowsiness

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Breivik (1998)	Low	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for vomiting (co-primary outcome)

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Brown (2013)	Low	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Bugada (2015)	Low	Some concerns	High	Some concerns	Low	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Akinbade (2019)	Low	Low	Low	Low	Some concerns	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Desjardins (2020)	Low	Low	Low	Low	Some concerns	Some concerns
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for pruritus

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Weinheimer (2019)	High	High	Low	Low	Some concerns	High
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for headache

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Brown (2013)	Low	High	High	Low	Some concerns	High
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Da Silva (2021)	Low	Low	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns

Risk of bias assessment for confusion

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for diarrhoea

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for difficulty urinating

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for indigestion

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns

Risk of bias assessment for nausea or vomit

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Lysell (1992)	Some concerns	High	Low	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Spagnoli (2011)	Some concerns	High	High	Low	Some concerns	High
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns

Risk of bias assessment for bleeding

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT03605914 (2021)	Low	High	High	High	Low	High

Risk of bias assessment for dry mouth

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns

Risk of bias assessment for sleep problems

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Collins (1997)	Some concerns	High	High	Low	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High

Risk of bias assessment for hypotension

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Desjardins (2020)	Low	Low	Low	Low	Some concerns	Some concerns

Risk of bias assessment for difficulty concentrating

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Zuniga (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for acid reflux

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns

Risk of bias assessment for skin rash

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Comfort (2002)	Some concerns	High	High	Some concerns	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High

Risk of bias assessment for upset stomach

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Mitchell (2008)	Low	Low	Low	Low	Low	Low
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High

Risk of bias assessment for difficulty breathing

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Petrikovets (2019)	Low	High	High	Some concerns	Low	High

Risk of bias assessment for patient disposition

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Casey (1997)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Collins (1997)	Some concerns	High	High	Low	Some concerns	High
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Shah (2008)	Some concerns	High	Low	Low	Some concerns	High
Chen (2009)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Brown (2013)	Low	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Bugada (2015)	Low	Some concerns	High	Some concerns	Low	High
Best (2017)	Low	Low	Low	Low	Some concerns	Some concerns
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kim (2019)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Petrikovets (2019)	Low	High	High	Some concerns	Low	High

Risk of bias assessment for patient dissatisfaction

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Lownie (1992)	Some concerns	Some concerns	High	Low	Some concerns	High
Casey (1997)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Han (1998)	High	High	High	Low	Some concerns	High
Church (2006)	Some concerns	High	High	Low	Some concerns	High
Mitchell (2008)	Low	Low	Low	Low	Low	Low
Mitchell (2012)	Low	Low	Low	Low	Low	Low
Brown (2013)	Low	High	High	Low	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Helmerhorst (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Ilyas (2019)	Low	Some concerns	Low	Low	Some concerns	Some concerns
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
Vallecillo (2021)	Low	Some concerns	Low	Low	Low	Some concerns
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for healthcare reutilization

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Casey (1997)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Kim (2005)	Some concerns	High	High	Some concerns	Some concerns	High
Stessel (2014)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Best (2017)	Low	Low	Low	Low	Some concerns	Some concerns
Dinis (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
Brady (2021)	High	Some concerns	High	Some concerns	Low	High
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment for pain interference

Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Gimbel (2001)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Jildeh (2021) (A)	Some concerns	High	High	Some concerns	Low	High
Jildeh (2021) (B)	Low	Some concerns	High	Some concerns	Low	High
NCT04254679 (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns
NCT03818932 (2021)	Some concerns	Low	High	Some concerns	Low	High
NCT03818919 (2021)	Some concerns	High	High	Some concerns	Low	High

Risk of bias assessment for postoperative health status

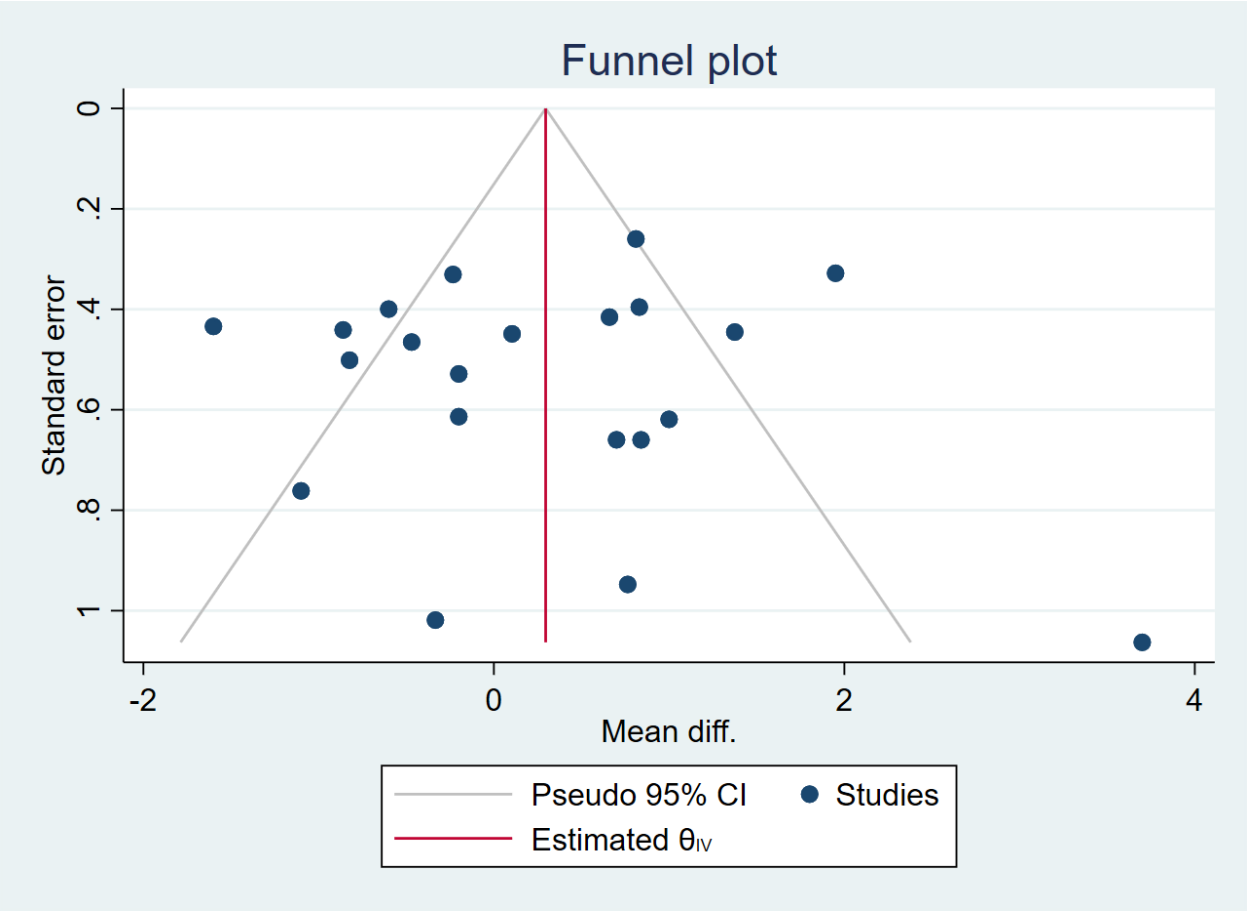
Study	Bias due to randomization	Bias due to deviation from intervention	Bias due to missing outcome data	Bias in the outcome measurement	Bias in selection of the reported results	Overall risk of bias
Petrikovets (2019)	Low	High	High	Some concerns	Low	High
NCT02647788 (2019)	Low	Low	Some concerns	Low	Low	Some concerns

Publication bias assessment via funnel plots (for meta-analyses including ≥ 10 studies)

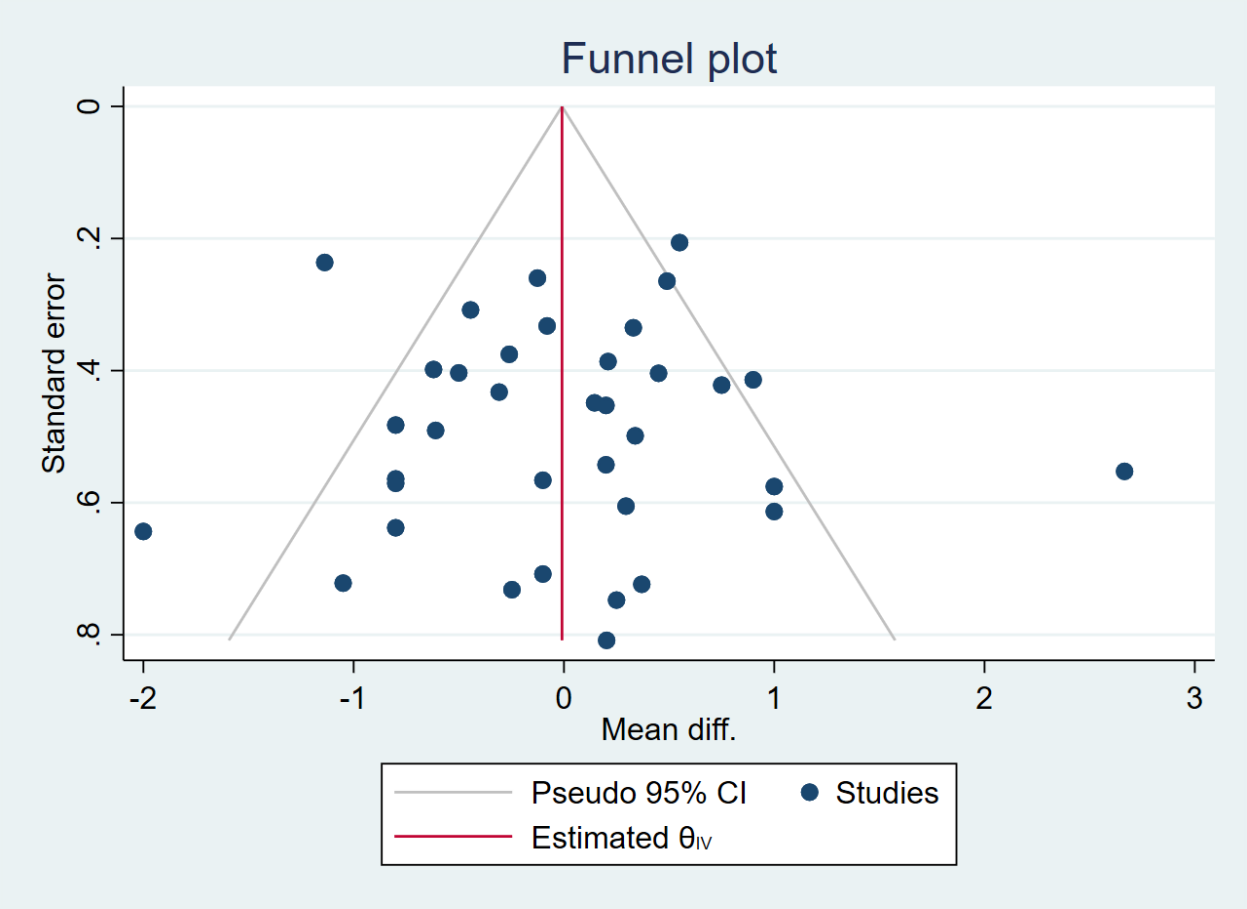
Note: Assessment of risk of bias due to missing results (publication bias) was assess by funnel plots only when at least 10 trials were available for meta-analysis. As a result, it was not possible to construct funnel plots for the following outcomes:

- Pain at post-discharge days 8-30
- Headache
- Confusion
- Diarrhoea
- Difficulty urinating
- Indigestion
- Nausea or vomit
- Bleeding
- Dry mouth
- Sleep problems
- Hypotension
- Difficulty concentrating
- Acid reflux
- Skin rash
- Upset stomach
- Difficulty breathing
- Pain interference (first week post-discharge)
- Quality of recovery (post-discharge day 2)
- Healthcare reutilization

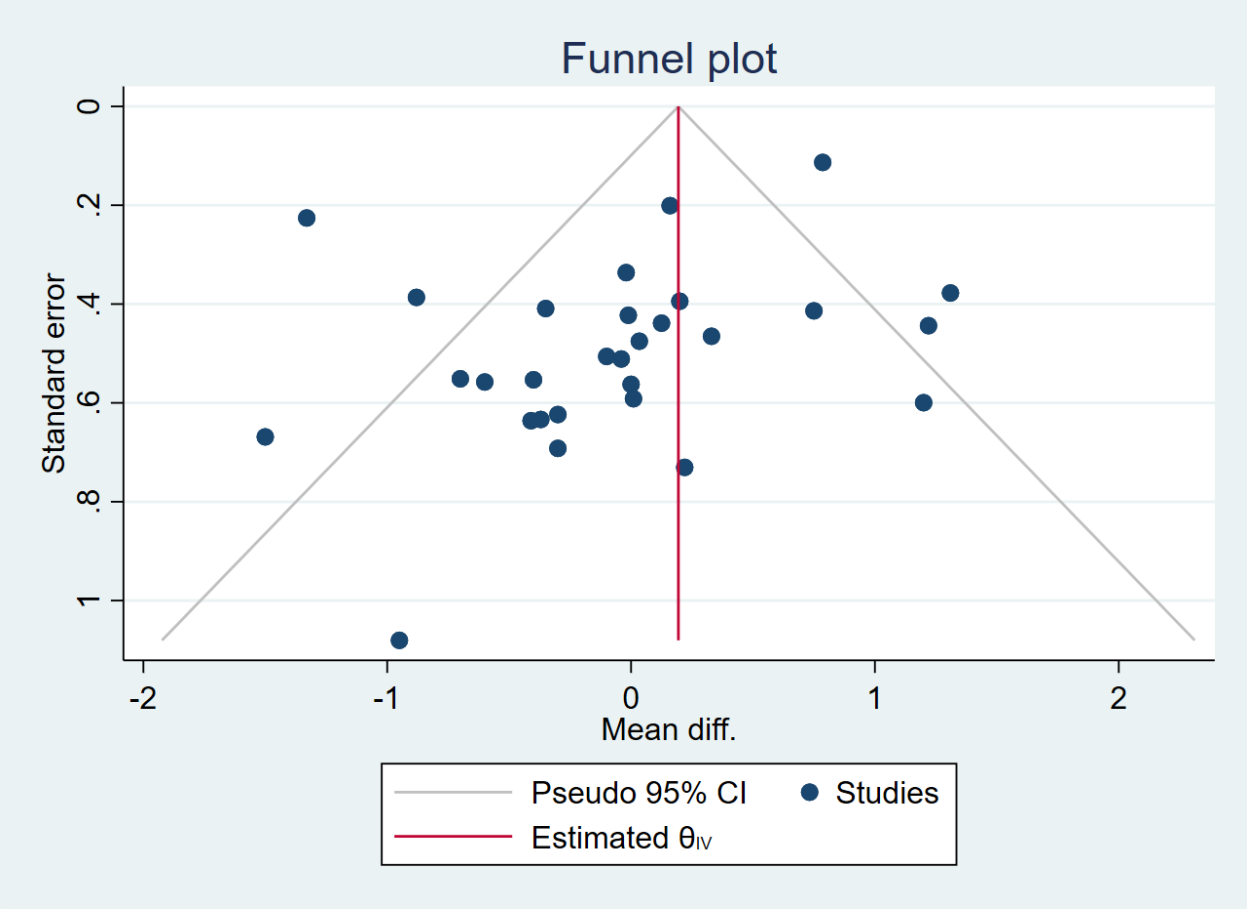
Funnel plot for pain at post-discharge day 0



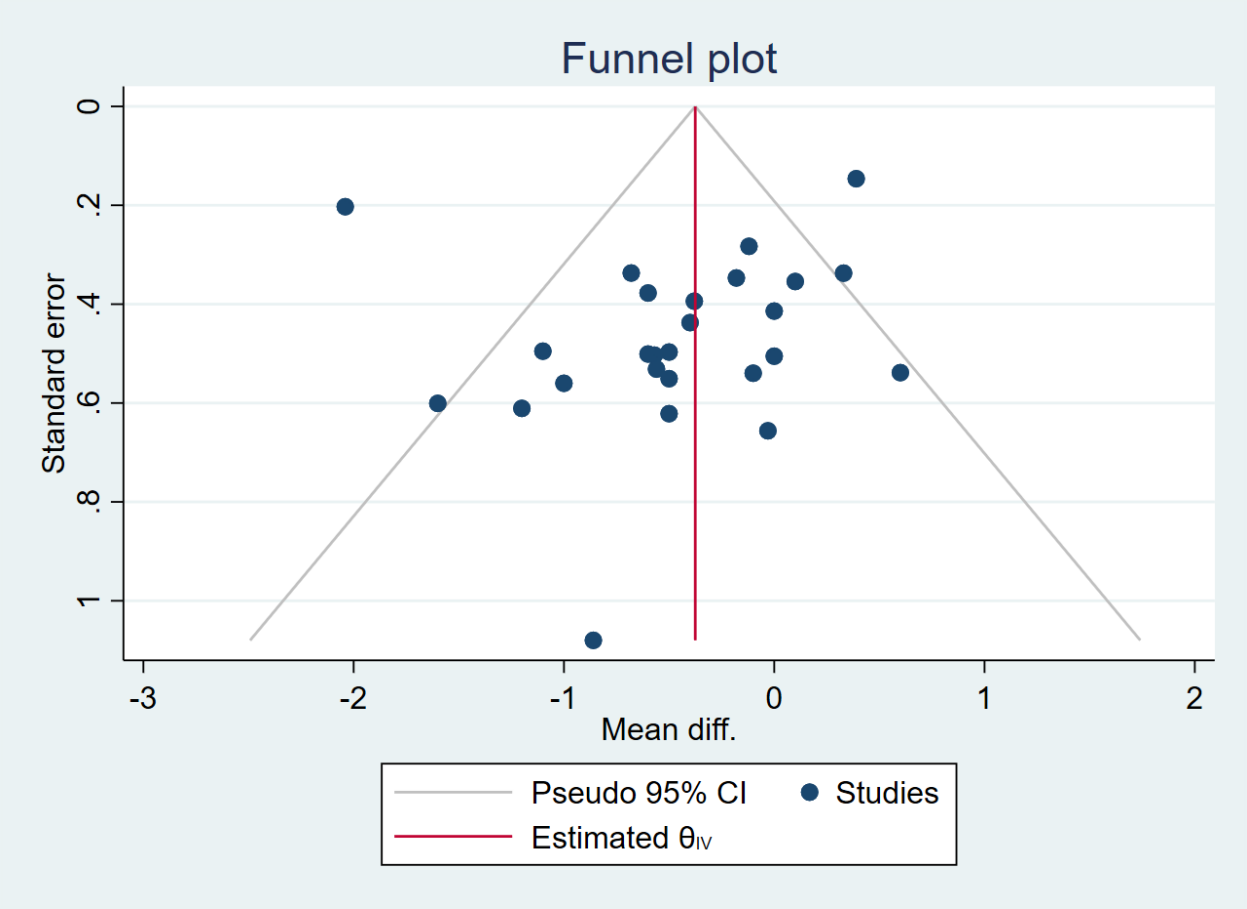
Funnel plot for pain at post-discharge day 1



