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SYSTEMATIC REVIEW

Comparative Effectiveness of Different Opioid Regimens, in Daily Dose or Treatment Duration, Prescribed at Surgical Discharge: a Systematic Review and Meta-Analysis

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Abstract

Background Opioids are prescribed for postsurgical pain management, but a balance between achieving adequate pain control and minimising opioid-related harm is required. This study aimed to investigate the effectiveness of different opioid regimens, in daily dose or treatment duration, prescribed at surgical discharge.

Methods A systematic search of MEDLINE, EMBASE, CENTRAL, and ICTRP was performed from inception to 12 January 2025. Randomised controlled trials (RCTs) and non-RCTs comparing different daily doses or treatment durations of opioid analgesics were included. All surgeries were included, except those related to cancer treatment or palliative care. Eligible populations were adults (≥ 18 years) or individuals classified as adults according to the criteria of the respective studies. Data were extracted at immediate-term (≤ 3 days), short-term (> 3 to ≤ 7 days), medium-term (> 7 to ≤ 30 days), and long-term (> 30 days). Data from RCTs were pooled using a random-effects model. Risk of bias was assessed. Certainty of evidence from RCTs was evaluated with Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). The primary outcome was pain intensity. Adverse events were also measured.

Results A total of 8432 records were identified. In total, 12 RCTs with 7128 patients and 24 non-RCTs with 118,849 patients were included. Studies included orthopaedic, gynaecology and obstetric surgeries, ranging from minor to major procedures. Higher-doses of opioids were more effective than lower-doses in reducing immediate pain intensity (mean difference (MD) 4.36, 95% confidence interval (CI) 0.50–8.23, $n = 364$, three studies, $I^2 = 0\%$, high certainty). No difference in pain was found between higher-doses and lower-doses at other time points (moderate to high certainty). Longer-durations of opioid treatment showed no difference in pain at any time point (low to moderate certainty). More adverse events were reported with higher doses of opioids.

Conclusions Higher-dose opioids provide a slight reduction in immediate post-discharge pain intensity but may lead to more adverse events. Longer durations of opioid treatment are probably not more effective in reducing pain than shorter treatment durations. Our findings suggest that clinicians may choose to prescribe lower doses of opioids or shorter durations of opioids without compromising pain control, even for major surgery.

1 Introduction

Opioid overuse and opioid-related harm are an ongoing global public health concern [1]. The World Health Organization reported that roughly 80% of the 600,000 worldwide drug-related deaths in 2019 were directly or indirectly related to opioids [2]. The risk of opioid overuse or harm increases substantially with longer treatment duration, and with increasing dose [3, 4]. A study conducted by The Centres for Disease Control and Prevention (CDC) found that the rate of long-term use for persons prescribed at least 1 day of opioid therapy was relatively low, with 6.0% taking opioids 1 year later [3]. However, this increased to 13.5% and 29.9% for persons whose first episode of use was for ≥ 8 days and ≥ 31 days, respectively [3]. Another study found that individuals receiving higher-doses of opioids (> 90 mg oral morphine equivalent per day) were more prone to reporting medication tampering, non-medical opioid use and developing dependence compared with those prescribed lower-doses [4]. Therefore, there is an impetus to review opioid prescribing practices to ensure that individuals are prescribed sufficient analgesia to adequately manage pain,

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Key Points

Higher doses of opioid treatment have a slightly (< 5 points out of 100) greater effect compared with lower doses in reducing immediate post-discharge pain.

Longer durations of opioid therapy following surgery are probably not more effective in reducing post-discharge pain.

Clinicians may choose to prescribe lower doses of opioids or shorter durations of opioids at surgical discharge without compromising pain control, even for major surgeries.

but at the lowest effective dose and in a time limited regimen [5, 6], including for acute post-surgical pain [7, 8].

