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

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Summary

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 randomised 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 definition (minor, moderate, major, and major complex). We screened articles, extracted data, and assessed risk of bias (Cochrane's risk-of-bias tool for randomised trials) in duplicate. The primary outcomes of interest were self-reported pain intensity on day 1 after discharge (standardised 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 reutilisation 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).

Findings 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% orthopaedic 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.

Interpretation 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.

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Introduction

Excessive opioid prescribing has contributed to a devastating crisis of addiction and overdose in North America.[1,2] Increasing rates of opioid prescription and opioid-related deaths have also been reported in other parts of the world.[3–6] Surgeons are responsible for the second-highest rate of opioid prescribing among all medical specialties,[7] and thus, are considered to be important contributors to the opioid crisis.[8] Although the prescription of opioids after surgery stems from well intended efforts to reduce the postoperative pain and discomfort of patients, studies have shown that even minor surgeries can serve as an initial event for patients who are opioid naive to become persistent opioid users.[9,10] Patients who do not become persistent users might also contribute to the opioid crisis by diverting unused tablets for non-medical use by others.[11] Given this scenario, evidence-based strategies are required to support judicious opioid prescribing while ensuring effective postoperative pain management.[12]

Studies suggest that to prevent postoperative opioid-related harms, surgeons and other perioperative care clinicians could consider prescribing only non-opioid drugs to manage pain after surgical discharge.[13–15]

Research in context

Evidence before this study

Opioid drugs are frequently used to manage pain after surgical discharge despite uncertainty regarding their impact on postoperative outcomes. In a recent scoping review (PMID 31563269), our group searched Medline, Cochrane Library, Scopus, AMED, BIOSIS, CINAHL, and PsycINFO databases without any language restrictions for multidose analgesia studies published between Jan 1, 1990, and Feb 19, 2019, that focused on opioid-free pain management after surgeries done in a hospital operating room. Of the 424 relevant studies identified, eight were randomised controlled trials (RCTs) comparing opioid versus opioid-free analgesia after postoperative discharge. Importantly, we did not identify any systematic review or meta-analysis synthesising the evidence from these RCTs to best inform prescription decision making. In patients undergoing minor surgery (eg, procedures done in an outpatient clinic), existing meta-analyses focused on single-dose trials that are often done under strict experimental conditions (ie, with patients kept in a surgical or research facility) and might not reflect real-world settings in which postoperative analgesia spans several days. Because of the scarcity of conclusive evidence, the decision to prescribe opioid versus opioid-free analgesia after postoperative discharge largely depends on clinicians' preference (or habit) and health-care culture.

Added value of this study

In this meta-analysis of 47 multidose RCTs involving 6607 patients discharged after undergoing an elective surgical procedure, opioid prescribing at postoperative discharge did not reduce self-reported pain intensity in the first day after discharge (moderate certainty of evidence) or at other postoperative timepoints (certainty of evidence varied from moderate to very low). Further, opioid prescribing was associated with an increased risk of vomiting (high certainty of evidence) and other adverse events, including nausea, constipation, dizziness, and drowsiness (certainty of evidence varied from high to moderate). Opioids did not affect other outcomes, including risk of dissatisfaction, pain interference, and health-care reutilisation.

Implications of all the available evidence

Findings from this meta-analysis support that opioid prescribing at surgical discharge does not reduce pain intensity and increases adverse events. Evidence relied on trials focused on elective surgeries of minor (eg, dental or hand procedures) and moderate extent (eg, minimally invasive orthopaedic surgery or general surgery procedures), suggesting that clinicians can consider prescribing opioid-free analgesia in these surgical settings. No trials investigated opioid-free analgesia after discharge after major (eg, lung, bowel, or liver resections) or major-complex (eg, thoracoabdominal procedures or multiorgan resections) procedures. In addition, importantly, data were largely derived from trials with high risk of bias. Given these limitations, there is a great need to advance the quality and scope of research in this field. Our meta-analysis bridges a crucial knowledge gap and, until new robust RCTs emerge, contributes the best available evidence to inform analgesia prescribing at surgical discharge.

However, while this practice is common outside North America,[16–20] evidence regarding the comparative effectiveness of opioid versus opioid-free postoperative analgesia remains uncertain.[21] Hence, we did a systematic review and meta-analysis to assess the extent to which opioid prescribing at surgical discharge affects pain intensity and adverse events in comparison with opioid-free analgesia.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement[22] and targeted the following PICO question: in patients discharged after undergoing a surgical procedure, to what extent does the prescription of opioids, in comparison to opioid-free analgesia, affect self-reported pain intensity and adverse events? Eligible studies were randomised controlled trials (RCTs) that had the following characteristics: a parallel design; enrolled young people, adults patients, or both (aged ≥15 years old) discharged after undergoing a surgical procedure according to the WHO definition (ie, any intervention involving the incision, excision, manipulation, or suturing of tissue and requiring regional or general anaesthesia or sedation);[23,24] compared an analgesia regimen after discharge, including opioids versus opioid-free analgesia; and 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 (ie, emergency and urgent surgeries) were considered for inclusion. Opioid analgesia was defined as any pain management regimen after discharge 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 in which opioids were offered to the opioid-free group as rescue analgesia were included only if the opioid drugs were not readily available to patients (ie, a new prescription was required via contact with a healthcare provider).