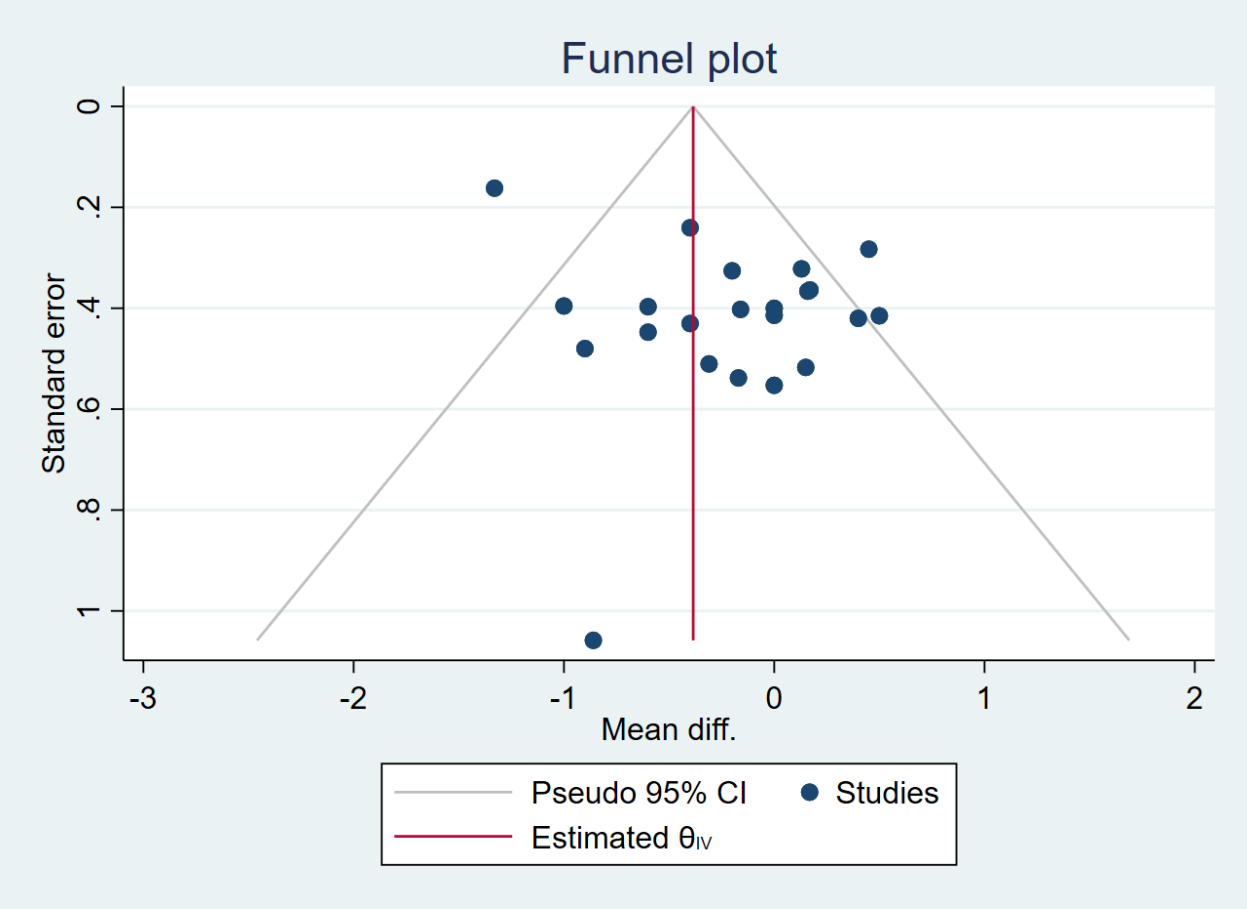
Funnel plot for pain at post-discharge day 2



Funnel plot for pain at post-discharge day 3

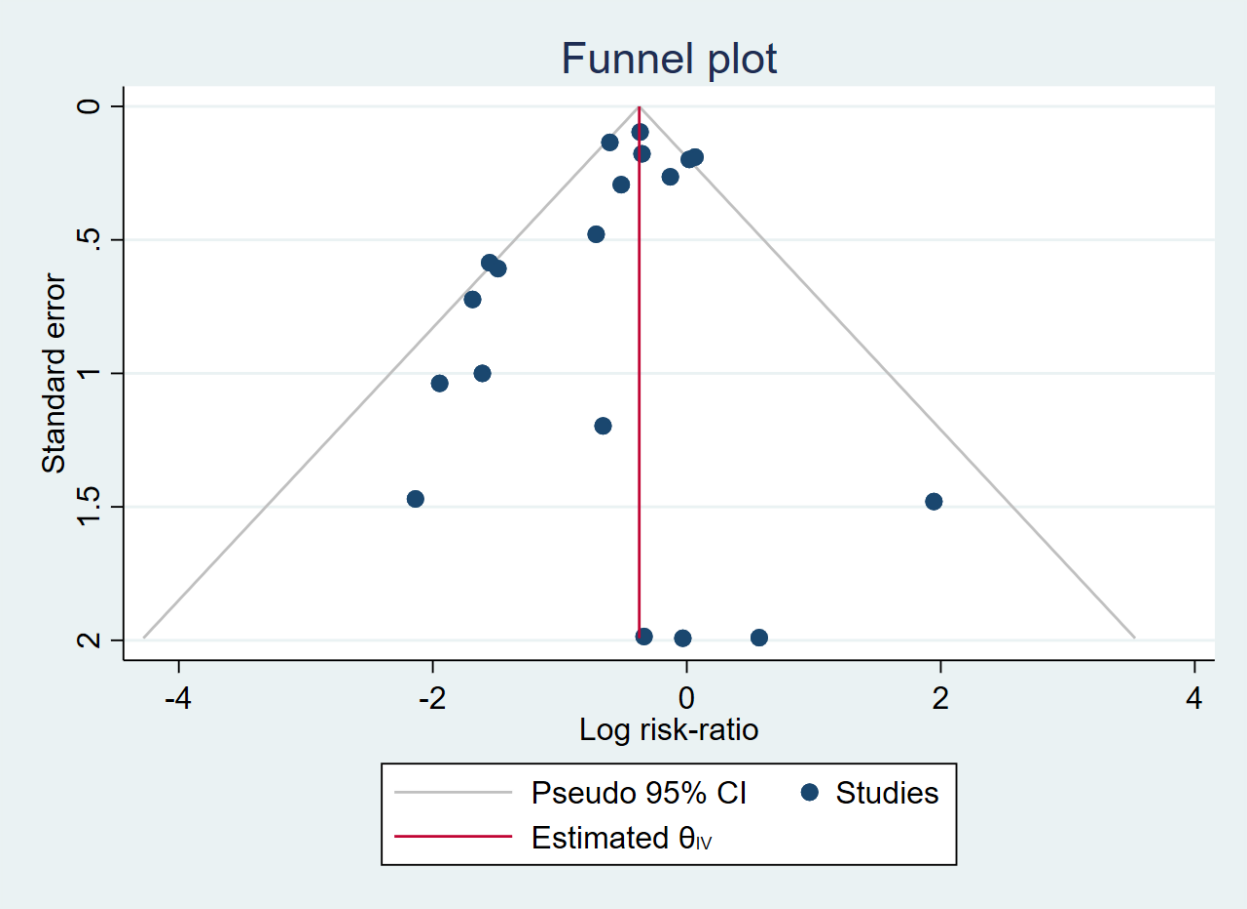


Funnel plot for pain at post-discharge days 4-7*

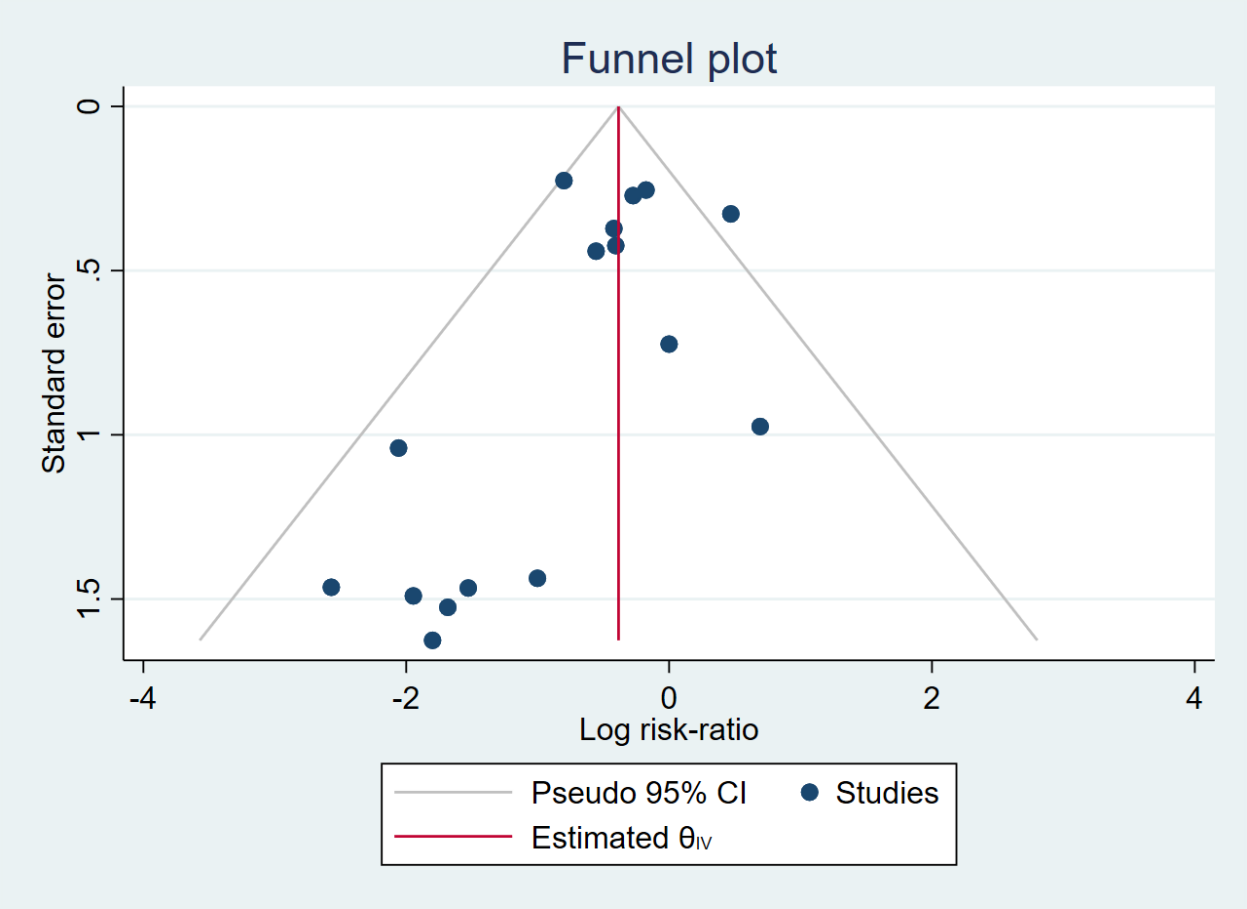


* Median post-discharge days until assessment = 7 (range 4 – 7).