The prescribing rate of opioids following surgery has been recognised as a significant public health concern in countries, such as the USA, Canada and Australia [9]. Excessive prescribing of opioids for post-surgical pain is a contributor to opioid-related harm [9, 10]. Recent evidence demonstrated that using opioids following surgical discharge did not reduce pain compared with non-opioids, but increased adverse events [11]. Studies included were of minor (e.g. molar extraction) and moderate (e.g. hernia repair) surgeries, yet the comparative effectiveness of opioid analgesia for pain relief after discharge from major surgery remains unclear. Recent research suggests that lower doses and shorter durations of opioids used after major surgeries (e.g. spine surgery [12] and arthroplasty [13] yield equivalent pain outcomes, but this has not been systematically analysed.

This systematic review and meta-analysis aims to investigate the comparative effectiveness and safety of different opioid regimens, in daily dose or treatment duration, prescribed at discharge from acute surgical care.

2 Methods

This systematic review and meta-analysis has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] and Assessing the methodological quality of systematic reviews (AMSTAR) [15] guidelines. The protocol was prospectively registered in PROSPERO (CRD42023402214).

2.1 Search Strategy and Study Selection

We searched MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid), clinicaltrials.gov and the International Clinical Trials Registry Platform from their inception to 12 January 2025. There were no language or geographic restrictions. We performed citation tracking on relevant systematic reviews and included studies. We developed our search strategy (provided in detail in eMethods in Supplementary Information) with assistance from a librarian at the University of Sydney.

2.2 Study Selection

Eligible studies were any randomised controlled trials (RCTs) including parallel, cross-over, factorial designs and non-RCTs including cohort studies, case-control studies and interrupted-time-series studies. Studies were eligible if they compared different daily doses (e.g. a higher-dose opioid group versus a lower-dose opioid group) or treatment durations of opioid analgesics (longer-duration versus shorter), where the daily dose was constant across groups. We grouped studies that did not specify a daily regimen but provided different quantities of opioids (e.g. 30 versus 90 tablets) under the category 'different treatment durations', assuming that the daily regimen was constant across groups. We did not specify a threshold to define weak/low-dose or strong/high-dose opioids; instead, studies were eligible if they described one group as receiving weak/low-dose opioids and another group as receiving strong/high-dose opioids, or if there was a difference in opioid dose between the two groups.

Eligible populations were adults (≥ 18 years) or individuals classified as adults according to the respective studies' criteria, who underwent an outpatient or inpatient surgical procedure. Any type of surgery was included, except surgery for cancer treatment or palliative care. Eligible interventions were any pharmaceutical opioid analgesic (single ingredient or combination), via any route, prescribed upon discharge from acute surgical care (e.g. to go home, to inpatient rehabilitation or convalescence; see eTable 1 in Supplementary Information for all excluded studies).

The primary outcome was pain intensity, measured by a self-reported tool (e.g. visual analogue scale (VAS), or numeric pain rating scale (NPRS)). Secondary outcomes were opioid use (calculated as oral morphine equivalents (OME)), physical function (measured by a self-reported tool), quality of life, adverse events (number of adverse events and number of participants with an adverse event, reported as any adverse event or serious adverse event as defined by each study), rates of continued opioid use and rates of hospital readmission. Opioid use could be measured

by consumption, dispensation or prescription; when multiple measures were reported, we prioritized extraction of consumption data, followed by dispensing, then prescription.

2.3 Screening and Data Extraction

Screening of titles, abstracts, then full texts was performed independently in duplicate using Covidence (Veritas Health Innovation), by two of four reviewers (A.V.L., C.M.P.J., D.J. and M.J.). In cases of disagreement, resolution was reached through consensus, or arbitrated by another independent researcher (C.L.). Data extraction, also conducted independently in duplicate, involved two of four reviewers (A.V.L., C.M.P.J., D.J. and M.J.) using a custom-designed extraction form. Discrepancies were identified and resolved through discussion, then arbitrated by another independent reviewer (C.L.) where necessary. Missing data were requested via email from the study authors, and attempts were made twice over a 2-week interval, if necessary.

The following data were extracted: study design, year of publication, funding source, participant characteristics (e.g. sample source, inclusion and exclusion criteria, age and sex), sample size, details of study treatment and control, assessment time points and outcomes.