We excluded cross-over trials because their results can be influenced by the natural history of postoperative pain improving over time regardless of the treatment

received.[25] We also excluded single-dose trials because they do not reflect real-world practices in which analgesia regimens span several days postoperatively.[26] Furthermore, single-dose analgesia trials focused on acute pain have been extensively reviewed in previous literature.[26,27] Other exclusion criteria were trials in which only placebo was offered to patients (because they do not reflect standard practice), analgesic administration via invasive routes (eg, intravenous or epidural; because they are rarely used after discharge), and analgesia for chronic postoperative pain (starting beyond 2 months after surgery).[28]

We 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 2–41) were developed by a medical librarian (TL) and peer reviewed (AA-Z, AB).[29] Searches were done on March 5–7, 2019, and updated on July 8, 2021. We targeted articles published after Jan 1, 1990, because earlier publications do not reflect current standards of surgical care with the widespread use of minimally invasive approaches and care pathways.[30–33] 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). Our study protocol (available in appendix pp 42–58, with amendments listed) was registered online (PROSPERO ID CRD42020153050) and published a priori.[44]

See Online for appendix

Selection of studies and data extraction

Screening of titles, abstracts, and full texts was done, independently and in duplicate, by pairs of reviewers (JFFJr, CE-K, M-AC, PN-P, UD, GO, FR, or AK). Disagreements were resolved by consensus or by consulting an adjudicator (LSF). The screening was facilitated by a systematic review online software (Covidence, Veritas Health Innovation). Data extraction was done, independently and in duplicate, by pairs of reviewers (CE-K, M-AC, PN-P, or UD) using a customised 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 [OMEs] for opioids,[34] 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.

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 h and 24 h). This timepoint was chosen to account for the duration of the effect of analgesic interventions used during surgery, inpatient stay, or both; for example after ambulatory surgery, evidence suggests that patients report most severe pain after approximately 24 h.[35,36] As per previous recommendations, we prioritised reports of dynamic pain (over pain at rest) and worst pain (over average pain).[37,38] The coprimary outcome of interest was risk of postoperative vomiting within the study follow-up period (up to 30 days). These outcomes were chosen on the basis of previous literature showing that, according to patient preference, good pain relief is the most desirable outcome in perioperative care, whereas postoperative vomiting is the least desirable outcome.[39–41] If data were available, we also assessed other endpoints recommended in core outcomes sets for perioperative care,[42,43] including pain intensity at other timepoints after discharge defined a priori (from day 0 after discharge, with latest assessment recorded between 6 h and 12 h, up to 30 days),[44] drug adverse events other than vomiting, pain interference, dissatisfaction with pain management, participant disposition (ie, withdrawal because of adverse events or ineffective treatment), self-reported health status (overall and domain-based scores, such as fatigue, and physical, emotional, social, and sleep functions), and health-care reutilisation (ie, 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.

Risk of bias assessment

Risk of bias assessment was done independently and in duplicate by two investigators (JFFJr, CE-K) using the Cochrane's Risk of Bias Tool 2.0,[45] which addresses five domains, comprising randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For each domain, risk of bias was judged as being 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.[45] Disagreements were resolved by consensus or by consulting an adjudicator (LSF).

Data analysis

The extent of agreement between reviewers during full-text screening was assessed using Kappa statistics.[46] When two or more trials assessed the same outcome, data were pooled using random-effects models according to the Hartung-Knapp-Sidik-Jonkman method.[47] Weighted mean differences (WMDs) and 95% CIs were calculated for pain intensity and other continuous outcomes.[48] For dichotomous measures, we

calculated relative risks (RRs) and 95% CIs on the basis of the frequency of events in each treatment group. For trials reporting zero events in one or both groups, we used continuity correction by adding 0·5 to all the cells in 2×2 tables containing empty cells.[49] Post-hoc sensitivity analyses were done using different approaches to address zero cell values, including no correction and correction proportional to the inverse of the opposite group size.[50] Forest plots were used to display the meta-analyses findings. Analyses were done using Stata, version 16. Comparisons were two 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 (eg, estimating means and SD from medians and other measures of variance).[51] When trials had several treatment groups, data from opioid groups, opioid-free groups, or both were aggregated according to Cochrane recommendations.[51] If ordinal or continuous scales were used to assess satisfaction with pain management, data were