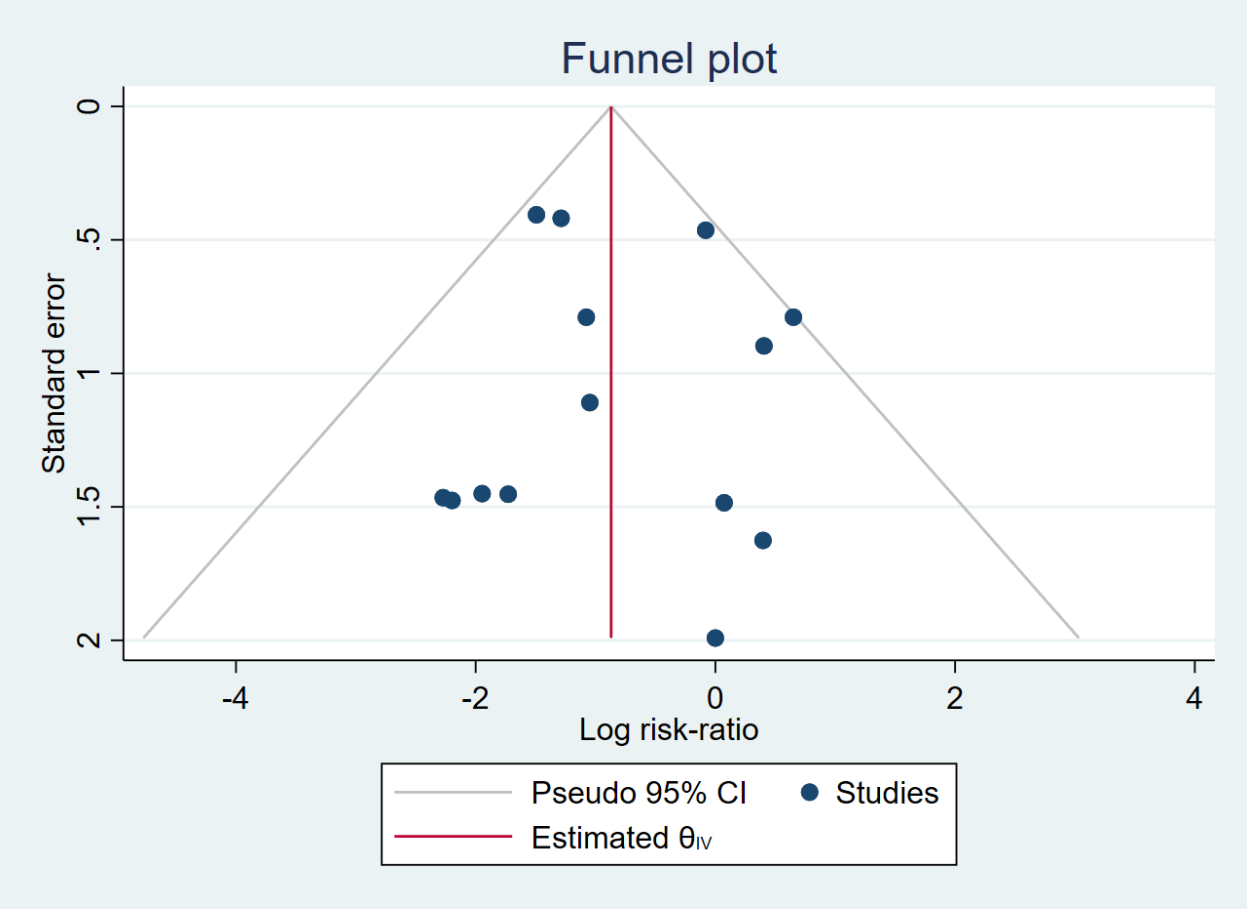
Funnel plot for any adverse event



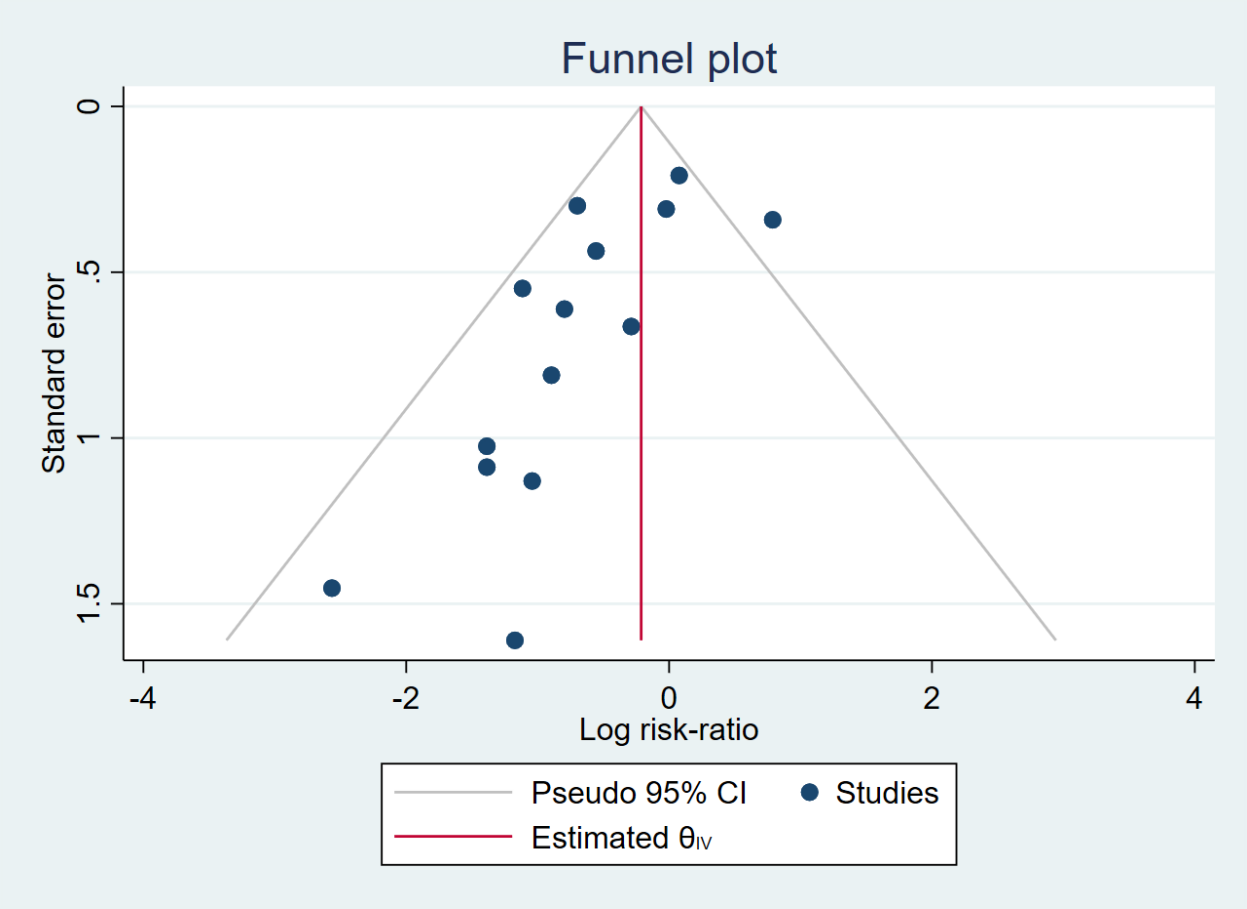
Funnel plot for constipation



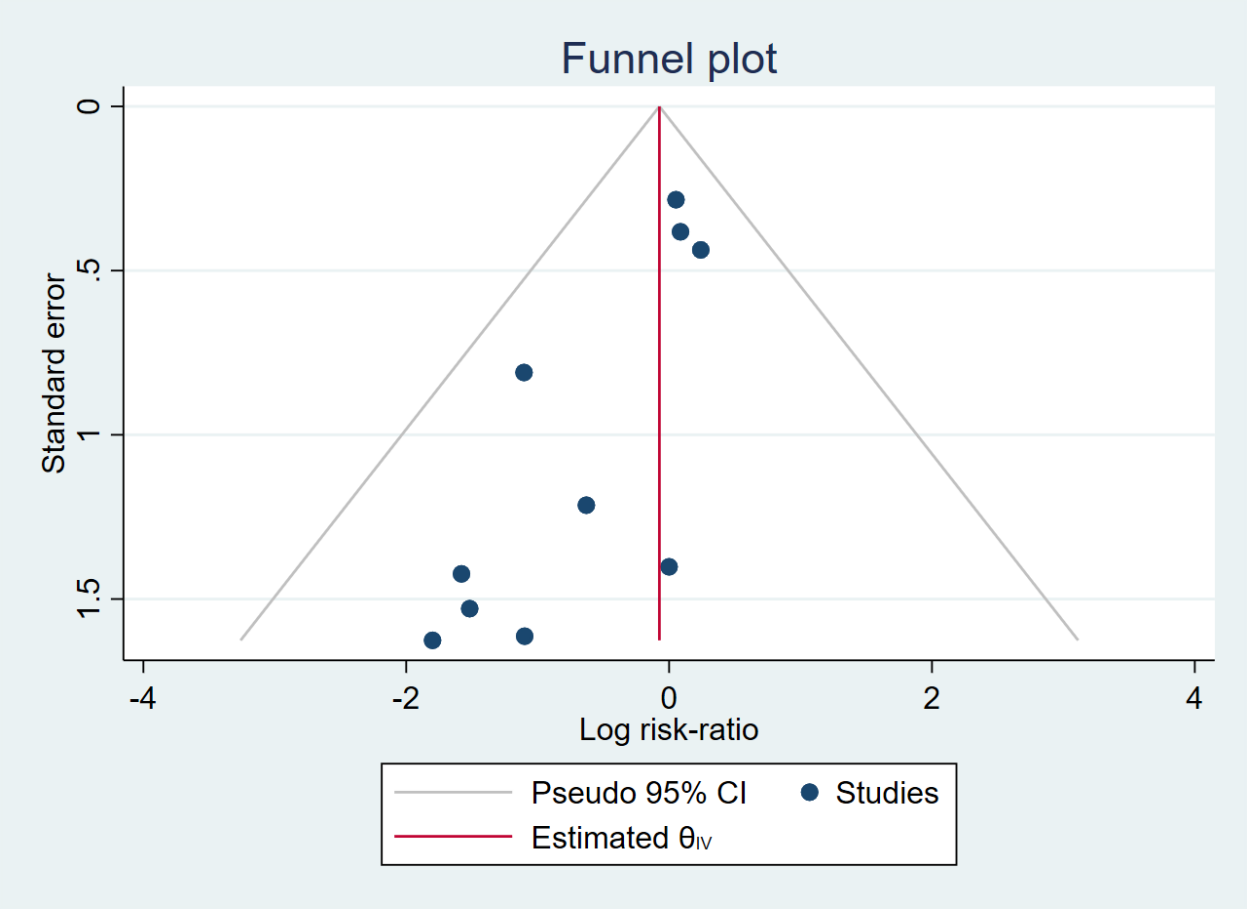
Funnel plot for dizziness



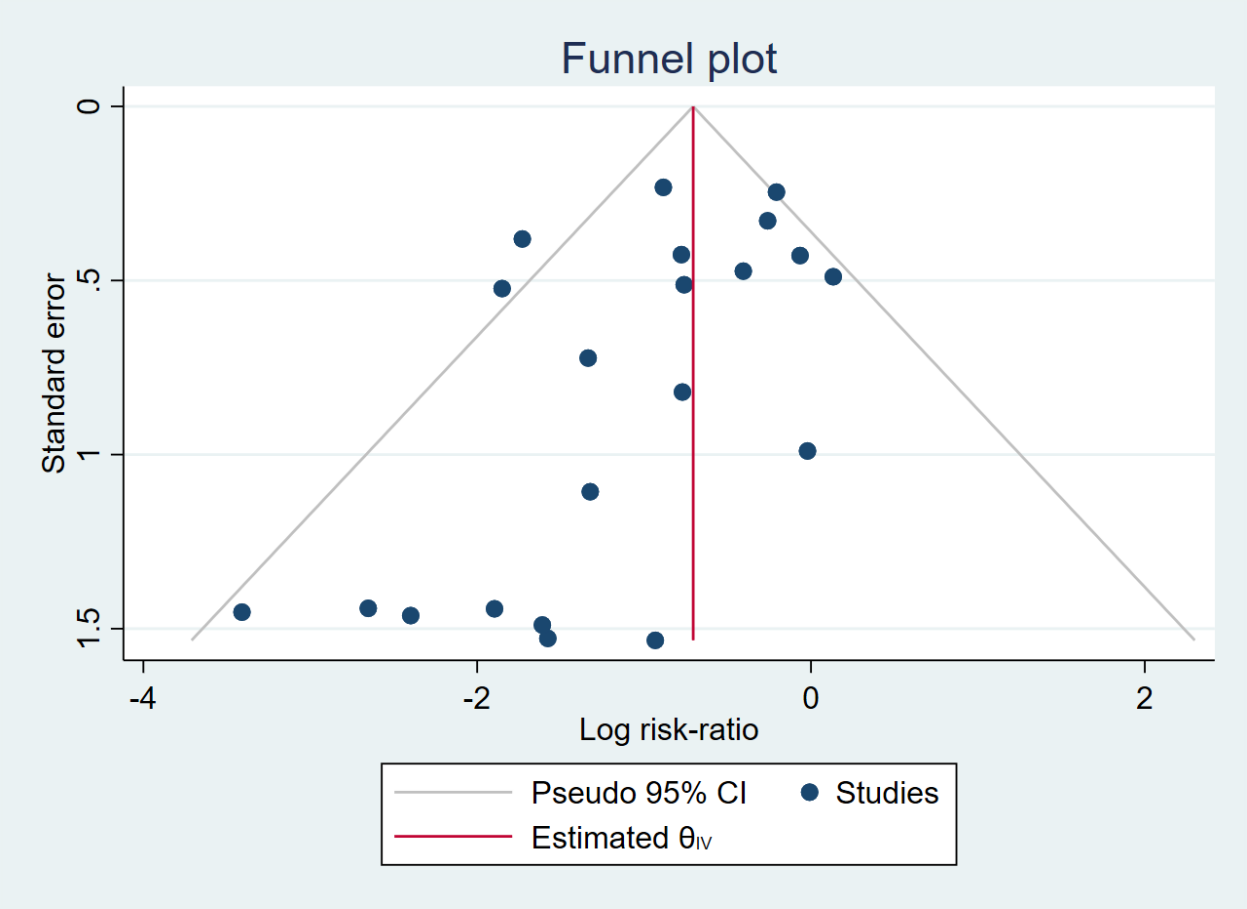
Funnel plot for any drowsiness



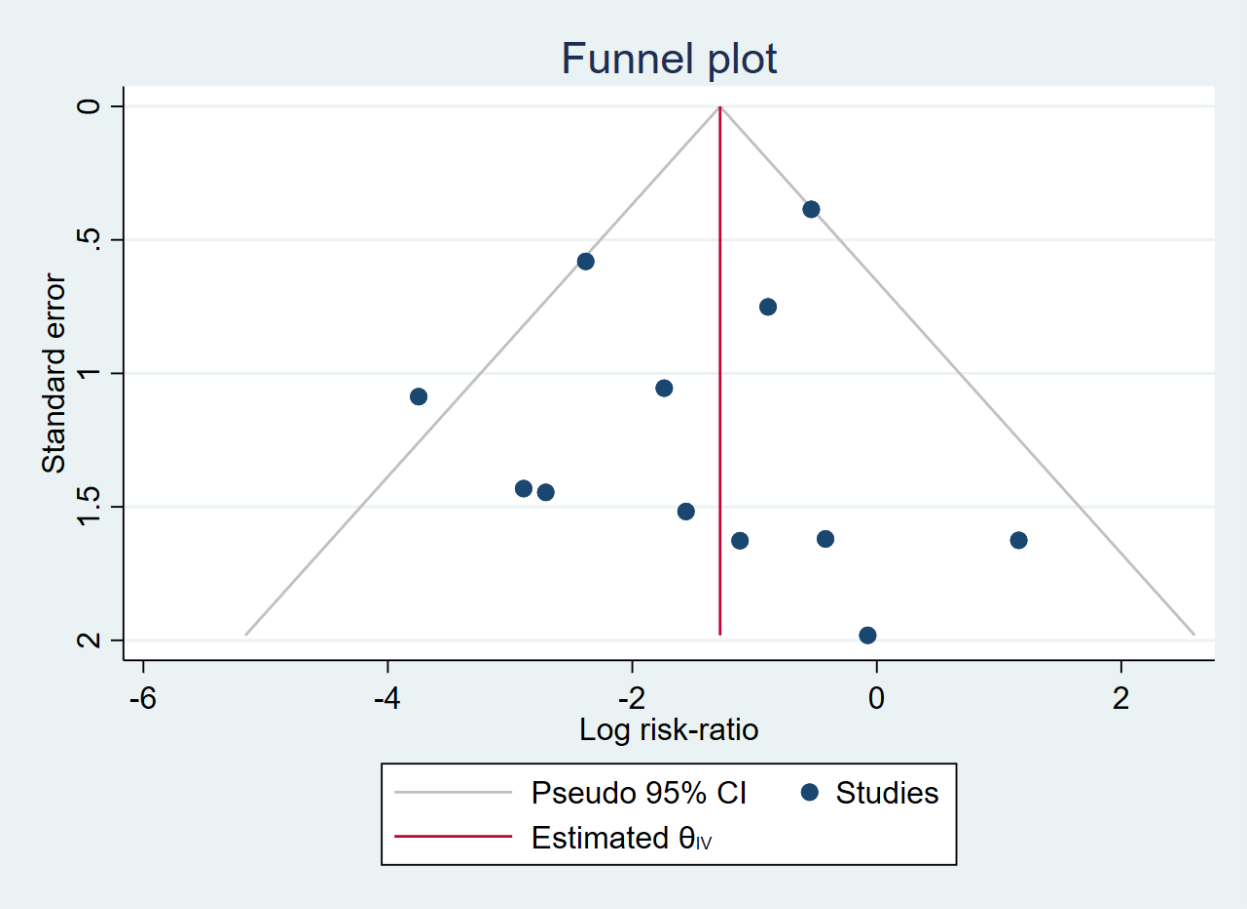
Funnel plot for pruritus



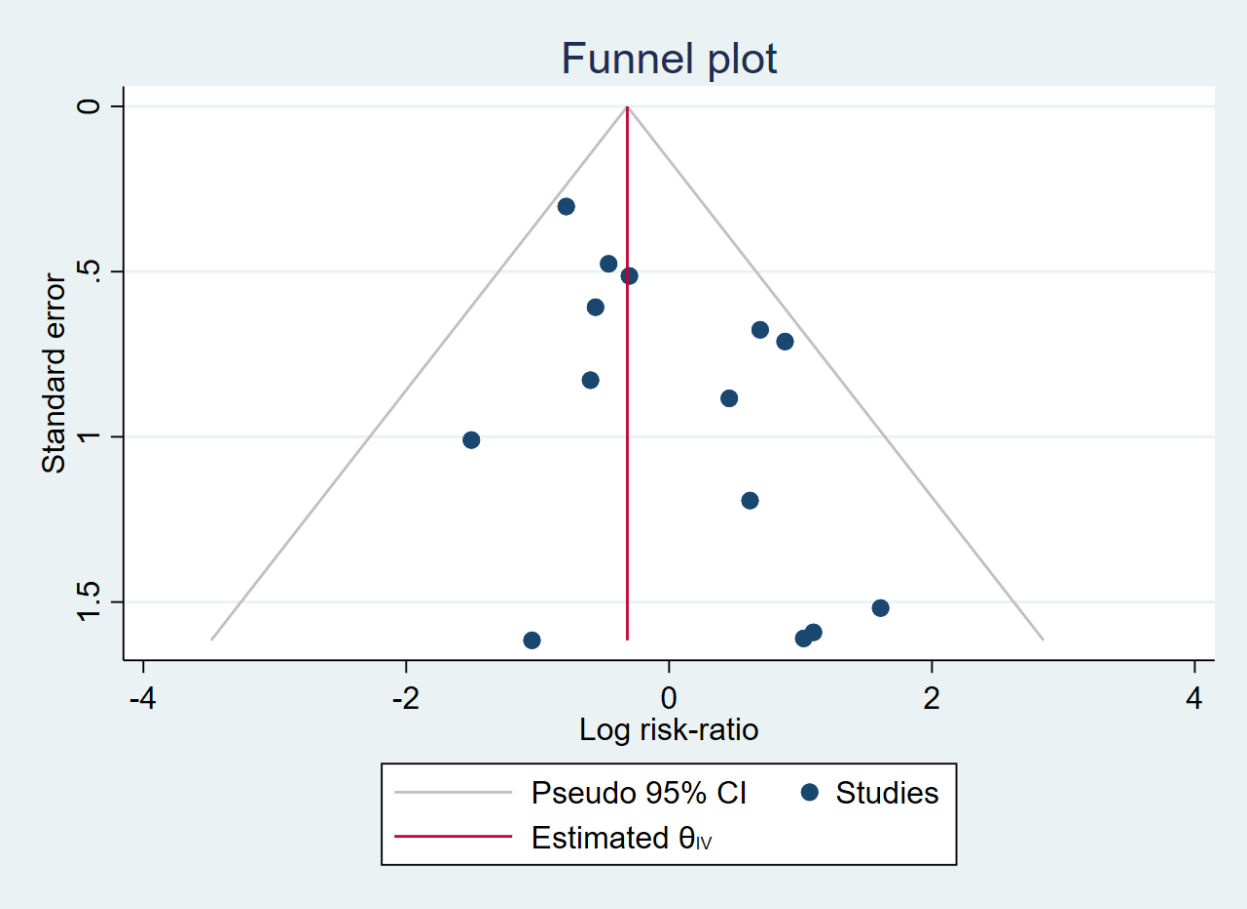
Funnel plot for nausea



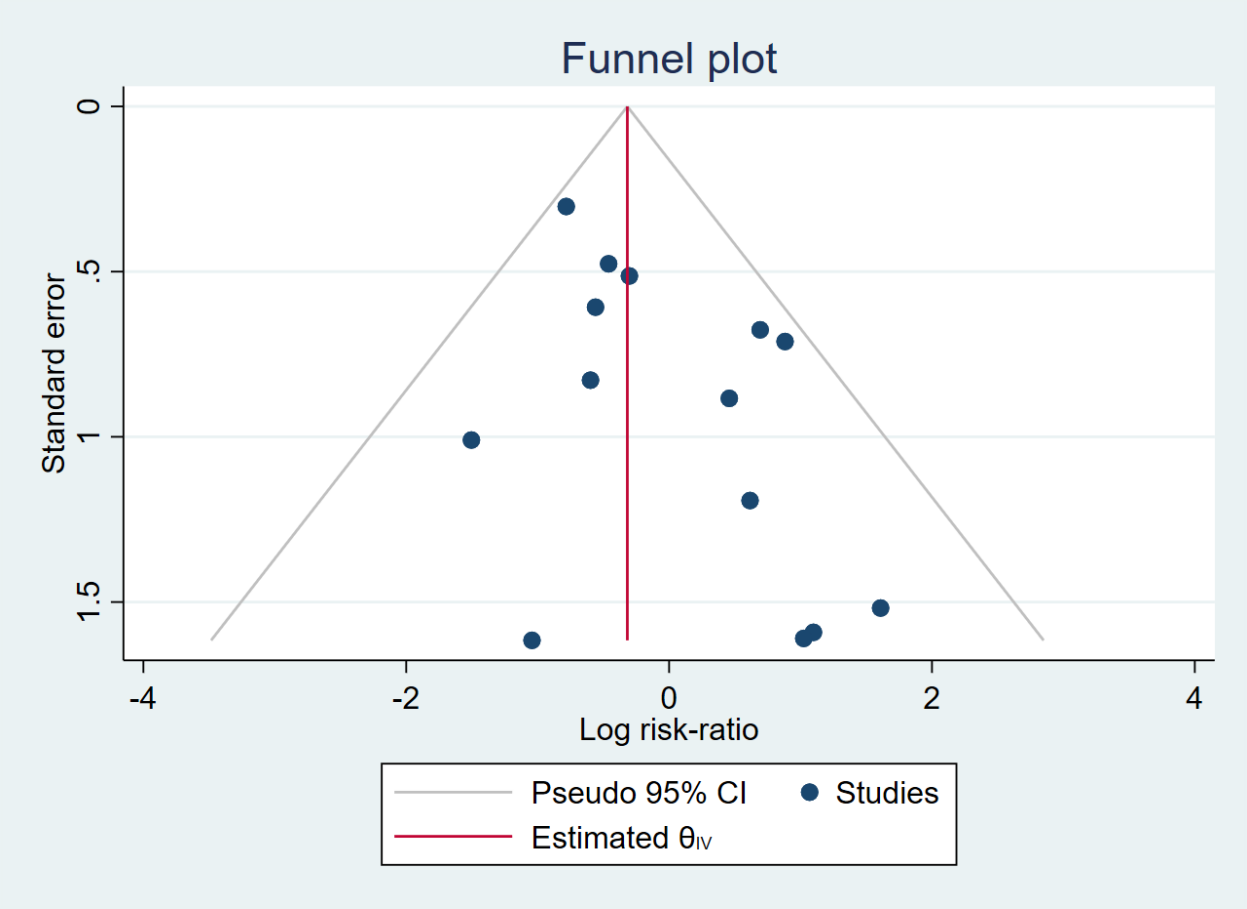
Funnel plot for vomiting



Funnel plot for patient disposition



Funnel plot for patient dissatisfaction



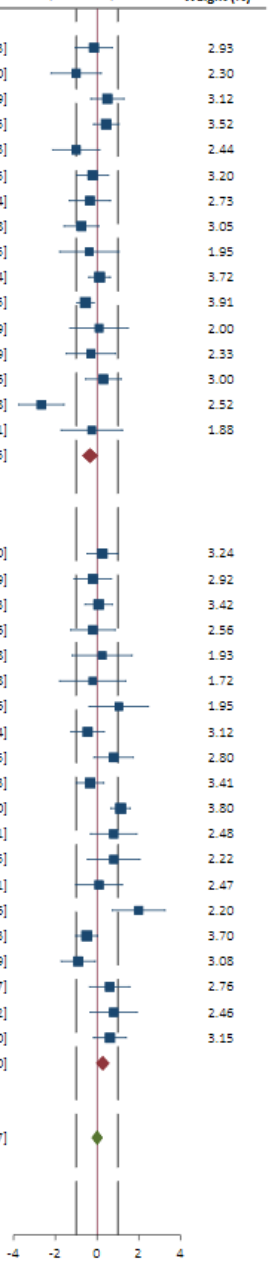
Subgroup analyses for pain at post-discharge day 1

Note: Subgroup analyses were limited to instances where there were two or more trials available in each subgroup. Given this criterion, it was not possible to conduct the following analysis:

- Only women participants vs. men (or both sexes)

Subgroup analysis of surgeries conducted in an outpatient clinic vs. hospital operating room procedures

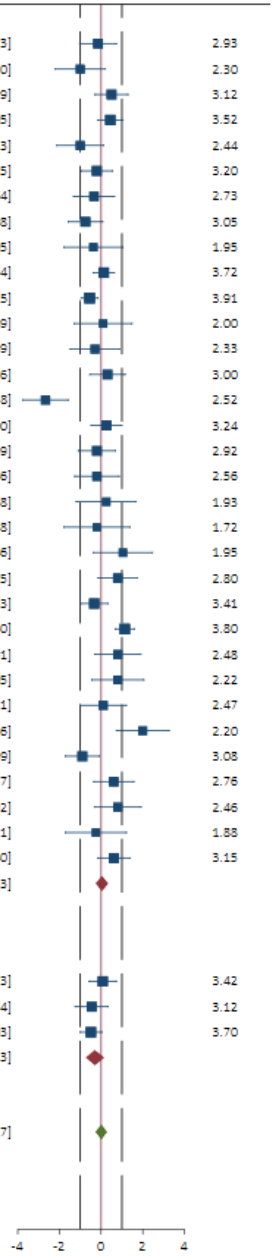
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Outpatient clinic											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Heterogeneity: χ^2 = 38.48, df = 15 (p < 0.01); I^2 = 69.63%										-0.33 [-0.72, 0.05]	
Operating room											
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Papolan (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 51.92, df = 19 (p < 0.01); I^2 = 62.99%										0.27 [-0.05, 0.60]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 5.59, df = 1 (p = 0.02)											



* Unpublished studies

Subgroup analysis of day-surgery vs. in-patient surgery

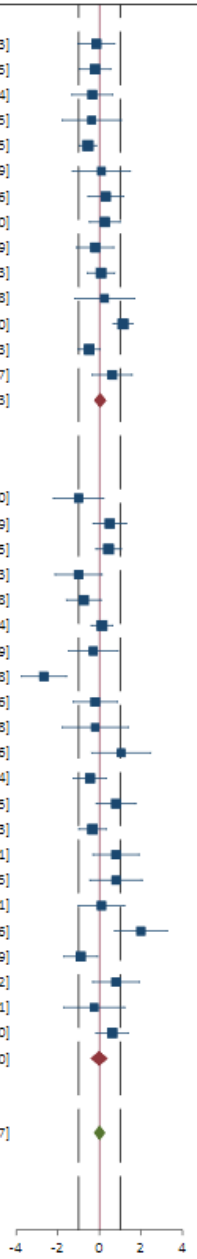
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Day-surgery											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Papolan (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 98.35, df = 32 (p < 0.01); I^2 = 71.72%										0.04 [-0.25, 0.33]	
In-patient surgery											
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Heterogeneity: χ^2 = 1.96, df = 2 (p = 0.38); I^2 = 26.75%										-0.30 [-0.73, 0.13]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 38.48, df = 15 (p < 0.01); I^2 = 69.63%											
Group differences χ^2 = 1.61, df = 1 (p = 0.20)											



* Unpublished studies

Subgroup analysis of lower risk of bias vs. high risk of bias

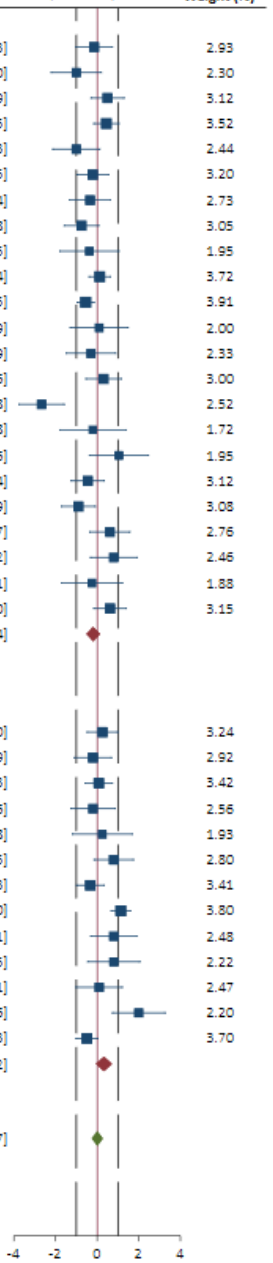
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Lower risk of bias											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Heterogeneity: χ^2 = 37.70, df = 13 (p < 0.01); I^2 = 51.01%										0.04 [-0.26, 0.33]	
High risk of bias											
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 65.97, df = 21 (p < 0.01); I^2 = 75.78%										-0.01 [-0.42, 0.40]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 0.03, df = 1 (p = 0.85)											



* Unpublished studies

Subgroup analysis of minor vs. moderate surgery

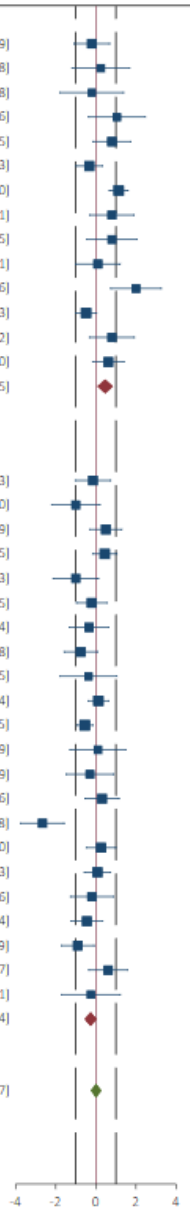
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Minor surgery											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 55.04, df = 22 (p < 0.01); I^2 = 69.17%										-0.19 [-0.52, 0.14]	
Moderate surgery											
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Papolan (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Heterogeneity: τ^2 = 0.32, I^2 = 65.83%, H^2 = 2.93										0.33 [-0.07, 0.72]	