Data were extracted for four time points. Our primary time point for studies examining different daily doses was the immediate-term (≤ 3 days; closest to 24 h if multiple data points were available). Other time points were short-term (> 3 but ≤ 7 days; closest to 7 days if multiple data points were available), medium-term (> 7 but ≤ 30 days; closest to 30 days if multiple data points were available) and long-term (> 30 days; closest to 90 days if multiple time points were available). For studies examining different treatment durations, we modified the primary time point from immediate-term to medium-term after a review of included studies, revealing that the regimens between groups were comparable in the immediate-term (see eTable 2 in Supplementary Information for all protocol deviations).

2.4 Risk of Bias Assessment and Certainty of Evidence

Two of four reviewers (A.V.L., CM.P.J., D.J. and MJ) independently assessed risk of bias for RCTs using the Cochrane Risk of Bias 1 tool [16]. A study was considered to have an overall low risk of bias if it demonstrated 'low risk" in at least four out of the six domains. Studies with 'high-risk' or 'unclear' rating in three or more of six domains were considered overall at high risk of bias. We used ROBINS-I to assess risk of bias in non-RCTs [17].

The certainty of evidence from RCTs was evaluated using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE; see eGRADE in Supplementary Information).

2.5 Statistical Analysis

Studies were separated into RCTs and non-RCTs. Studies were categorized by their comparison (differences in daily dose or treatment duration), then by surgical type (e.g. orthopaedic). We also used the Physiological and Operative Severity Score for the Enumeration of Mortality and morbidity (POSSUM) system to measure operative severity (minor, intermediate, major and major plus) [18].

For RCTs, continuous variables, such as pain intensity, physical function and quality of life outcomes, were converted to a 0–100 scale to improve the comparability and interpretation of effects. Studies were pooled using a random-effects model and reported with the mean difference (MD) or risk difference (RD) and 95% confidence interval (CI). We categorized effect sizes as follows: < 5 out of 100 = slight, between 5 and 10 = small, between 10 and 20 = medium, and > 20 = large [19]. For continuous outcomes we prioritized the extraction of change scores at the most relevant time points. For measures of dispersion, we preferred standard deviations (SDs) [20]. If studies only reported medians, we included them in the meta-analysis as if they were means. In instances where no measure of dispersion was available, we borrowed the SDs from the study most closely aligned in clinical characteristics. For dichotomous measures, we used the Mantel–Haenszel method to calculate RDs and 95% CIs. Analyses were done using Review Manager version 5.1 [21]. For continued opioid use, we reported the number of individuals still using opioids at each follow-up point.

We converted opioid doses to OME for comparison between studies, using an opioid equianalgesic calculator [22]. We reported data from non-RCTs descriptively (using critical appraisal and narrative synthesis) and did not pool their data.

3 Results

A total of 8432 records were identified. After screening, 12 RCTs and 24 non-RCTs were included (Fig. 1). Of the RCTs, three evaluated different daily doses of opioids while nine assessed different opioid treatment durations. Only two studies [23, 24] reported discharge destination.

3.1 Results of RCTs

3.2 Different Daily Dose

Three RCTs included a total of 389 patients with mean ages ranging from 37 to 49 years (Table 1). Of these studies, two investigated orthopaedic surgeries (minor and intermediate/major surgeries) [25, 26] while the other investigated general surgery (intermediate surgery) [23]. The orthopaedic studies tested a 14-day course of oxycodone 30–60 OME per day against codeine 4–8 OME per day in one study [25], and oxycodone, codeine or hydromorphone (341 OME total dose with an unspecified duration) against hydromorphone (40 OME total dose) in the other study [26]. The general surgery study [23] tested a de-escalation schedule of controlled-release codeine (39 OME on day 1 and 26 OME on day 2) compared with codeine combined with acetaminophen (31 OME on day 1 and 16 OME on day 2). Both studies examining orthopaedic surgeries had a low risk of bias, whereas the general surgery study had a high risk of bias (eFig. 1 in Supplementary Information).

3.2.1 Pain Outcome

Higher-doses of opioids were slightly more effective than lower-doses in reducing immediate pain intensity (MD 4.36, 95% CI 0.50–8.23, $n = 364$, 3 studies, $I^2 = 0\%$, high certainty evidence). There were no differences between higher and lower-dose groups at all other time points, with moderate to high certainty evidence (Fig. 2, eTable3).