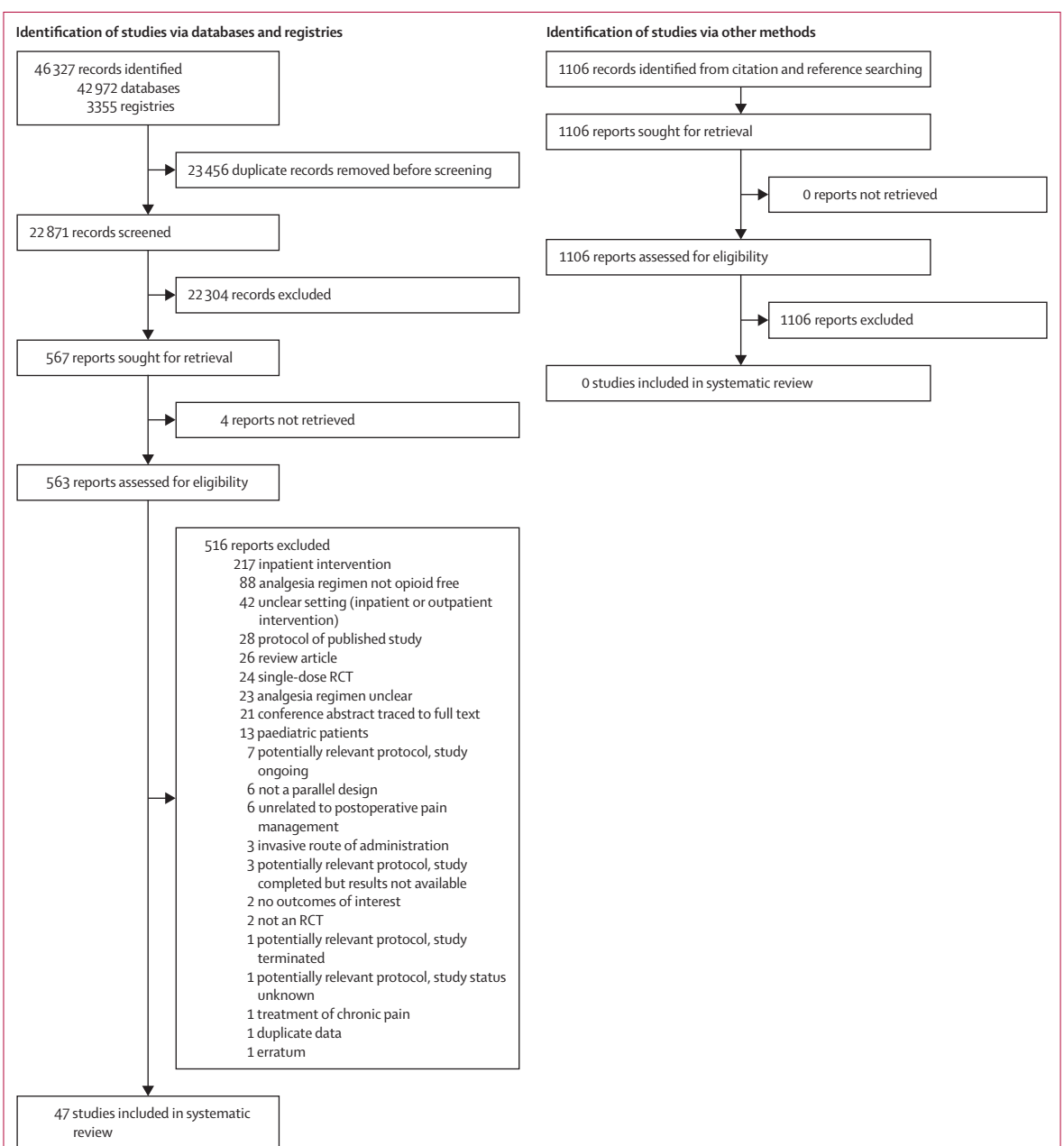

Figure 1: **PRISMA diagram**

dichotomised to facilitate interpretation (with dissatisfied comprising very dissatisfied, dissatisfied, or a satisfaction score <5 out of 10, and not dissatisfied comprising very satisfied, satisfied, neutral, or a satisfaction score ≥5 out of 10).[51] Interpreting effect estimates of pain intensity is challenging because this outcome can be assessed using different scales (eg, visual analogue scale [VAS], numerical rating scale, SF-36 bodily pain scale). To address this issue, we followed specific guidelines to transform pain intensity measures into a standard metric (appendix p 59).[52–54] 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.[38,55,56] Once VAS WMDs were calculated, we contextualised them in relation to the minimally important difference (MID; the smallest change in score that patients perceive as important)[57] established in previous surgical literature, being 1 cm in 10 cm.[58] To guide the contextualisation of VAS data on the basis of this MID, we followed recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (also known as IMMPACT),[59] a clinically meaningful difference in VAS was deemed achieved if WMD 95% CIs were outside the MID thresholds (–1 cm to +1 cm), unlikely if 95% CIs were within the MID thresholds, and inconclusive if 95% CIs crossed the MID thresholds.