Test of $\theta_i = \theta_j$: Q(12) = 37.12, p = 0.00											
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 3.86, df = 1 (p = 0.05)											



* Unpublished studies

Subgroup analysis of stronger opioids (OME ≥ 1) vs. weaker opioids (OME < 1)

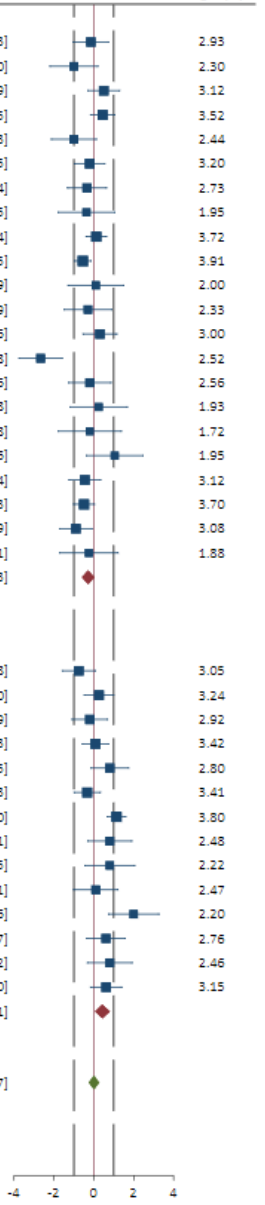
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Mean difference with 95% CI
Stronger opioids (OME ≥ 1)											
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 37.82, df = 13 (p < 0.01); I^2 = 60.71%										0.46 [0.07, 0.85]	
Weaker opioids (OME < 1)											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Heterogeneity: χ^2 = 46.96, df = 21 (p < 0.01); I^2 = 65.88%										-0.26 [-0.57, 0.04]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 8.12, df = 1 (p < 0.01)											



* Unpublished studies

Subgroup analysis of around the clock opioid analgesia vs. as needed opioid analgesia

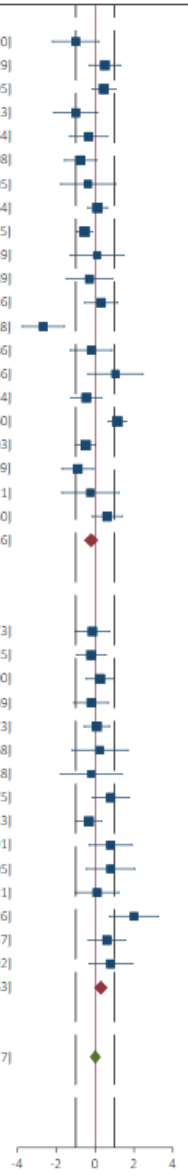
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Opioid analgesia around the clock											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Heterogeneity: χ^2 = 44.28, df = 21 (p < 0.01); I^2 = 65.08%										-0.29 [-0.60, 0.03]	
Opioid analgesia as needed											
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 33.59, df = 13 (p < 0.01); I^2 = 63.55%										0.43 [0.05, 0.81]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 8.13, df = 1 (p < 0.01)											



* Unpublished studies

Subgroup analysis of unimodal opioid-free analgesia regimen vs. multimodal opioid-free analgesia regimen

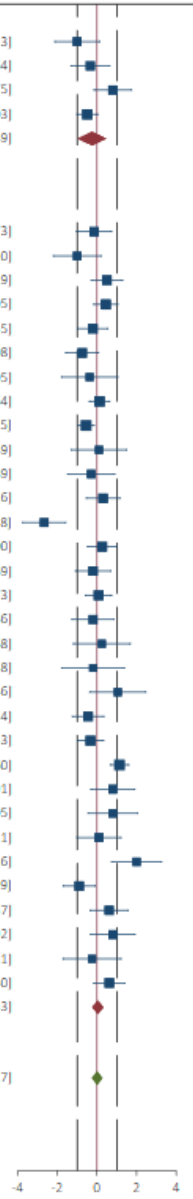
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Unimodal opioid-free analgesia regimen											
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 80.78, df = 20 (p < 0.01); I^2 = 76.76%										-0.21 [-0.57, 0.16]	
Multimodal opioid-free analgesia regimen											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Heterogeneity: χ^2 = 18.61, df = 14 (p = 0.18); I^2 = 47.41%										0.29 [-0.05, 0.63]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 3.82, df = 1 (p = 0.05)											



* Unpublished studies

Subgroup analysis of unimodal opioid analgesia regimen vs. multimodal opioid analgesia regimen

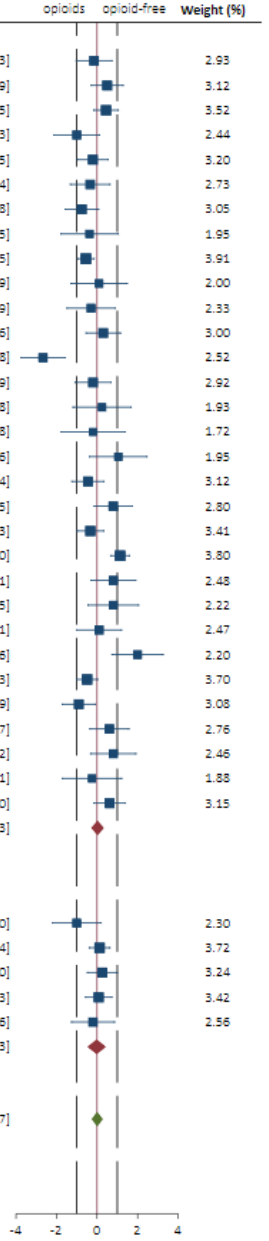
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Unimodal opioid analgesia regimen											
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Heterogeneity: χ^2 = 7.20, df = 3 (p = 0.07); I^2 = 65.89%										-0.25 [-0.99, 0.49]	
Multimodal opioid analgesia regimen											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 93.55, df = 31 (p < 0.01); I^2 = 71.69%										0.04 [-0.25, 0.33]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 0.52, df = 1 (p = 0.47)											



* Unpublished studies

Subgroup analysis of no industry funding vs. reported industry funding

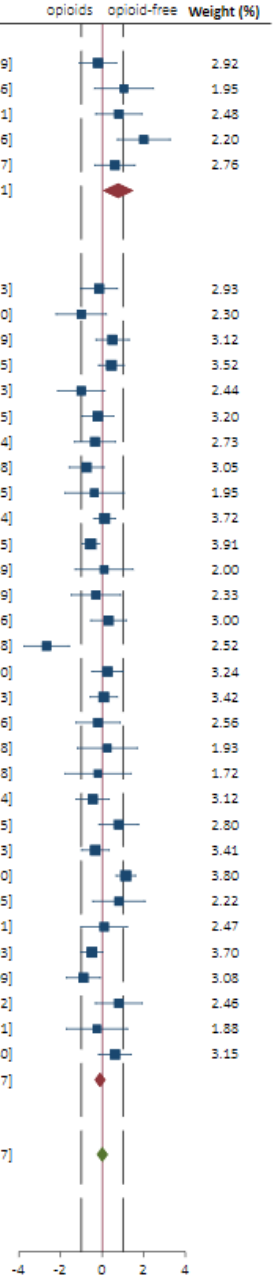
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Industry funding not reported											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Papolan (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 100.17, df = 30 (p < 0.01); I^2 = 73.11%										0.02 [-0.28, 0.33]	
Industry funding reported											
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Heterogeneity: χ^2 = 3.53, df = 4 (p = 0.47); I^2 = 41.37%										-0.02 [-0.47, 0.43]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 0.03, df = 1 (p = 0.87)											