3.3 Different Treatment Duration

In total, nine RCTs [24, 27–34], totalling 6739 participants with mean ages ranging from 30 to 64 years were included

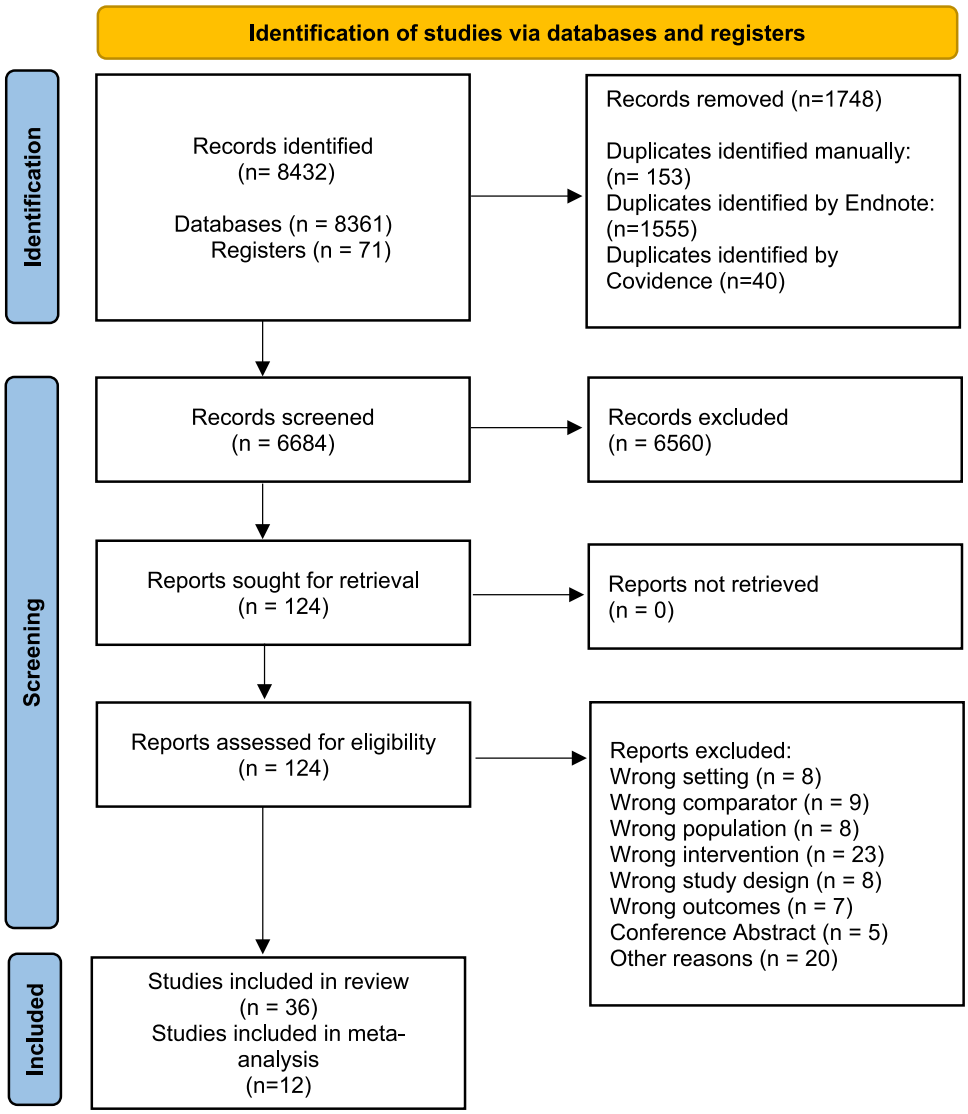

Fig. 1 PRISMA flow diagram of article screening and selection

Table 1 Study characteristics

Study [country]	Surgery [surgical severity]	Participants randomised (*n*) Sex (*n*)	Intervention (I)/control (C) [total opioid prescribed in OME]
RCTs			
Different daily dose			
Orthopaedics			
Jenkin et al., 2021 [Australia] [25]	Fracture surgical treatment [intermediate/major]	120 Female: 30 Male: 90	(I) Codeine 8 mg, 1 or 2 tablets administered four times daily, for 14 days [58.24–116.48] (C) Oxycodone hydrochloride IR 5 mg, one or two tablets administered four times daily, for 14 days [420–840]
The NO PAin Investigators, 2022 [Canada] [26]	Knee or shoulder arthroscopy [minor]	200[a] Female: 73 Male: 120	(I) Hydromorphone 1 mg, taken every 4 h as needed, 10 tablets [40.4] (C) Oxycodone, codeine or hydromorphone taken on as a needed basis ranging from 20 to 80 tablets [341.2]
General surgery			
Chung et al., 2004 [Canada] [23]	Cholecystectomy [intermediate]	69[b] Female: NR Male: NR	(I) Codeine 30 mg, two tablets taken every 6 h for 1 day [31], and one tablet every 6 h for 2 days [16] (C) Controlled-release codeine 150 mg, taken every 12 h for 1 day [39], and controlled-release codeine 100 mg, taken every 12 h for 2 days [26]
Different treatment duration			
Gynaecology and obstetrics			