Subgroup analyses

Heterogeneity between the RCTs was assessed using the I^2 test.[60] To explore potential sources of heterogeneity in the analysis of the coprimary outcomes, we did subgroup analyses if there were two or more trials in each subgroup. We tested a-priori hypotheses that larger opioid effect sizes would be observed in trials involving the following characteristics: surgeries done in an outpatient clinic versus in a hospital operating room (as per the WHO definition of minor versus major surgery);[23,24] day surgery (ie, same-day discharge) versus inpatient surgery (ie, at least one overnight stay); only women as participants (reports of sex-specific data or sex-specific surgeries, such as gynaecological or breast surgery) versus men (or both sexes);[25,61] and trials with high versus lower risk of bias.[62,63] In post-hoc subgroup analyses, we explored the hypotheses that opioid effect sizes would be larger in trials involving the following characteristics: surgeries of larger extent, as classified on the basis of the Physiological and Operative Severity Score for the Enumeration of Mortality and morbidity (POSSUM) scoring system, as minor (ie, dental, skin, or hand surgery), moderate (eg, minimally invasive orthopaedic or general surgery), major (ie, bowel, liver, and lung resections), and major-complex (ie, thoracoabdominal, multiorgan resections, and procedures under extracorporeal circulation;[64] appendix p 60) surgeries; opioid analgesia with stronger opioids (OME ≥1; ie, morphine, oxycodone, or hydrocodone) versus weaker (OME <1; ie, codeine, dihydrocodeine, or tramadol);[65] opioid analgesia prescribed around the clock (ie, at regularly-scheduled intervals) versus as needed;[66] unimodal opioid-free analgesia (only one non-opioid drug prescribed) versus multimodal opioid-free analgesia (more than one non-opioid drug prescribed);[67] multimodal opioid analgesia (opioid prescribed in addition to a non-opioid drug) versus unimodal opioid analgesia (only opioids prescribed);[67] industry funding versus no industry funding;[68] and published versus unpublished data.[69] Tests of interaction were done to establish whether the differences between subgroups were statistically significant.[70] In subgroup analyses of pain outcomes, intervention effects within subgroups were interpreted according to MIDs and 95% CIs.[59]

Certainty of evidence

Certainty of evidence was rated as high, moderate, low, or very low using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[71] Assessment was done, independently and in duplicate (JFFJr, CE-K), on an outcome-by-outcome basis.[72] Disagreements were resolved by consensus or by consulting an adjudicator (LSF). GRADE items concerning risk of bias, inconsistency, indirectness, imprecision, and publication bias were appraised according to specific criteria (appendix pp 61–62). When there were at least ten RCTs available for meta-analysis, risk of publication bias was assessed by visual appraisal of funnel plot asymmetry[73] and Begg's test.[74]

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.

Results

A total of 23 977 unique articles were identified and 567 underwent full-text review. Of those, 520 full-text reports were excluded (articles and reasons for exclusion are listed in the appendix, pp 63–86), and 47 met eligibility criteria (figure 1).[75–121] Among the included trials, 36 addressed pain intensity on the first day after discharge[75–77,82–87,90,91,93,94,97–110,112–120] and 12 addressed risk of postoperative vomiting (coprimary outcomes).[75,79,80,86–90,93,95,115,118] There was substantial agreement between reviewers during full-text screening (κ=0·79).[46] Trial characteristics are described in the appendix (pp 87–90, 91–185). In total, the included trials involved 6607 patients; 59% were female patients and 41% were male patients, and the average age range was 21–63 years. The majority of the trials were done in North America (25 [53%] of the 47 trials included)[77,79,81–84,88–93,96,98–101,108–111,116,117,120,121] and Europe (11 [23%] of 47 trials).[78,80,85,95,104,107,112,114,115,118,119] Median duration of patient follow-up was 7 days (IQR 4·25–10·0).

	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%
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