* Unpublished studies

Subgroup analysis of unpublished studies vs. published studies

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Unpublished study											
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.80 (2.11 to 3.49)	37	3.00 (2.45 to 3.55)	-0.20 [-1.09, 0.69]	2.92
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	26	2.39 (2.06 to 2.72)	31	2.94 (2.71 to 3.17)	1.05 [-0.36, 2.46]	1.95
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.70 (3.88 to 5.52)	34	3.90 (3.16 to 4.64)	0.80 [-0.31, 1.91]	2.48
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	5.70 (4.95 to 6.45)	17	3.70 (2.65 to 4.75)	2.00 [0.74, 3.26]	2.20
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	53	3.51 (2.79 to 4.23)	49	2.90 (2.28 to 3.52)	0.61 [-0.35, 1.57]	2.76
Heterogeneity: χ^2 = 8.31, df = 4 (p = 0.08); I^2 = 55.56%										0.77 [0.03, 1.51]	
Published study											
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	2.02 (1.39 to 2.65)	49	2.17 (1.55 to 2.78)	-0.15 [-1.03, 0.73]	2.93
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.40 (0.53 to 2.27)	27	2.40 (1.57 to 3.23)	-1.00 [-2.20, 0.20]	2.30
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.30 (0.74 to 1.86)	60	0.80 (0.24 to 1.36)	0.50 [-0.29, 1.29]	3.12
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	2.60 (2.12 to 3.08)	144	2.16 (1.80 to 2.52)	0.44 [-0.16, 1.05]	3.52
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3.00 (2.21 to 3.79)	29	4.00 (3.20 to 4.80)	-1.00 [-2.13, 0.13]	2.44
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.99 (1.45 to 2.53)	67	2.20 (1.67 to 2.73)	-0.21 [-0.97, 0.55]	3.20
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.51 (1.90 to 3.12)	45	2.85 (2.08 to 3.61)	-0.34 [-1.32, 0.64]	2.73
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	2.82 (2.39 to 3.25)	38	3.57 (2.78 to 4.36)	-0.75 [-1.58, 0.08]	3.05
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.72 to 3.84)	34	3.15 (2.22 to 4.08)	-0.37 [-1.79, 1.05]	1.95
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	5.83 (5.56 to 6.10)	96	5.70 (5.33 to 6.08)	0.13 [-0.38, 0.64]	3.72
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	2.39 (2.95 to 5.19)	38	2.94 (2.13 to 3.91)	-0.55 [-0.95, -0.15]	3.91
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	2.50 (1.53 to 3.47)	19	2.40 (1.41 to 3.39)	0.10 [-1.29, 1.49]	2.00
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	4.83 (4.14 to 5.51)	20	5.12 (4.15 to 6.09)	-0.30 [-1.48, 0.89]	2.33
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.00 (0.20 to 1.80)	262	0.69 (0.42 to 0.96)	0.31 [-0.54, 1.16]	3.00
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	1.93 (1.19 to 2.67)	31	4.60 (3.81 to 5.38)	-2.67 [-3.75, -1.58]	2.52
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	71	3.97 (3.45 to 4.49)	69	3.71 (3.19 to 4.23)	0.26 [-0.48, 1.00]	3.24
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	56	2.04 (1.58 to 2.50)	59	1.96 (1.50 to 2.42)	0.08 [-0.57, 0.73]	3.42
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	5.20 (4.39 to 6.01)	51	5.40 (4.71 to 6.09)	-0.20 [-1.26, 0.86]	2.56
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	2.92 (2.11 to 3.73)	35	2.67 (1.44 to 3.90)	0.25 [-1.19, 1.68]	1.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.74 (1.66 to 3.82)	14	2.94 (1.79 to 4.10)	-0.20 [-1.79, 1.38]	1.72
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	7.45 (6.93 to 7.97)	30	7.90 (7.51 to 8.29)	-0.45 [-1.24, 0.34]	3.12
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	2.40 (1.68 to 3.12)	49	1.60 (0.98 to 2.22)	0.80 [-0.15, 1.75]	2.80
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5.67 (5.12 to 6.22)	64	6.00 (5.64 to 6.36)	-0.33 [-0.99, 0.33]	3.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.83 (6.50 to 7.16)	185	5.69 (5.37 to 6.02)	1.14 [0.67, 1.60]	3.80
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.90 (4.02 to 5.78)	24	4.10 (3.22 to 4.98)	0.80 [-0.45, 2.05]	2.22
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.80 (2.01 to 3.59)	31	2.70 (1.92 to 3.48)	0.10 [-1.01, 1.21]	2.47
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	4.46 (4.09 to 4.83)	46	4.95 (4.59 to 5.31)	-0.49 [-1.01, 0.03]	3.70
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (0 to 0)	57	0.90 (0.33 to 1.47)	-0.90 [-1.71, -0.09]	3.08
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	3.00 (2.21 to 3.79)	30	2.20 (1.41 to 2.99)	0.80 [-0.32, 1.92]	2.46
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.12 (1.07 to 3.17)	18	2.37 (1.35 to 3.39)	-0.25 [-1.71, 1.21]	1.88
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	26	2.46 (1.73 to 3.19)	38	1.84 (1.43 to 2.25)	0.62 [-0.16, 1.40]	3.15
Heterogeneity: χ^2 = 87.80, df = 30 (p < 0.01); I^2 = 68.48%										-0.10 [-0.37, 0.17]	
Overall										0.01 [-0.26, 0.27]	
Heterogeneity: χ^2 = 103.72, df = 35 (p < 0.01); I^2 = 71.44%											
Group differences χ^2 = 4.69, df = 1 (p = 0.03)											



* Unpublished studies

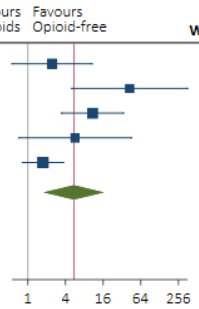
Sensitivity analyses for vomiting

Results obtained with no continuity correction

						Opioid analgesia		Opioid-free analgesia			
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	No. of incidents	No. of patients	No. of incidents	No. of patients	Risk ratio with 95% CI	Weight (%)
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	20.08
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	14.52
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	23.36
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	14.98
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	27.05
Overall										5.41 [1.77, 16.53]	

Heterogeneity: χ^2 = 12.78, df = 4 (p = 0.01); I^2 = 69.76%

Test for overall effect: Z = 2.97, (p < 0.01)



* Unpublished studies

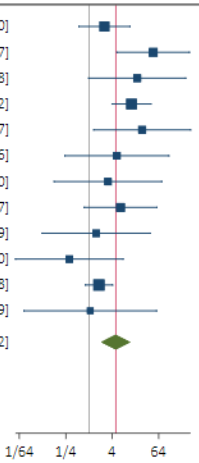
Please note that trials containing zero cells are excluded from the analysis when no continuity correction is applied.

Results obtained with treatment-arm continuity correction (TACC) method (https://pubmed.ncbi.nlm.nih.gov/15116347/)

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Odds ratio with 95% CI	Weight (%)
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.51 [0.55, 11.50]	12.29
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	46.05 [5.29, 401.07]	8.97
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	17.73 [0.98, 320.48]	6.30
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	12.64 [3.96, 40.32]	14.50
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	23.84 [1.33, 427.87]	6.33
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	5.27 [0.24, 117.26]	5.73
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.09 [0.12, 76.90]	5.45
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	6.55 [0.75, 57.27]	8.95
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.53 [0.06, 38.59]	5.42
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.70]	5.45
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.81 [0.81, 4.08]	16.63
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 56.39]	3.98
Overall										4.92 [2.03, 11.92]	

Heterogeneity: χ^2 = 18.63, df = 11 (p = 0.07); I^2 = 52.37%

Test for overall effect: Z = 3.52, (p < 0.01)



* Unpublished studies

Please note that results are presented as odds ratios; Stata does not apply the treatment-arm continuity correction (TACC) to risk ratios.

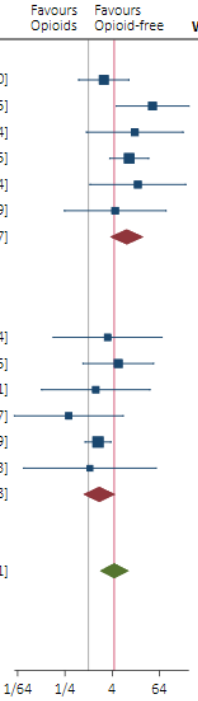
Subgroup analyses for vomiting

Note: Subgroup analyses were limited to instances where there were two or more trials available in each subgroup. Given this criterion, it was not possible to conduct the following analyses:

- Only women participants vs. men (or both sexes)
- Unpublished studied vs. published studies
- Unimodal opioid analgesia vs. multimodal opioid analgesia

Subgroup analysis of minor surgery vs. moderate surgery

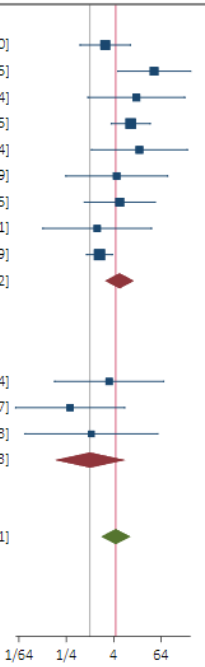
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Outpatient clinic											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
Heterogeneity: χ^2 = 5.70, df = 5 (p = 0.34); I^2 = 32.58%										9.34 [3.48, 25.07]	
Operating room											
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 2.54, df = 5 (p = 0.77); I^2 = 17.70%										1.86 [0.73, 4.78]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 5.37, df = 1 (p = 0.02)											



* Unpublished studies

Subgroup analysis of day-surgery vs. in-patient surgery

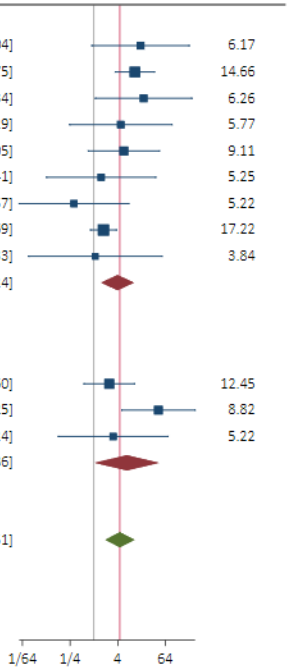
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Day-surgery											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Heterogeneity: χ^2 = 15.21, df = 8 (p = 0.06); I^2 = 48.23%										5.59 [2.42, 12.92]	
In-patient surgery											
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 0.99, df = 2 (p = 0.61); I^2 = 9.66%										1.00 [0.13, 7.83]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 2.30, df = 1 (p = 0.13)											



* Unpublished studies

Subgroup analysis of lower risk of bias vs. high risk of bias

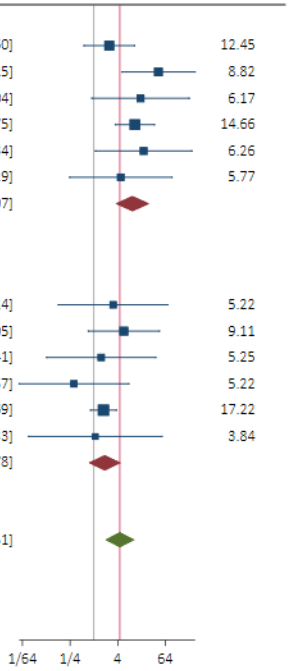
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Lower risk of bias											
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 12.43, df = 8 (p = 0.13); I^2 = 47.63%										3.93 [1.50, 10.24]	
High risk of bias											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
Heterogeneity: χ^2 = 4.84, df = 2 (p = 0.09); I^2 = 55.53%										6.75 [1.04, 43.86]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 0.26, df = 1 (p = 0.61)											



* Unpublished studies

Subgroup analysis of minor vs. moderate surgery

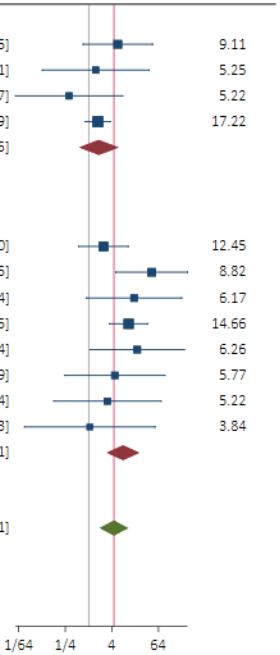
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Minor surgery											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
Heterogeneity: χ^2 = 5.70, df = 5 (p = 0.34); I^2 = 32.58%										9.34 [3.48, 25.07]	
Moderate surgery											
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 2.54, df = 5 (p = 0.77); I^2 = 17.70%										1.86 [0.73, 4.78]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 5.37, df = 1 (p = 0.02)											



* Unpublished studies

Subgroup analysis of stronger opioids (OME ≥ 1) vs. weaker opioids (OME < 1)

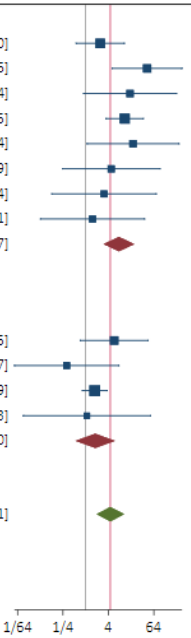
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Stronger opioids (OME ≥ 1)											
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Heterogeneity: χ^2 = 2.37, df = 3 (p = 0.50); I^2 = 32.77%										1.83 [0.56, 5.95]	
Weaker opioids (OME < 1)											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 7.13, df = 7 (p = 0.42); I^2 = 33.94%										7.72 [2.92, 20.41]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 3.41, df = 1 (p = 0.06)											



* Unpublished studies

Subgroup analysis of around the clock opioid analgesia vs. as needed opioid analgesia

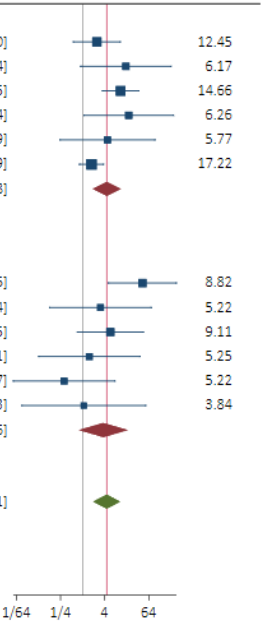
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Opioid analgesia around the clock											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Heterogeneity: χ^2 = 7.15, df = 7 (p = 0.41); I^2 = 32.62%										7.60 [2.95, 19.57]	
Opioid analgesia as needed											
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 2.42, df = 3 (p = 0.49); I^2 = 32.02%										1.79 [0.53, 6.00]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 3.41, df = 1 (p = 0.06)											



* Unpublished studies

Subgroup analysis of unimodal opioid-free analgesia regimen vs. multimodal opioid-free analgesia regimen

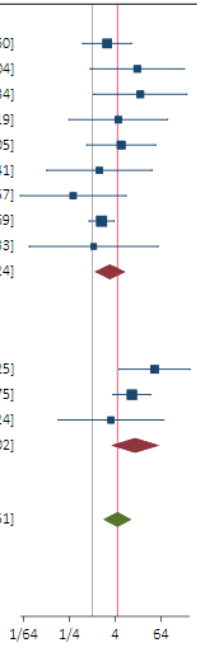
Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Unimodal opioid-free analgesia regimen											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Heterogeneity: χ^2 = 9.67, df = 5 (p = 0.09); I^2 = 45.11%										4.52 [1.86, 10.98]	
Multimodal opioid-free analgesia regimen											
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 8.01, df = 5 (p = 0.16); I^2 = 43.97%										3.65 [0.79, 16.96]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 0.06, df = 1 (p = 0.81)											



* Unpublished studies

Subgroup analysis of no industry funding vs. reported industry funding

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Industry funding not reported											
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	3	146	2.43 [0.56, 10.60]	12.45
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	45	0	45	15.00 [0.88, 255.04]	6.17
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	9	36	0	34	17.97 [1.09, 297.34]	6.26
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	2	20	0	19	4.76 [0.24, 93.19]	5.77
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	9.11
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	5.25
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	0	81	1	76	0.31 [0.01, 7.57]	5.22
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	17	181	10	185	1.74 [0.82, 3.69]	17.22
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.84
Heterogeneity: χ^2 = 6.97, df = 8 (p = 0.54); I^2 = 38.71%										2.87 [1.14, 7.24]	
Industry funding reported											
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	62	1	526	42.42 [5.04, 357.25]	8.82
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	97	619	3	207	10.81 [3.46, 33.75]	14.66
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	1	96	0	98	3.06 [0.13, 74.24]	5.22
Heterogeneity: χ^2 = 2.07, df = 2 (p = 0.35); I^2 = 38.90%										13.14 [3.08, 56.02]	
Overall										4.50 [1.93, 10.51]	
Heterogeneity: χ^2 = 17.97, df = 11 (p = 0.08); I^2 = 51.13%											
Group differences χ^2 = 3.00, df = 1 (p = 0.08)											