Davidson et al., 2020 [USA] [30]	Prolapse repair [intermediate]	118 Female: 118	(I) Oxycodone 5 mg, five tablets [38] (C) Oxycodone 5 mg, 28 tablets [210]
Delara et al., 2022 [USA] [27]	Minimally invasive hysterectomy [minor]	73 Female: 73	(I) Oxycodone 5 mg, 15 tablets [112.5] (C) Oxycodone 5 mg, 30 tablets [225]
Gold et al., 2020 [Canada] [32]	Caesarean [intermediate]	40 Female: 40	(I) Hydromorphone 1 mg, 10 tablets [50] (C) Hydromorphone 1 mg, 20 tablets [100]
Osmundson et al., 2018 [USA] [33]	Caesarean [intermediate]	190 Female: 190	(I) Oxycodone 5 mg, 14 tablets [105] (C) Oxycodone 5 mg, 30 tablets [225]
Smid et al., 2024 [USA] [29]	Caesarean [intermediate]	5521 Female: 5521	(I) Oxycodone 5 mg, (0–20) tablets [105] (C) Oxycodone 5 mg, 20 tablets [150]
Serna-Gallegos et al., 2024 [USA] [34] (a)	Pelvic floor [major]	107 Female: 107	(I) Oxycodone 5 mg, (0–30) tablets [150] (C) Oxycodone 5 mg, 30 tablets [225]
Serna-Gallegos et al., 2024 [USA] [34] (b)	Pelvic floor [minor]	47 Female: 47	(I) Oxycodone 5 mg, (0–12) tablets [0-90] (C) Oxycodone 5 mg, 12 tablets [90]
Orthopaedics			
Fleischman et al., 2019 [USA] [28]	Hip replacement [major]	156 Female: 72 Male: 84	(I) Oxycodone IR 5 mg, taken every 4 h as needed, 10 tablets for 2 days Tramadol 50mg, taken every 6 h as needed, 10 tablets for 2 days [175] C) Oxycodone IR 5 mg, taken every 4 h as needed, 60 tablets for 2 weeks Tramadol 50mg, taken every 6 h as needed, 60 tablets for 2 weeks [1050]

Table 1 (continued)