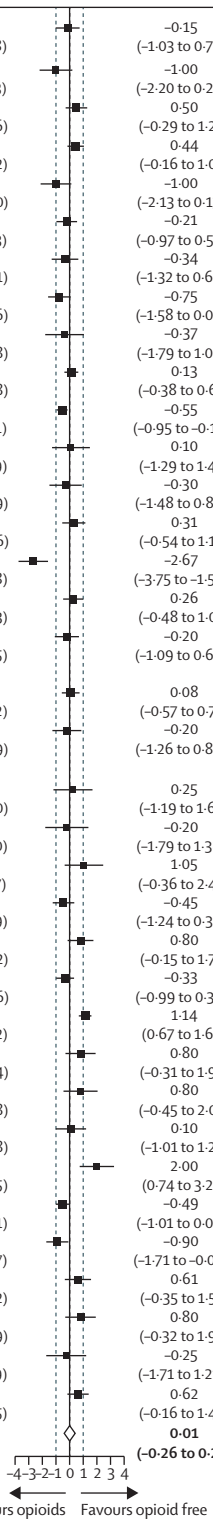

Figure 2: **Forest plot for pain on day 1 after discharge**

	Number of trials	Number of patients	Serious risk of bias	I^2	Serious indirectness or imprecision	Likelihood of publication bias	Effect size in WMD (95% CI) or RR (95% CI)	Quality of evidence
Postoperative pain								
Day 0 after discharge	21	2317	↓1 level	82·23%	No	No	−0·25 (−0·74 to 0·24)*	Low
Day 1 after discharge (coprimary outcome)	36	3848	↓1 level	71·44%	No	No	0·01 (−0·26 to 0·27)*	Moderate
Day 2 after discharge	29	3054	↓1 level	68·82%	No	No	0·01 (−0·26 to 0·28)*	Moderate
Day 3 after discharge	26	2321	↓1 level	63·00%	No	No	0·44 (0·18 to 0·70)*	Moderate
Day 4–7 after discharge‡	22	1946	↓1 level	54·09%	↓1 level	No	0·23 (−0·01 to 0·47)*	Low
Day 8–30 after discharge§	9	677	↓1 level	87·09%	↓1 level	No	0·33 (−0·32 to 0·99)*	Very low
Adverse events								
Nausea	21	3544	No	60·82%	No	No	2·37 (1·59 to 3·55)†	High
Overall non-specific adverse events	19	2804	No	84·16%	↓1 level	No	1·78 (1·20 to 2·66)†	Low
Constipation	16	2227	No	65·00%	No	No	1·63 (1·04 to 2·57)†	High
Dizziness	14	2878	No	42·31%	No	No	2·22 (1·20 to 4·08)†	High
Drowsiness	14	1695	No	58·39%	↓1 level	No	1·57 (1·02 to 2·42)†	Moderate
Vomiting (coprimary outcome)	12	2789	No	51·13%	No	No	4·50 (1·93 to 10·51)†	High
Pruritus	10	1730	No	32·08%	↓2 levels	No	1·27 (0·73 to 2·21)†	Low
Headache	8	1892	No	58·95%	↓1 level	No	1·40 (0·72 to 2·70)†	Moderate
Confusion	5	671	↓1 level	22·95%	↓2 levels	No	0·73 (0·27 to 1·97)†	Very low
Diarrhoea	5	370	↓1 level	2·08%	↓2 levels	No	1·53 (0·48 to 4·91)†	Very low
Difficulty urinating	4	670	No	2·29%	↓2 levels	No	0·93 (0·33 to 2·60)†	Low
Indigestion	4	588	No	23·33%	↓2 levels	No	0·58 (0·17 to 1·95)†	Low
Nausea or vomit	4	373	↓1 level	37·77%	↓2 levels	No	1·88 (0·57 to 6·26)†	Very low
Bleeding	4	358	No	3·10%	↓2 levels	No	1·05 (0·26 to 4·18)†	Low
Dry mouth	3	920	No	32·94%	↓2 levels	No	1·57 (0·57 to 4·32)†	Low
Sleep problems	3	570	↓2 levels	35·90%	↓3 levels	No	1·01 (0·38 to 2·71)†	Very low
Hypotension	2	919	No	1·88%	↓2 levels	No	2·01 (0·19 to 21·33)†	Low
Difficulty concentrating	2	537	No	25·91%	↓2 levels	No	0·89 (0·31 to 2·54)†	Low
Acid reflux	2	262	No	10·04%	↓2 levels	No	0·90 (0·24 to 3·42)†	Low
Skin rash	2	316	↓2 levels	0%	↓2 levels	No	1·63 (0·14 to 19·18)†	Very low
Upset stomach	2	177	↓1 level	0·44%	↓2 levels	No	1·23 (0·67 to 2·26)†	Very low
Difficulty breathing	2	91	↓2 levels	5·48%	↓2 levels	No	0·35 (0·03 to 3·99)†	Very low
Pain interference (first week after discharge)¶	6	657	↓1 level	64·92%	↓1 level	No	3·51 (1·01 to 6·02)*	Low
Quality of recovery (day 2 after discharge)‖	2	156	No	0·44%	↓1 level	No	−0·34 (−0·87 to 0·19)*	Moderate
Patient disposition	15	2612	No	54·40%	No	No	2·05 (0·95 to 4·42)†	High
Patient dissatisfaction	14	1750	No	42·46%	↓2 levels	No	1·14 (0·67 to 1·94)†	Low
Health-care reutilisation	8	778	No	51·69%	↓3 levels	No	0·88 (0·30 to 2·61)†	Very low