* Unpublished studies

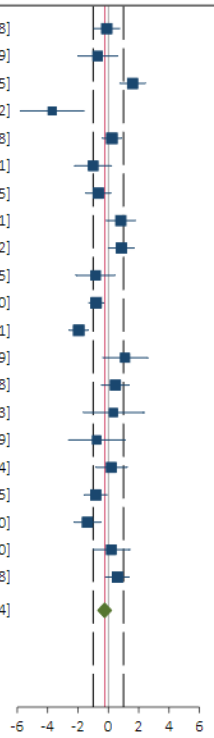
Forest plots of secondary outcomes

Forest plot for pain at post-discharge day 0

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	1.77 (1.15 to 2.4)	49	1.88 (1.26 to 2.49)	-0.10 [-0.98, 0.78]	5.19
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.8 (0.87 to 2.73)	27	2.5 (1.6 to 3.4)	-0.70 [-1.99, 0.59]	4.35
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	2.6 (2 to 3.2)	60	1 (0.4 to 1.6)	1.60 [0.75, 2.45]	5.25
Breivik (1998)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	10	1.11 (-0.36 to 2.58)	10	4.81 (3.34 to 6.28)	-3.70 [-5.78, -1.62]	2.94
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	80	3.01 (2.49 to 3.53)	146	2.78 (2.39 to 3.16)	0.23 [-0.42, 0.88]	5.62
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	3 (2.15 to 3.85)	29	4 (3.13 to 4.87)	-1.00 [-2.21, 0.21]	4.51
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	2.41 (1.83 to 2.99)	67	3.07 (2.5 to 3.64)	-0.66 [-1.47, 0.15]	5.32
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	4.07 (3.32 to 4.82)	45	3.25 (2.61 to 3.88)	0.82 [-0.16, 1.81]	4.98
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	4.47 (4 to 4.94)	38	3.61 (2.81 to 4.41)	0.86 [-0.00, 1.72]	5.22
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.42 (1.52 to 3.32)	34	3.26 (2.33 to 4.19)	-0.84 [-2.13, 0.45]	4.35
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	3.63 (3.36 to 3.89)	96	4.44 (4.06 to 4.82)	-0.81 [-1.32, -0.30]	5.84
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	3.22 (2.9 to 3.54)	38	5.17 (4.61 to 5.73)	-1.95 [-2.59, -1.31]	5.63
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	3.6 (2.56 to 4.64)	19	2.5 (1.43 to 3.57)	1.10 [-0.39, 2.59]	3.95
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	1.47 (0.6 to 2.33)	262	1 (0.71 to 1.29)	0.47 [-0.44, 1.38]	5.13
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	33	3.83 (2.95 to 4.72)	30	3.5 (1.64 to 5.36)	0.33 [-1.66, 2.33]	3.07
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	3.09 (1.95 to 4.22)	14	3.85 (2.38 to 5.32)	-0.76 [-2.62, 1.09]	3.29
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	3 (2.13 to 3.87)	49	2.8 (2.21 to 3.39)	0.20 [-0.84, 1.24]	4.88
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	6.67 (6.12 to 7.22)	64	7.5 (6.96 to 8.04)	-0.83 [-1.61, -0.05]	5.39
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0.2 (-0.42 to 0.82)	57	1.58 (0.96 to 2.19)	-1.38 [-2.25, -0.50]	5.20
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	2.4 (1.55 to 3.25)	30	2.2 (1.35 to 3.05)	0.20 [-1.00, 1.40]	4.53
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	29	3.14 (2.5 to 3.78)	41	2.54 (2.06 to 3.02)	0.60 [-0.18, 1.38]	5.38
Overall										-0.25 [-0.74, 0.24]	

Heterogeneity: χ^2 = 97.32, df = 20 (p < 0.01); I^2 = 82.23%

Test for overall effect: Z =-0.99, p = 0.32



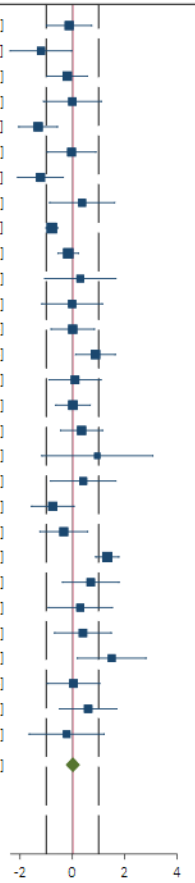
* Unpublished studies

Forest plot for pain at post-discharge day 2

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	1.35 (0.74 to 1.96)	49	1.48 (0.87 to 2.08)	-0.13 [-0.98, 0.73]	3.74
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	1.7 (0.85 to 2.55)	27	2.9 (2.09 to 3.71)	-1.20 [-2.38, -0.02]	2.81
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	1.2 (0.65 to 1.75)	60	1.4 (0.85 to 1.95)	-0.20 [-0.97, 0.57]	4.03
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	1 (0.23 to 1.77)	29	1 (0.21 to 1.79)	0.00 [-1.10, 1.10]	3.00
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	64	1.84 (1.31 to 2.37)	67	3.15 (2.63 to 3.67)	-1.31 [-2.05, -0.57]	4.15
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	45	2.44 (1.82 to 3.06)	45	2.47 (1.78 to 3.16)	-0.03 [-0.97, 0.90]	3.51
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	68	1.94 (1.45 to 2.43)	38	3.16 (2.39 to 3.93)	-1.22 [-2.09, -0.35]	3.71
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	36	2.78 (1.84 to 3.72)	34	2.41 (1.61 to 3.21)	0.37 [-0.87, 1.61]	2.65
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	288	2.71 (2.6 to 2.83)	96	3.5 (3.34 to 3.66)	-0.79 [-1.01, -0.56]	5.78
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	0.78 (0.41 to 1.15)	38	0.94 (0.81 to 1.07)	-0.16 [-0.55, 0.23]	5.33
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	1.8 (0.85 to 2.75)	19	1.5 (0.53 to 2.47)	0.30 [-1.06, 1.66]	2.39
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	2.51 (1.84 to 3.18)	20	2.52 (1.57 to 3.47)	-0.01 [-1.17, 1.15]	2.85
Torabinejad (1994)	Dental Surgery	Root canal	Minor	Clinic/day-surgery	Some concerns	29	0.49 (-0.3 to 1.28)	262	0.48 (0.22 to 0.74)	0.01 [-0.82, 0.84]	3.84
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	64	4.44 (3.91 to 4.97)	61	3.56 (3.02 to 4.1)	0.88 [0.12, 1.64]	4.08
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.7 (1.98 to 3.42)	37	2.6 (1.92 to 3.28)	0.10 [-0.89, 1.09]	3.32
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	49	1.75 (1.28 to 2.22)	55	1.73 (1.27 to 2.19)	0.02 [-0.64, 0.68]	4.43
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	1.65 (1.18 to 2.12)	35	1.3 (0.66 to 1.94)	0.35 [-0.45, 1.15]	3.93
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	3.58 (2.05 to 5.11)	14	2.63 (1.17 to 4.09)	0.95 [-1.17, 3.07]	1.28
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	27	2.83 (1.95 to 3.71)	32	2.42 (1.55 to 3.29)	0.41 [-0.84, 1.66]	2.64
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	6.65 (6.14 to 7.16)	30	7.4 (6.86 to 7.94)	-0.75 [-1.56, 0.06]	3.90
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	5 (4.26 to 5.74)	64	5.33 (4.79 to 5.87)	-0.33 [-1.24, 0.58]	3.57
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6 (5.69 to 6.31)	185	4.67 (4.36 to 4.98)	1.33 [0.89, 1.77]	5.18
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	5.5 (4.7 to 6.3)	34	4.8 (4.07 to 5.53)	0.70 [-0.38, 1.78]	3.07
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4.3 (3.44 to 5.16)	24	4 (3.14 to 4.86)	0.30 [-0.92, 1.52]	2.70
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	3.2 (2.43 to 3.97)	31	2.8 (2.04 to 3.56)	0.40 [-0.68, 1.48]	3.06
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	4.7 (3.89 to 5.51)	17	3.2 (2.17 to 4.23)	1.50 [0.19, 2.81]	2.49
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	47	2.4 (1.68 to 3.12)	43	2.36 (1.67 to 3.05)	0.04 [-0.96, 1.04]	3.29
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	2.2 (1.43 to 2.97)	30	1.6 (0.83 to 2.37)	0.60 [-0.49, 1.69]	3.03
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	2.14 (1.11 to 3.17)	18	2.36 (1.36 to 3.36)	-0.22 [-1.65, 1.21]	2.24
Overall										0.01 [-0.26, 0.28]	

Heterogeneity: χ^2 = 118.87, df = 28 (p < 0.01); I^2 = 68.82%

Test for overall effect: Z = 0.10, p = 0.92



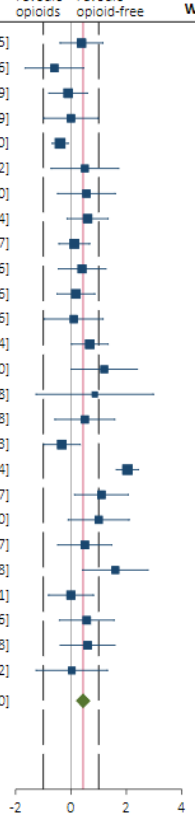
* Unpublished studies

Forest plot for pain at post-discharge day 3

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	48	1.56 (1.01 to 2.11)	49	1.18 (0.64 to 1.72)	0.38 [-0.39, 1.15]	4.34
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	2.3 (1.54 to 3.06)	27	2.9 (2.17 to 3.63)	-0.60 [-1.66, 0.46]	3.26
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	0.9 (0.41 to 1.39)	60	1 (0.51 to 1.49)	-0.10 [-0.79, 0.59]	4.69
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	30	1 (0.31 to 1.69)	29	1 (0.29 to 1.71)	0.00 [-0.99, 0.99]	3.48
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	0.28 (0.1 to 0.46)	38	0.67 (0.45 to 0.89)	-0.39 [-0.68, -0.10]	6.50
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	20	0.5 (-0.35 to 1.35)	19	0 (-0.87 to 0.87)	0.50 [-0.72, 1.72]	2.76
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	40	1.55 (0.95 to 2.15)	20	0.99 (0.14 to 1.84)	0.56 [-0.48, 1.60]	3.30
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	51	3.66 (3.14 to 4.18)	55	3.06 (2.54 to 3.58)	0.60 [-0.14, 1.34]	4.49
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	96	2.74 (2.33 to 3.15)	98	2.62 (2.24 to 3)	0.12 [-0.43, 0.67]	5.34
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	2.1 (1.47 to 2.73)	37	1.7 (1.12 to 2.28)	0.40 [-0.46, 1.26]	3.99
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	42	1.71 (1.2 to 2.22)	48	1.53 (1.08 to 1.98)	0.18 [-0.50, 0.86]	4.76
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	53	4.8 (4.05 to 5.55)	51	4.7 (3.96 to 5.44)	0.10 [-0.96, 1.16]	3.25
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	70	1.48 (1.05 to 1.91)	35	0.8 (0.46 to 1.14)	0.68 [0.02, 1.34]	4.84
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	33	2.87 (1.99 to 3.75)	30	1.67 (0.88 to 2.46)	1.20 [0.00, 2.40]	2.82
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	3.12 (1.35 to 4.89)	14	2.26 (1.09 to 3.43)	0.86 [-1.26, 2.98]	1.24
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	28	2.79 (1.98 to 3.6)	31	2.29 (1.57 to 3.01)	0.50 [-0.58, 1.58]	3.18
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	4 (3.63 to 4.37)	64	4.33 (3.79 to 4.87)	-0.33 [-0.99, 0.33]	4.84
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	6.37 (6.09 to 6.65)	185	4.33 (4.05 to 4.61)	2.04 [1.64, 2.44]	6.06
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.6 (3.88 to 5.32)	34	3.5 (2.85 to 4.15)	1.10 [0.13, 2.07]	3.55
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	4 (3.22 to 4.78)	24	3 (2.22 to 3.78)	1.00 [-0.10, 2.10]	3.12
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.9 (2.21 to 3.59)	31	2.4 (1.72 to 3.08)	0.50 [-0.47, 1.47]	3.54
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	4.4 (3.67 to 5.13)	17	2.8 (1.88 to 3.72)	1.60 [0.42, 2.78]	2.88
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (-0.57 to 0.57)	57	0 (-0.57 to 0.57)	0.00 [-0.81, 0.81]	4.18
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	40	2.26 (1.52 to 3)	37	1.69 (1.05 to 2.33)	0.57 [-0.42, 1.56]	3.50
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	1.9 (1.21 to 2.59)	30	1.3 (0.61 to 1.99)	0.60 [-0.38, 1.58]	3.51
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	17	1.62 (0.7 to 2.54)	18	1.59 (0.69 to 2.49)	0.03 [-1.26, 1.32]	2.58
Overall										0.44 [0.18, 0.70]	

Heterogeneity: χ^2 = 118.63, df = 25 (p < 0.01); I^2 = 63.00%

Test for overall effect: Z = 3.30, p < 0.01



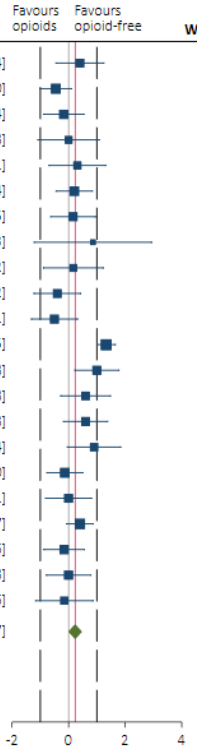
* Unpublished studies

Forest plot for pain at post-discharge days 4-7

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	2.5 (1.89 to 3.11)	27	2.1 (1.52 to 2.68)	0.40 [-0.44, 1.24]	4.24
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	0.2 (-0.19 to 0.59)	60	0.65 (0.26 to 1.04)	-0.45 [-1.00, 0.10]	6.14
Samieirad (2017)	Dental Surgery	Implant	Minor	Clinic/day-surgery	Some concerns	38	0 (-0.7 to 0.7)	38	0.17 (0.05 to 0.29)	-0.17 [-0.88, 0.54]	5.02
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	33	0 (-0.75 to 0.75)	31	0 (-0.78 to 0.78)	0.00 [-1.08, 1.08]	3.13
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	18	2.43 (1.65 to 3.21)	32	2.12 (1.51 to 2.73)	0.31 [-0.69, 1.31]	3.47
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	1.1 (0.6 to 1.6)	37	0.9 (0.51 to 1.29)	0.20 [-0.44, 0.84]	5.52
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	25	1.23 (0.65 to 1.81)	29	1.07 (0.54 to 1.6)	0.16 [-0.63, 0.95]	4.55
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	2.86 (1.17 to 4.55)	14	2 (0.8 to 3.2)	0.86 [-1.21, 2.93]	1.13
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	24	1.89 (1.14 to 2.64)	30	1.72 (0.99 to 2.45)	0.17 [-0.88, 1.22]	3.25
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	5.8 (5.3 to 6.3)	30	6.2 (5.59 to 6.81)	-0.40 [-1.22, 0.42]	4.35
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	62	2.17 (1.43 to 2.91)	64	2.67 (2.31 to 3.03)	-0.50 [-1.31, 0.31]	4.41
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	5.33 (5.1 to 5.56)	185	4 (3.78 to 4.22)	1.33 [1.01, 1.65]	7.96
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.8 (4.23 to 5.37)	34	3.8 (3.28 to 4.32)	1.00 [0.22, 1.78]	4.63
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	2.6 (1.98 to 3.22)	24	2 (1.38 to 2.62)	0.60 [-0.28, 1.48]	4.06
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.2 (1.65 to 2.75)	31	1.6 (1.05 to 2.15)	0.60 [-0.18, 1.38]	4.62
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	3.1 (2.52 to 3.68)	17	2.2 (1.46 to 2.94)	0.90 [-0.04, 1.84]	3.74
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	47	3.91 (3.43 to 4.39)	46	4.04 (3.63 to 4.45)	-0.13 [-0.76, 0.50]	5.58
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	57	0 (-0.57 to 0.57)	57	0 (-0.57 to 0.57)	0.00 [-0.81, 0.81]	4.42
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	62	2.9 (2.51 to 3.29)	126	2.5 (2.23 to 2.77)	0.40 [-0.07, 0.87]	6.78
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	27	1.01 (0.55 to 1.47)	23	1.17 (0.61 to 1.73)	-0.16 [-0.88, 0.56]	4.99
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	30	1.3 (0.75 to 1.85)	30	1.3 (0.75 to 1.85)	0.00 [-0.78, 0.78]	4.58
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	29	3.14 (2.37 to 3.91)	41	3.29 (2.63 to 3.95)	-0.15 [-1.16, 0.86]	3.41
Overall										0.23 [-0.01, 0.47]	