QoR=Quality of Recovery. RR=risk ratio. WMD=weighted mean difference. PROMIS-PI=Patient Reported Outcomes Measurement Information System-Pain Interference. *Effect estimate measured as WMD and 95% CI on the visual analogue scale. †Effect estimate measured as RR and 95% CI. ‡In studies with several timepoints, we extracted data from the timepoint closest to 7 days. Median number of days after discharge until assessment was 7 days (range 4–7). §In studies with several timepoints, we extracted data from the timepoint closest to 30 days. Median number of days after discharge until assessment was 12 days (range 10–28). ¶Pain interference was measured using the PROMIS-PI, American Pain Society, and Brief Pain Inventory questionnaires. For meta-analysis, measures were standardised to PROMIS-PI scores (minimal important difference 9).[122] ‖Quality of recovery was measured using the QoR-9 and QoR-40 questionnaires. For meta-analysis, measures were standardised to QoR-9 scores (minimal important difference 0·9.[123]

Table: **GRADE evidence profile**

Ten (21%) trials reported industry funding.[79,80,85,88,92,106,108,109,112,121] 17 relevant unpublished RCTs were identified within the literature search period (eight completed, seven ongoing, one terminated, and one with unknown status). After contacting authors, we obtained data and risk of bias information from five

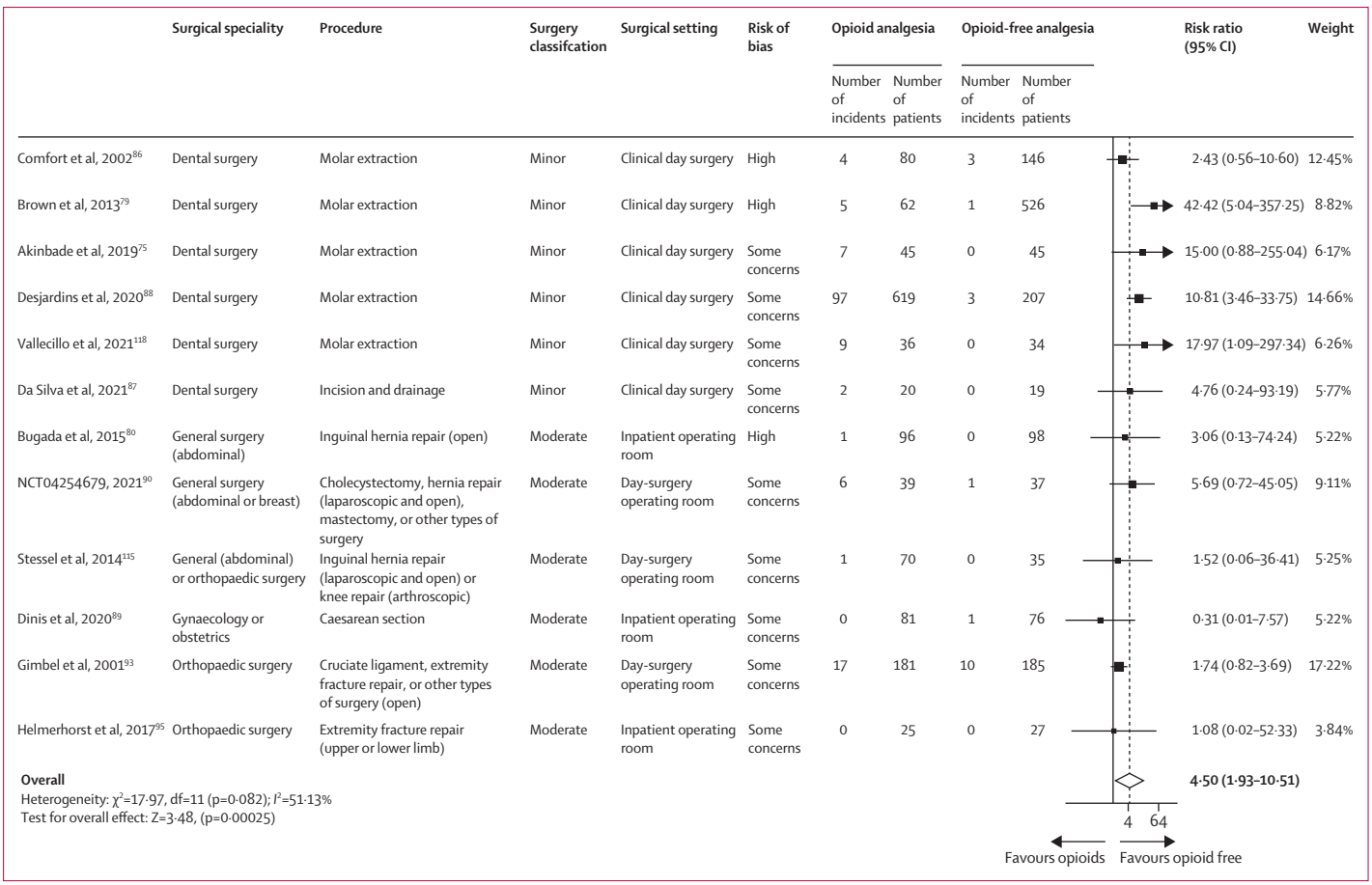

Figure 3: **Forest plot for vomiting after surgical discharge**

unpublished trials.[84,90,98,99,116] In addition, we queried missing information from 14 published trials; four authors provided additional data.[80,83,95,100]

23 (49%) of 47 trials involved patients having surgeries done in an outpatient clinic[75,76,78,79,81,82,85–88,91,92,94,97,104–107,113,117–119,121] and 24 (51%) involved surgeries done in a hospital operating room.[77,80,83,84,89,90,93,95,96,98–103,108–112,114–116,120] 40 (85%) trials involved day surgery [75–79,81–88,90–94,96–101,104–107,109,110,112–121] and seven (15%) involved in-patient procedures with at least one overnight hospital stay.[80,89,95,102,103,108,111] Among the trials identified, 30 (64%) involved surgeries of minor extent[75,76,78,79,81–88,91,92,94,96,97,102,104–107,113,114,116–121] and 17 (36%) involved surgeries of moderate extent.[77,80,89,90,93,95,98–101,103,108–112,115] 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 or urgent procedures (appendix pp 87–90, 91–185).

Most opioid-free analgesia regimens were unimodal (26 [55%] of 47 trials),[75,81,82,84–88,91–94,96,97,102–107,112–114,117,118,121] involved drugs prescribed around the clock (25 [53%] of 47 trials),[75,76,78-80,82,83,86–88,90,94,97,102,103,105–107,112–115,117–119] and included non-steroidal anti-inflammatory drugs (NSAIDs; 42 [89%] of 47 trials)[75–81,83,84,86,88–112,115–121] and, or, acetaminophen (27 [57%] of 47 trials).[76–80,83,85,87,89,90,95,96,98–101,108–111,113–117,119,120] Opioid analgesia regimens were most often multimodal (42 [89%] of 47 trials)[76–95,98–102,104–109,111–121] and had opioids prescribed around the clock (25 [53%] of 47 trials).[75,76,78–80,82,83,85–88,94,97,102,103,105–107,112–115,117–119] The opioid drugs most commonly prescribed were codeine (20 [43%] of 47 trials),[76,78,79,81,82,86,87,92,94,102,104,106–109,112,113,116,117,119] hydrocodone (11 [23%] of 47 trials),[83,84,89,91,93,98–101,120,121] and tramadol (nine [19%] of 47 trials).[75,80,85,88,95,97,105,114,118] The median OME dose prescribed per day was 27 mg (IQR 12·0–41·25). Only one study described the use of non-pharmacological analgesia interventions (ice packs).[111]

A complete description of risk of bias assessment results by outcome measure is reported in the appendix (pp 186–218). In the 36 RCTs assessing pain on the first day after discharge,[75–77,82–87,90,91,93,94,97–110,112–120] risk of bias was low in two (6%) trials,[108–109] of some concern in 12 (33%) trials,[75,76,87,90,93,103,113,115–119] and high in 22 (61%) trials.[77,82–86,91,94,97–102,104–107,110,112,114,120] Of the 12 trials assessing vomiting,[75,79,80,86–90,93,95,115,118] nine (75%) had some concerns of bias[75,87–90,93,95,115,118] and three (25%) had high risk of bias.[79,80,86] The most common reasons for increased risk

of bias were potential deviations from intended interventions (eg, non-compliance with intention-to-treat principle), poor description of the randomisation process, and potential selective reporting (ie, trial protocol not available). There was no clear evidence of publication bias in the statistical or visual appraisal of funnel plots (appendix pp 219–33).

Evidence of moderate certainty (36 trials, 3848 patients)[75–77,82–87,90,91,93,94,97–110,112–120] supported that the prescription of opioids was not associated with decreased pain intensity on day 1 after discharge (WMD 0·01 cm, 95% CI –0·26 to 0·27 cm; figure 2; table). The observed 95% CI was 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 (all p<0·05 for interactions) were surgery done 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 234–44). 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; appendix pp 256–60).

High-certainty evidence (12 trials, 2789 patients)[75,79,80,86–90,93,95,115,118] supported that opioid prescribing was associated with increased risk of vomiting in comparison with opioid-free analgesia (10·9% *vs* 1·3%; RR 4·50, 95% CI 1·93–10·51; figure 3; table). Post-hoc sensitivity analyses using different approaches to address zero-cell values were consistent with our primary analysis (appendix pp 245–46). Subgroup analyses indicated that potential sources of heterogeneity (p<0·05 for all interactions) were surgery done in an outpatient clinic (versus hospital operating room) and minor surgery (versus surgery of moderate extent; appendix pp 247–55). 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; appendix pp 261–65). No between-group differences were observed in risk for other adverse events (certainty of evidence varied from very low to moderate; table; appendix pp 266–81).