Heterogeneity: χ^2 = 66.32, df = 21 (p < 0.01); I^2 = 54.09%

Test for overall effect: Z = 1.92, p = 0.06



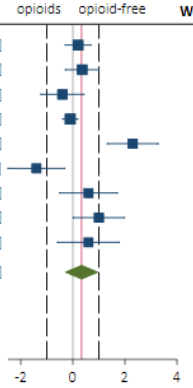
* Unpublished studies

Forest plot for pain at post-discharge days 8-30

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	0.5 (0.09 to 0.91)	37	0.3 (0.04 to 0.56)	0.20 [-0.29, 0.69]	12.79
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	76	1.59 (1.13 to 2.05)	73	1.23 (0.78 to 1.68)	0.36 [-0.28, 1.00]	12.16
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	60	5.8 (5.3 to 6.3)	30	6.2 (5.59 to 6.81)	-0.40 [-1.22, 0.42]	11.29
Papoian (2020)	Head and Neck Surgery	Thyroidectomy (total, partial)	Moderate	Operating room/day-surgery	High	46	0.1 (-0.07 to 0.27)	49	0.2 (-0.02 to 0.42)	-0.10 [-0.39, 0.19]	13.43
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	4.7 (3.98 to 5.42)	34	2.4 (1.74 to 3.06)	2.30 [1.32, 3.28]	10.52
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	25	5.5 (4.68 to 6.32)	27	6.9 (6.18 to 7.62)	-1.40 [-2.49, -0.31]	9.95
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	2.5 (1.72 to 3.28)	24	1.9 (1.12 to 2.68)	0.60 [-0.50, 1.70]	9.87
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	2.3 (1.6 to 3)	31	1.3 (0.61 to 1.99)	1.00 [0.02, 1.98]	10.51
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	3 (2.26 to 3.74)	17	2.4 (1.47 to 3.33)	0.60 [-0.58, 1.78]	9.47
Overall										0.33 [-0.32, 0.99]	

Heterogeneity: χ^2 = 35.61, df = 8 (p < 0.01); I^2 = 87.09%

Test for overall effect: Z = 1.01, p = 0.31



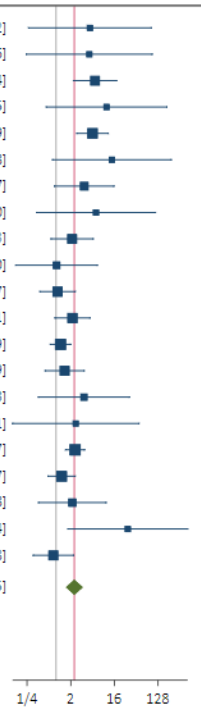
* Unpublished studies

Forest plot for nausea

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Breivik (1998)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	2	10	0	10	5.00 [0.27, 92.62]	1.61
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	2	30	0	29	4.84 [0.24, 96.66]	1.54
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	6	62	8	526	6.36 [2.28, 17.74]	6.23
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	5	45	0	45	11.00 [0.63, 193.25]	1.66
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	118	619	7	207	5.64 [2.67, 11.89]	7.68
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	7	36	0	34	14.19 [0.84, 239.28]	1.70
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	8	20	2	19	3.80 [0.92, 15.67]	4.56
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	6	40	0	20	6.66 [0.39, 112.60]	1.70
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	11	71	5	69	2.14 [0.78, 5.83]	6.33
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	2	96	2	98	1.02 [0.15, 7.10]	3.05
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	9	39	8	37	1.07 [0.46, 2.47]	7.18
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	15	70	7	71	2.17 [0.94, 5.01]	7.21
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	23	53	18	51	1.23 [0.76, 1.99]	9.08
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	15	70	5	35	1.50 [0.59, 3.79]	6.72
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	4	81	1	76	3.75 [0.43, 32.83]	2.59
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	2	60	0	30	2.54 [0.13, 51.31]	1.53
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	53	181	22	185	2.46 [1.57, 3.87]	9.22
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	10	18	9	21	1.30 [0.68, 2.47]	8.24
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	4	25	2	27	2.16 [0.43, 10.78]	3.92
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	7	62	0	126	30.24 [1.75, 521.04]	1.68
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	7	70	8	70	0.88 [0.34, 2.28]	6.56
Overall										2.37 [1.59, 3.55]	

Heterogeneity: χ^2 = 33.77, df = 20 (p = 0.03); I^2 = 60.82%

Test for overall effect: Z = 4.20, (p < 0.01)



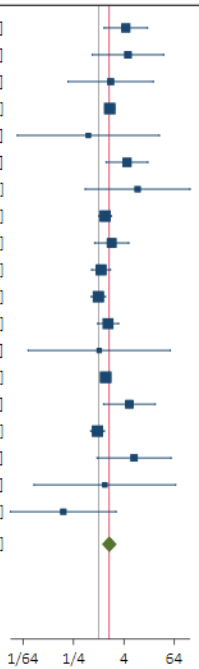
* Unpublished studies

Forest plot for overall adverse events

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Walton (1990)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	13	48	3	49	4.42 [1.34, 14.55]	5.30
Breivik (1998)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	5	10	1	10	5.00 [0.70, 35.50]	2.93
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	2	30	1	29	1.93 [0.19, 20.18]	2.24
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	263	619	48	207	1.83 [1.41, 2.39]	9.66
La Monaca (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	0	68	0	38	0.57 [0.01, 27.93]	0.94
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	15	36	3	34	4.72 [1.50, 14.88]	5.49
Li (2005)	Eye Surgery	LASIK	Minor	Clinic/day-surgery	High	4	33	0	31	8.47 [0.47, 151.14]	1.61
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	41	71	28	69	1.42 [1.00, 2.02]	9.37
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	12	96	6	98	2.04 [0.80, 5.22]	6.46
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	18	39	15	37	1.14 [0.68, 1.91]	8.62
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	29	70	30	71	0.98 [0.66, 1.45]	9.20
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	25	81	14	76	1.68 [0.94, 2.98]	8.34
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	0	62	0	64	1.03 [0.02, 51.20]	0.94
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	125	181	87	185	1.47 [1.22, 1.76]	9.88
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	10	25	2	27	5.40 [1.31, 22.28]	4.43
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	30	70	32	70	0.94 [0.65, 1.36]	9.27
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	7	30	1	30	7.00 [0.92, 53.47]	2.78
Frants (2021)	Plastic Surgery	Rhinoplasty	Minor	Clinic/day-surgery	High	0	29	0	41	1.40 [0.03, 68.60]	0.95
Casey (1997)	Urology	Vasectomy	Minor	Clinic/day-surgery	High	0	20	3	20	0.14 [0.01, 2.60]	1.59
Overall										1.78 [1.20, 2.66]	

Heterogeneity: χ^2 = 32.56, df = 18 (p = 0.02); I^2 = 84.16%

Test for overall effect: Z = 2.85, (p < 0.01)



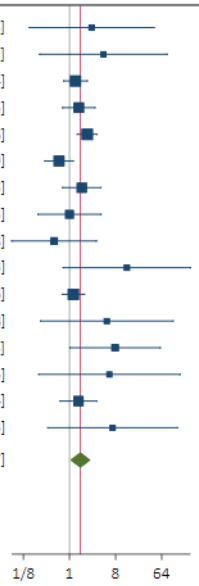
* Unpublished studies

Forest plot for constipation

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	11	413	0	48	2.72 [0.16, 45.48]	2.19
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	4	40	0	20	4.61 [0.26, 81.63]	2.11
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	23	71	17	69	1.31 [0.77, 2.24]	11.44
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	15	70	10	71	1.52 [0.73, 3.15]	10.06
Raeder (2001)	General (abdominal)/Others	Hernia repair (open), haemorrhoidectomy, phlebectomy	Moderate	Operating room/day-surgery	High	37	53	16	51	2.23 [1.43, 3.46]	12.02
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	15	70	12	35	0.63 [0.33, 1.19]	10.68
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	13	81	7	76	1.74 [0.73, 4.13]	9.11
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	3	14	3	14	1.00 [0.24, 4.13]	5.85
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	2	60	2	30	0.50 [0.07, 3.38]	4.00
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	6	181	0	185	13.29 [0.75, 234.13]	2.12
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	13	20	12	22	1.19 [0.72, 1.96]	11.66
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	2	25	0	27	5.38 [0.27, 106.98]	1.98
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	8	47	1	46	7.83 [1.02, 60.14]	3.64
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	1	62	0	126	6.05 [0.25, 146.35]	1.77
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	12	70	8	70	1.50 [0.65, 3.44]	9.33
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	3	30	0	30	7.00 [0.38, 129.93]	2.06
Overall										1.63 [1.04, 2.57]	

Heterogeneity: χ^2 = 20.93, df = 15 (p = 0.14); I^2 = 65.00%

Test for overall effect: Z = 2.11, (p = 0.03)



* Unpublished studies

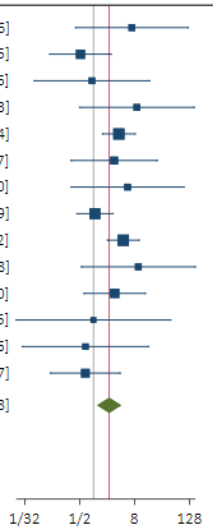
Forest plot for dizziness

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Breivik (1998)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	3	10	0	10	7.00 [0.41, 120.16]	3.78
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	2	80	7	146	0.52 [0.11, 2.45]	8.92
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	0	62	4	526	0.93 [0.05, 17.06]	3.63
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	4	45	0	45	9.00 [0.50, 162.43]	3.67
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	65	619	6	207	3.62 [1.59, 8.24]	15.18
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	3	20	1	19	2.85 [0.32, 25.07]	5.72
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	5	40	0	20	5.63 [0.33, 97.10]	3.77
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	8	39	7	37	1.08 [0.44, 2.69]	14.29
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	31	181	7	185	4.53 [2.05, 10.02]	15.46
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	4	25	0	27	9.69 [0.55, 171.38]	3.71
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	6	47	2	46	2.94 [0.62, 13.80]	8.92
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	0	57	0	57	1.00 [0.02, 49.55]	2.19
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	0	62	1	126	0.67 [0.03, 16.26]	3.12
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	2	70	3	70	0.67 [0.11, 3.87]	7.64
Overall										2.22 [1.20, 4.08]	

Heterogeneity: χ^2 = 16.03, df = 13 (p = 0.25); I^2 = 42.31%

Test for overall effect: Z = 2.56, (p = 0.01)

Test of θ = 0: z = 2.56, p = 0.01



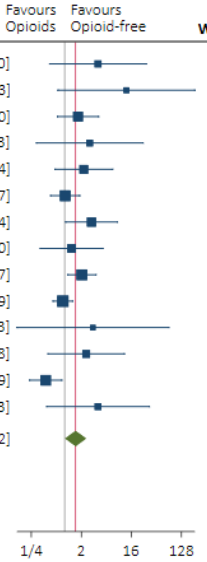
* Unpublished studies

Forest plot for drowsiness

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Breivik (1998)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	10	1	10	4.00 [0.54, 29.80]	3.59
Akinbade (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	6	45	0	45	13.00 [0.75, 224.13]	2.02
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	75	413	5	48	1.74 [0.74, 4.10]	9.80
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	3	36	1	34	2.83 [0.31, 25.93]	3.08
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	7	20	3	19	2.22 [0.67, 7.34]	7.16
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	14	39	13	37	1.02 [0.56, 1.87]	12.10
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	13	81	4	76	3.05 [1.04, 8.94]	8.01
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	4	14	3	14	1.33 [0.36, 4.90]	6.52
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	30	181	15	185	2.04 [1.14, 3.67]	12.30
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	12	18	18	25	0.93 [0.62, 1.39]	13.90
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	1	25	0	27	3.23 [0.14, 75.83]	1.68
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	5	47	2	46	2.45 [0.50, 11.98]	5.06
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	10	70	22	70	0.45 [0.23, 0.89]	11.49
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	4	30	1	30	4.00 [0.47, 33.73]	3.27
Overall										1.57 [1.02, 2.42]	

Heterogeneity: χ^2 = 24.67, df = 13 (p = 0.03); I^2 = 58.39%

Test for overall effect: Z = 2.05, (p = 0.04)



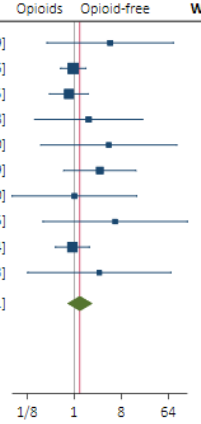
* Unpublished studies

Forest plot for pruritus

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	20	413	0	48	4.85 [0.30, 78.99]	3.60
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	15	39	15	37	0.95 [0.54, 1.66]	27.42
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	11	70	7	35	0.79 [0.33, 1.85]	19.94
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	2	81	1	76	1.88 [0.17, 20.28]	4.77
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	2	33	0	30	4.56 [0.23, 91.30]	3.16
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	6	181	2	185	3.07 [0.63, 14.99]	9.27
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	1	57	1	57	1.00 [0.06, 15.60]	3.70
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	1	62	0	126	6.05 [0.25, 146.35]	2.82
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	11	70	12	70	0.92 [0.43, 1.94]	22.45
Weinheimer (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger, others)	Minor	Operating room/day-surgery	High	1	30	0	30	3.00 [0.13, 70.83]	2.86
Overall										1.27 [0.73, 2.21]	

Heterogeneity: χ^2 = 6.32, df = 9 (p = 0.71); I^2 = 33.08%

Test for overall effect: Z = 0.84, (p =0.40)



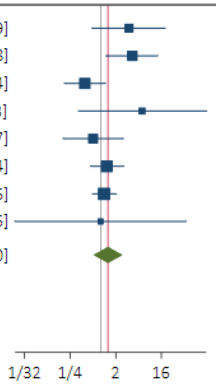
* Unpublished studies

Forest plot for headache

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	80	2	146	3.65 [0.68, 19.49]	9.59
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	4	62	8	526	4.24 [1.32, 13.68]	14.08
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	21	413	5	48	0.49 [0.19, 1.24]	16.88
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	3	36	0	34	6.62 [0.35, 123.63]	4.21
Da Silva (2021)	Dental Surgery	Incision & drainage	Minor	Clinic/day-surgery	Some concerns	3	20	4	19	0.71 [0.18, 2.77]	12.19
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	8	14	6	14	1.33 [0.63, 2.84]	19.04
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	23	181	20	185	1.18 [0.67, 2.06]	21.45
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	0	57	0	57	1.00 [0.02, 49.55]	2.55
Overall										1.40 [0.72, 2.70]	

Heterogeneity: χ^2 = 11.68, df = 7 (p = 0.11); I^2 = 58.95%

Test for overall effect: Z = 1.00, (p = 0.32)



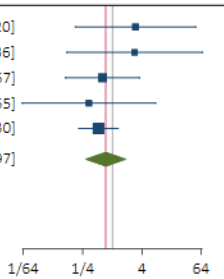
* Unpublished studies

Forest plot for confusion

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	12	413	0	48	2.96 [0.18, 49.20]	10.72
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	1	36	0	34	2.84 [0.12, 67.36]	8.68
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	2	39	3	37	0.63 [0.11, 3.57]	23.29
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	0	14	1	14	0.33 [0.01, 7.55]	8.92
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	4	14	12	22	0.52 [0.21, 1.30]	48.39
Overall										0.73 [0.27, 1.97]	

Heterogeneity: χ^2 = 2.34, df = 4 (p = 0.67); I^2 = 22.95%

Test for overall effect: Z =-0.62, (p = 0.54)



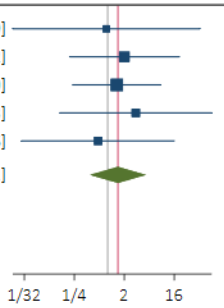
* Unpublished studies

Forest plot for diarrhoea

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	0	36	0	34	0.95 [0.02, 46.39]	8.91
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	2	14	1	14	2.00 [0.20, 19.62]	25.40
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	2	13	2	19	1.46 [0.23, 9.10]	38.99
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	1	25	0	27	3.23 [0.14, 75.83]	13.48
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	0	62	1	126	0.67 [0.03, 16.26]	13.23
Overall										1.53 [0.48, 4.91]	

Heterogeneity: χ^2 = 0.59, df = 4 (p = 0.96); I^2 = 2.08%

Test for overall effect: Z = 0.71, (p = 0.48)



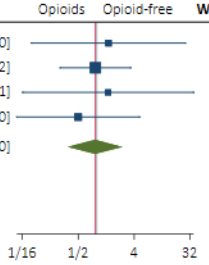
* Unpublished studies

Forest plot for difficulty urinating

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	6	413	0	48	1.54 [0.09, 26.90]	12.67
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	4	39	4	37	0.95 [0.26, 3.52]	57.28
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	1	70	0	35	1.52 [0.06, 36.41]	10.31
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	1	14	2	14	0.50 [0.05, 4.90]	19.73
Overall										0.93 [0.33, 2.60]	

Heterogeneity: χ^2 = 0.50, df = 3 (p = 0.92); I^2 = 2.29%

Test for overall effect: Z =-0.13, (p = 0.89)



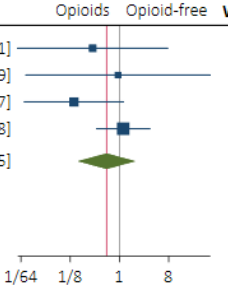
* Unpublished studies

Forest plot for indigestion

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	0	30	1	29	0.32 [0.01, 7.61]	12.77
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	0	36	0	34	0.95 [0.02, 46.39]	8.81
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	1	181	7	185	0.15 [0.02, 1.17]	25.07
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	6	47	5	46	1.17 [0.39, 3.58]	53.36
Overall										0.58 [0.17, 1.95]	

Heterogeneity: χ^2 = 3.25, df = 3 (p = 0.35); I^2 = 23.33%

Test for overall effect: Z =-0.88, (p =0.38)