The prescription of opioids was not associated with increased rates of dissatisfaction with pain management (RR 1·14, 95% CI 0·67–1·94; low-certainty evidence), participant disposition (RR 2·05, 0·95–4·42; high-certainty evidence), or health-care reutilisation (RR 0·88, 0·30–2·61; very-low-certainty evidence; table; appendix pp 282–84). Opioid prescribing also did not reduce pain interference (WMD 3·51, 95% CI 1·01–6·02; evidence of low certainty; table; appendix p 285) and self-reported postoperative health status (quality of recovery; WMD –0·34, –0·87 to 0·19; evidence of moderate certainty; table; appendix p 286). No trials reported on prolonged opioid use, misuse, dependence, or overdose after surgical discharge.

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 with 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 crucial knowledge gap regarding the comparative effectiveness of multidose opioid versus opioid-free analgesia after surgical discharge.[21] Previous meta-analyses in this field targeted single-dose RCTs which are often placebo controlled, of short duration, and done under strict experimental conditions (ie, with patients kept in a research facility).[26,27] Although these trials are important to ascertain drug efficacy for regulatory approval purposes, they do not reflect real-world settings in which postoperative pain management spans several days after discharge.[26] 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 or postoperative pain,[26] and that they increase adverse events.[27] 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.[16–20] In a study focused on international prescribing patterns after discharge following general surgery, opioids were prescribed to 95% of patients undergoing surgery in the USA compared with only 5% in European, Asian, South American, and Middle Eastern countries.[16] Although patient and procedure characteristics might have affected these findings (eg, preoperative opioid use or

emergency surgery), similar results were observed in other international comparisons focused on different surgical specialties.[17–20] 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 health-care reutilisation because of uncontrolled pain.[124] Findings from this meta-analysis indicate that none of these concerns are supported by comparative-effectiveness evidence. Although guidelines support the prescription of opioids as part of multimodal analgesia after surgical discharge,[67,125,126] we found no evidence that this approach is superior to opioid-free analgesia. Our results are in line with reports supporting that the removal of opioids from postoperative discharge prescriptions does not affect patient satisfaction or postoperative outcomes after minor and moderate elective surgeries.[13–15]

This review must be interpreted considering several limitations. There are inherent challenges in doing and interpreting meta-analyses that include heterogeneous populations and interventions.[127] In fact, heterogeneity between the trials included was substantial (>50% for primary outcomes), which might affect the interpretation of overall effect estimates. To address this concern, we did a-priori and post-hoc subgroup analyses that 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 might have been affected by type 1 error given multiple comparisons. We prioritised the assessment of dynamic pain scores,[37,38] but pain at rest (not relieved by staying still) is also concerning to patients and clinicians. Our findings are not generalisable to surgeries that were not subject to RCTs on this topic, including major and major-complex procedures. Although these procedures are associated with higher postoperative pain and analgesic requirements,[128] they are usually done in inpatient settings in which 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 generalisable to emergency or urgent procedures, which were not addressed in the available trials. Most of the RCTs involved the prescription of weak opioids (ie, codeine or tramadol), with limited attention to stronger opioids that are commonly used in surgical practice (ie, oxycodone or hydromorphone).[129] Further, there was limited attention to non-pharmacological interventions that might contribute to postoperative pain management (eg, expectation setting, relaxation, or ice packs).[67] 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,[130] but we did not target this outcome a priori. Only one of the identified trials (open inguinal hernia repair with high risk of bias) reported on risk of chronic pain supporting no difference between groups.[80] Factors known to affect opioid consumption and prolonged opioid use after surgery (ie, preoperative pain and opioid use, anxiety, depression, and pain catastrophising)[131–133] were rarely considered in trial design. Although many trials focused on adverse events common to opioid analgesia (eg, vomiting, nausea, and constipation), there was limited focus on the potential side-effects of non-opioid drugs, including NSAIDs (eg, bleeding or kidney failure) and acetaminophen (ie, liver failure), hindering robust conclusions. Although subgroup analysis indicated that study quality (high risk versus lower risk of bias) did not have a substantial effect 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 opioid versus opioid-free analgesia after discharge, which justifies and encourages the conduct of high-quality trials to address the aforementioned knowledge gaps.

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 with 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 having major or major-complex procedures. Although our findings support that clinicians should 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.

Contributors

JFF, CE-K, AD, TL, AA-Z, AVR, MM, LL, GB, and LSF designed the study. JFF and CE-K coordinated the study. TL, AA-Z, AB, JFF, and CE-K designed the literature search; TL, AA-Z, and AB ran the search. JFF, CE-K, M-AC, PN-P, UD, GO, FR, and AK screened records. CE-K, M-AC, PN-P, and UD extracted data. JFF and CE-K assessed risk of bias and GRADE. CE-K, JFF, and AVR did the statistical analyses. All authors contributed to the data interpretation. JFF and CE-K 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 for publication. JFF and CE-K have accessed and verified the data reported.

Declaration of interests

JFF declares receiving research funding from Merck and honorarium from Shionogi outside the submitted work. LSF 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. All other authors declare no competing interests.

Data sharing

Extracted data are available on request to the corresponding author.

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