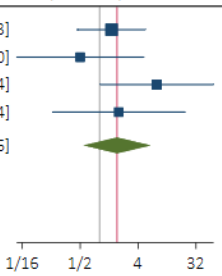
* Unpublished studies

Forest plot for nausea or vomiting

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Lysell (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	6	68	4	70	1.54 [0.46, 5.23]	39.25
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	1	14	2	14	0.50 [0.05, 4.90]	19.51
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	8	47	1	46	7.83 [1.02, 60.14]	22.76
Spagnoli (2011)	Orthopaedic/Plastic Surgery	Hand and foot repair (carpal tunnel, bunion, others)	Minor	Operating room/day-surgery	High	2	57	1	57	2.00 [0.19, 21.44]	18.48
Overall										1.88 [0.57, 6.26]	

Heterogeneity: χ^2 = 3.27, df = 3 (p = 0.35); I^2 = 37.77%

Test for overall effect: Z = 1.03, (p = 0.30)



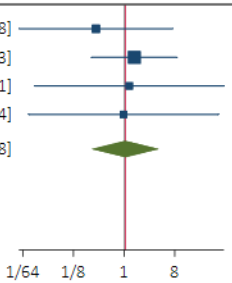
* Unpublished studies

Forest plot for bleeding

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	0	36	1	34	0.32 [0.01, 7.48]	18.55
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	3	70	2	71	1.52 [0.26, 8.83]	56.64
NCT03605914 (2021)*	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	0	24	0	30	1.24 [0.03, 60.31]	12.45
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	0	47	0	46	0.98 [0.02, 48.34]	12.36
Overall										1.05 [0.26, 4.18]	

Heterogeneity: χ^2 = 0.73, df = 3 (p = 0.87); I^2 = 3.10%

Test for overall effect: Z = 0.07, (p = 0.95)



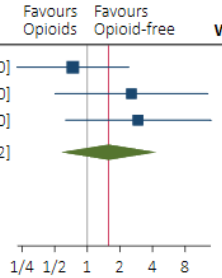
* Unpublished studies

Forest plot for dry mouth

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	19	413	3	48	0.74 [0.23, 2.40]	42.29
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	5	181	2	185	2.56 [0.50, 13.00]	27.83
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	6	47	2	46	2.94 [0.62, 13.80]	29.88
Overall										1.57 [0.57, 4.32]	

Heterogeneity: χ^2 = 2.53, df = 2 (p = 0.28); I^2 = 32.94%

Test for overall effect: Z = 0.88, (p = 0.38)



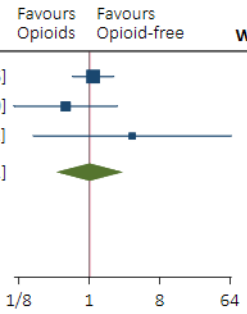
* Unpublished studies

Forest plot for sleep problems

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	41	340	12	112	1.13 [0.61, 2.06]	62.40
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	2	14	4	14	0.50 [0.11, 2.30]	27.64
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	3	60	0	30	3.56 [0.19, 66.72]	9.96
Overall										1.01 [0.38, 2.71]	

Heterogeneity: χ^2 = 1.62, df = 2 (p = 0.44); I^2 = 35.90%

Test for overall effect: Z = 0.02, (p = 0.99)



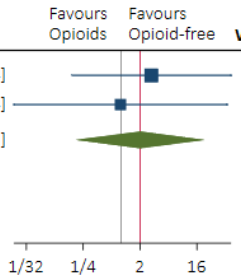
* Unpublished studies

Forest plot for hypotension

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Desjardins (2020)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	4	619	0	207	3.02 [0.16, 55.84]	63.84
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	0	47	0	46	0.98 [0.02, 48.34]	36.16
Overall										2.01 [0.19, 21.33]	

Heterogeneity: χ^2 = 0.21, df = 1 (p = 0.65); I^2 = 1.88%

Test for overall effect: Z = 0.58, (p = 0.56)



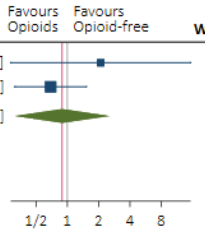
* Unpublished studies

Forest plot for difficulty concentrating

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Zuniga (2019)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	18	413	1	48	2.09 [0.29, 15.33]	23.07
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	8	39	11	37	0.69 [0.31, 1.52]	76.93
Overall										0.89 [0.31, 2.54]	

Heterogeneity: χ^2 = 1.03, df = 1 (p = 0.31); I^2 = 25.91%

Test for overall effect: Z =-0.22, (p = 0.83)



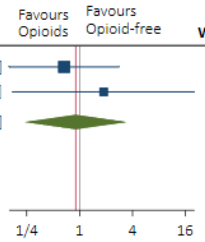
* Unpublished studies

Forest plot for acid reflux

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	4	70	3	35	0.67 [0.16, 2.82]	70.85
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	2	81	1	76	1.88 [0.17, 20.28]	29.15
Overall										0.90 [0.24, 3.42]	

Heterogeneity: χ^2 = 0.53, df = 1 (p = 0.47); I^2 = 10.04%

Test for overall effect: Z =-0.15, (p = 0.88)



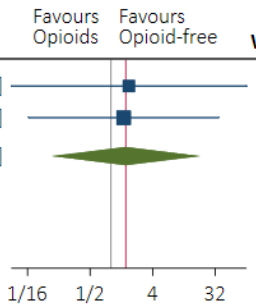
* Unpublished studies

Forest plot for skin rash

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Comfort (2002)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	0	80	0	146	1.81 [0.04, 90.61]	39.67
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	1	60	0	30	1.52 [0.06, 36.34]	60.33
Overall										1.63 [0.14, 19.18]	

Heterogeneity: χ^2 = 0.00, df = 1 (p = 0.95); I^2 = 0.00%

Test for overall effect: Z = 0.39, (p = 0.70)



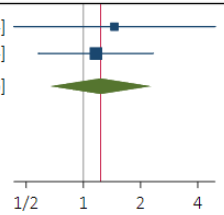
* Unpublished studies

Forest plot for upset stomach

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	6	71	4	69	1.46 [0.43, 4.94]	24.62
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	8	16	9	21	1.17 [0.58, 2.34]	75.38
Overall										1.23 [0.67, 2.26]	

Heterogeneity: χ^2 = 0.10, df = 1 (p = 0.76); I^2 = 0.44%

Test for overall effect: Z = 0.68, (p = 0.50)



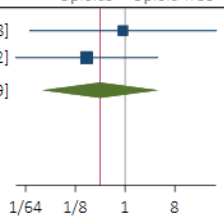
* Unpublished studies

Forest plot for difficulty breathing

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	0	33	0	30	0.91 [0.02, 44.58]	37.27
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	0	14	2	14	0.20 [0.01, 3.82]	62.73
Overall										0.35 [0.03, 3.99]	

Heterogeneity: χ^2 = 0.37, df = 1 (p = 0.54); I^2 = 5.48%

Test for overall effect: Z =-0.84, (p = 0.40)



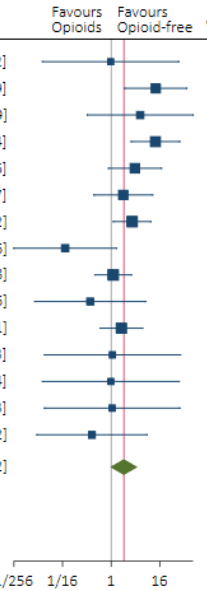
* Unpublished studies

Forest plot for patient disposition

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Shah (2008)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	0	30	0	29	0.97 [0.02, 47.22]	3.07
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	3	62	2	526	12.73 [2.17, 74.69]	8.26
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	2	64	0	67	5.23 [0.26, 106.89]	4.49
Collins (1997)	Dental Surgery	Dento-alveolar procedures	Minor	Clinic/day-surgery	High	76	340	2	112	12.52 [3.13, 50.14]	9.95
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	8	71	2	69	3.89 [0.86, 17.66]	9.37
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	4	100	2	100	2.00 [0.37, 10.67]	8.66
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	13	70	4	71	3.30 [1.13, 9.62]	11.47
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	0	70	3	35	0.07 [0.00, 1.36]	4.66
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	7	76	6	73	1.12 [0.40, 3.18]	11.61
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	0	32	1	29	0.30 [0.01, 7.16]	4.20
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	7	181	4	185	1.79 [0.53, 6.01]	10.79
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	0	25	0	27	1.08 [0.02, 52.33]	3.08
Kim (2019)	Orthopaedic/Neurosurgery	Laminectomy, discectomy	Moderate	Operating room/in-patient	Some concerns	0	47	0	46	0.98 [0.02, 48.34]	3.06
Chen (2009)	Plastic Surgery	Rhinoplasty, rhytidectomy, otoplasty, others	Minor	Clinic/day-surgery	High	0	17	0	18	1.06 [0.02, 50.43]	3.10
Casey (1997)	Urology	Vasectomy	Minor	Clinic/day-surgery	High	0	20	1	20	0.33 [0.01, 7.72]	4.24
Overall										2.05 [0.95, 4.42]	

Heterogeneity: χ^2 = 21.53, df = 14 (p = 0.09); I^2 = 54.40%

Test for overall effect: Z = 1.84, (p = 0.07)



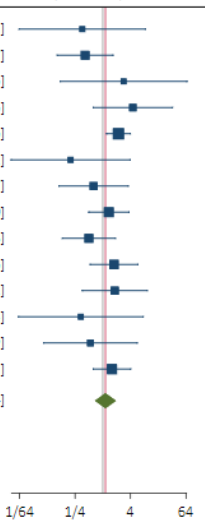
* Unpublished studies

Forest plot for patient dissatisfaction

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Lownie (1992)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	25	25	26	27	0.36 [0.02, 8.43]	2.46
Brown (2013)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	High	60	62	485	526	0.41 [0.10, 1.67]	8.38
Vallecillo (2021)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	35	36	34	34	2.84 [0.12, 67.36]	2.45
Han (1998)	Dental Surgery	Periodontal procedures	Minor	Clinic/day-surgery	High	30	40	17	18	4.50 [0.62, 32.56]	5.26
Mitchell (2008)	General Surgery (abdominal)	Cholecystectomy, hernia repair (lap, open)	Moderate	Operating room/day-surgery	Low	44	71	57	69	2.19 [1.21, 3.96]	16.03
Bugada (2015)	General Surgery (abdominal)	Inguinal hernia repair (open)	Moderate	Operating room/in-patient	High	20	20	18	20	0.20 [0.01, 3.92]	2.73
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	37	39	34	37	0.63 [0.11, 3.57]	6.36
Mitchell (2012)	General Surgery (breast)	Mastectomy, lumpectomy	Moderate	Operating room/in-patient	Low	62	70	65	71	1.35 [0.49, 3.70]	11.63
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	66	70	31	35	0.50 [0.13, 1.88]	8.88
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	78	85	81	85	1.75 [0.53, 5.76]	9.95
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	29	33	28	30	1.82 [0.36, 9.22]	6.94
Church (2006)	Head and Neck Surgery	Functional endoscopic sinus surgery	Minor	Operating room/day-surgery	High	14	14	13	14	0.33 [0.01, 7.55]	2.51
Helmerhorst (2017)	Orthopaedic Surgery	Extremity fracture repair (upper, lower limb)	Moderate	Operating room/in-patient	Some concerns	24	25	25	27	0.54 [0.05, 5.59]	4.07
Ilyas (2019)	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	48	55	103	112	1.58 [0.62, 4.03]	12.35
Overall										1.14 [0.67, 1.94]	

Heterogeneity: χ^2 = 13.86, df = 13 (p = 0.38); I^2 = 42.46%

Test for overall effect: Z = 0.49, (p = 0.62)



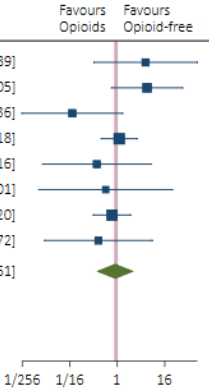
* Unpublished studies

Forest plot for healthcare reutilization

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of incidents	Opioid analgesia No. of patients	Opioid-free analgesia No. of incidents	Opioid-free analgesia No. of patients	Risk ratio with 95% CI	Weight (%)
Best (2017)	Dental Surgery	Molar extraction	Minor	Clinic/day-surgery	Some concerns	2	64	0	67	5.23 [0.26, 106.89]	8.92
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	6	39	1	37	5.69 [0.72, 45.05]	14.05
Stessel (2014)	General (abdominal)/Orthopaedic Surgery	Inguinal hernia repair (lap, open), knee repair (arthrosc)	Moderate	Operating room/day-surgery	Some concerns	0	70	3	35	0.07 [0.00, 1.36]	9.26
Dinis (2020)	Gynaecology/Obstetrics	Caesarean section	Moderate	Operating room/in-patient	Some concerns	7	76	6	73	1.12 [0.40, 3.18]	22.67
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	0	32	1	29	0.30 [0.01, 7.16]	8.36
Kim (2005)	Head and Neck Surgery	Tonsillectomy	Minor	Operating room/in-patient	High	0	60	0	30	0.51 [0.01, 25.01]	6.11
Brady (2021)	Head and Neck Surgery	Thyroidectomy (total, partial), parathyroidectomy	Moderate	Operating room/day-surgery	High	5	62	7	64	0.74 [0.25, 2.20]	22.20
Casey (1997)	Urology	Vasectomy	Minor	Clinic/day-surgery	High	0	20	1	20	0.33 [0.01, 7.72]	8.43
Overall										0.88 [0.30, 2.61]	

Heterogeneity: χ^2 = 8.39, df = 7 (p = 0.30); I^2 = 51.69%

Test for overall effect: Z =-0.23, (p = 0.82)



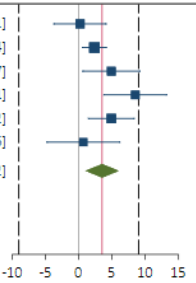
* Unpublished studies

Forest plot for pain interference

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
NCT04254679 (2021)*	General Surgery (abdominal, breast)	Cholecystectomy, hernia repair (lap, open), mastectomy, others	Moderate	Operating room/day-surgery	Some concerns	39	55.7 (53.1 to 58.3)	37	55.5 (52.57 to 58.43)	0.20 [-3.71, 4.11]	16.47
Gimbel (2001)	Orthopaedic Surgery	Cruciate ligament, extremity fracture repair, others (open)	Moderate	Operating room/day-surgery	Some concerns	181	59.56 (58.29 to 60.83)	185	57.2 (55.95 to 58.45)	2.36 [0.58, 4.14]	24.13
NCT03818932 (2021)*	Orthopaedic Surgery	Cruciate ligament repair (arthrosc)	Moderate	Operating room/day-surgery	High	28	66.3 (63.3 to 69.3)	34	61.4(58.4 to 64.4)	4.90 [0.63, 9.17]	15.30
Jildeh (2021) (A)	Orthopaedic Surgery	Labrum repair (arthrosc)	Moderate	Operating room/day-surgery	High	24	62.7 (60.0 to 65.4)	24	54.2 (50.4 to 58.0)	8.50 [3.79, 13.21]	13.97
Jildeh (2021) (B)	Orthopaedic Surgery	Meniscus repair (arthrosc)	Moderate	Operating room/day-surgery	High	30	59.8 (57.47 to 62.13)	31	54.9 (52.4 to 57.4)	4.90 [1.48, 8.32]	18.19
NCT03818919 (2021)*	Orthopaedic Surgery	Rotator cuff repair (arthrosc)	Moderate	Operating room/day-surgery	High	27	60 (56.49 to 63.51)	17	59.3 (55.26 to 63.34)	0.70 [-4.76, 6.16]	11.93
Overall										3.51 [1.01, 6.02]	

Heterogeneity: χ^2 = 10.32, df = 5 (p = 0.07); I^2 = 64.92%

Test for overall effect: Z = 2.75, p = 0.01



* Unpublished studies

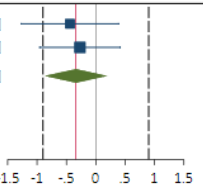
Pain interference was measured using Patient Reported Outcomes Measurement Information System-Pain Interference (PROMIS-PI), American Pain Society (APS) questionnaire, and Brief Pain Inventory (BPI). For meta-analysis, measures were standardized to the PROMIS-PI score [minimal important difference ≈ 9 (J Hand Surg Am 2019;44(8):635-640)].

Forest plot for self-reported postoperative health status (quality of recovery)

Source	Surgical speciality	Procedure	Surgery classifcation	Surgical setting	Risk of bias	Opioid analgesia No. of patients	Opioid analgesia Mean (95% CI), cm	Opioid-free analgesia No. of patients	Opioid-free analgesia Mean (95% CI), cm	Mean difference with 95% CI	Weight (%)
Petrikovets (2019)	Gynaecology/Obstetrics	Hysterectomy, prolapse repair, others (transvaginal)	Moderate	Operating room/in-patient	High	33	16.21 (15.64 to 16.78)	30	16.65 (16.05 to 17.25)	-0.44 [-1.27, 0.39]	40.46
NCT02647788 (2019)*	Orthopaedic/Plastic Surgery	Hand repair (carpal tunnel, trigger finger)	Minor	Operating room/day-surgery	Some concerns	49	16.64 (16.11 to 17.17)	44	16.91 (16.5 to 17.32)	-0.27 [-0.95, 0.41]	59.54
Overall										-0.34 [-0.87, 0.19]	

Heterogeneity: χ^2 = 0.10, df = 1 (p = 0.76); I^2 = 0.44%

Test for overall effect: Z =-1.25, p = 0.76



* Unpublished studies

Quality of recovery was measured using Quality of Recovery (QoR) -9 and QoR-40. For meta-analysis, this outcome was standardized to QoR-9 scores [minimal important difference = 0.9 (Anesthesiology 2016;125(1):39-45)].