Study [country]	Surgery [surgical severity]	Participants randomised (*n*) Sex (*n*)	Intervention (I)/control (C) [total opioid prescribed in OME]
Hannon et al., 2019 [USA] [31]	Total Joint Arthroplasty [major]	418[c] Female: 164 Male: 140	(I) Oxycodone IR 5 mg, taken as a second breakthrough pain medication, 30 tablets. Tramadol 100 mg, taken every 8 h as needed for breakthrough pain [225] (C) Oxycodone IR 5 mg, taken as a second breakthrough pain medication, 90 tablets. Tramadol 100 mg every 8 h as needed for breakthrough pain [675]
Mixed surgery			
Stessel et al., 2014 [Netherlands] [24]	Knee arthroscopy or inguinal hernia repair [intermediate / minor]	70 Female: 17 Male: 53	(I) Oxycodone CR 10 mg, taken twice a day, for 24 h [30] (C) Oxycodone CR 10 mg, taken twice a day, for 48 h [60]
Non-RCTs			
Different daily dose			
Orthopaedics			
Garnaud et al., 2021 [France] [36]	Arthroscopic shoulder surgery [minor]	87 Female: 31 Male: 56	(I) Tramadol 100 mg, every 4–6 h with a maximum daily dose of 400mg [80] (Ca) IR oxycodone 10 mg, every 4–6 hours with a maximum daily dose of 60 mg [90] (Cb) ER oxycodone 20 mg, taken in a single dose per day at 8 pm on the night of surgery and stopped on day 2. Oxycodone IR 10 mg, every 4–6 hours with a maximum daily dose of 60 mg [120–90]
Landes et al., 2022 [USA] [38]	Fixation of fracture [intermediate/major]	1779 Female: 1084 Male: 695	(I) Tramadol 50 mg four times daily [150] (C) Oxycodone 5 mg, every 4–6 h as needed for pain [252.3]
Lim et al., 2023 [USA] [37]	Spine surgery [major]	20,239 Female: 9711 Male: 10528	(I) Not reported [≤ 225] (C) Not reported [> 225]
Magnan et al., 2022 [Canada] [39]	Spine surgery [major]	52 Female: 21 Male: 31	(I) Not reported [108] (C) Not reported [155]
General surgery			
Gudmundsdottir et al., 2023 [USA] [35]	General surgery [minor/ major]	741 Female: 376 Male: 365	(I) Not reported [60] (C) Not reported [140]
Lindros et al., 2022 [USA] [40]	Ventral hernia surgery [minor]	241[d] Female: 85 Male: 78	(I) Not reported [65] (C) Not reported [100]
Gynaecology and obstetrics			
Imo et al., 2024 [USA] [41]	Caesarean [intermediate]	779 Female: 779	(I) Oxycodone 5 mg, equal to five times the number of tablets used in the 24 h before discharge, [37.5] (C) Codeine 30 mg, 30 tablets [135]
Different treatment duration			
Orthopaedics			
Featherall et al., 2022 [USA] [43]	Total joint arthroplasty [major]	208 Female: 17 Male: 191	(I) Oxycodone 5 mg, 39 tablets [292] (C) Oxycodone 5 mg, 85 tablets [640]
Joo et al., 2020 [USA] [44]	Spine surgery [major]	83 Female: 1 Male: 82	(I) Not reported [280] (C) Not reported [630]

Table 1 (continued)

Study [country]	Surgery [surgical severity]	Participants randomised (*n*) Sex (*n*)	Intervention (I)/control (C) [total opioid prescribed in OME]
Krauss et al., 2021 [USA] [42]	Spine surgery [major]	1193 Female: 429 Male: 764	(I) Not reported [225] (C) Not reported [300]
Cardiac surgery			
Brescia et al., 2021 [USA] [45]	Cardiac surgery [minor/major/major+]	2543[e] Female: 382 Male: 1113	(I) Not reported [90] (C) Not reported [150]
Kidney surgery			
Dualeh et al., 2021 [USA] [46]	Kidney transplant [major]	179 Female: 76 Male: 103	(I) Oxycodone 5 mg, four tablets [30] (C) Oxycodone 5 mg, 60 tablets [300]
Different daily dose and duration or unclear			
Orthopaedics			
Chalmers et al., 2021 (A) [USA] [48]	Total hip and total knee arthroplasty [major]	19,428 Female: 10259 Male: 9169	(I) Oxycodone 5 mg, 42 tablets for both THA and TKA. [330] (Ca) Oxycodone 5 mg, 70 tablets after THA and 70 tablets after TKA. [518] (Cb) Oxycodone 5 mg, 90 tablets after THA and 120 tablets after TKA. [727]
Chalmers et al., 2021 (B) [USA] [51]	Total knee arthroplasty [major]	174[f] Female: 88 Male: 75	(I) Oxycodone 5 mg, routinely prescribed 42 tablets [150–315] (C) Oxycodone 5 mg, routinely prescribed 120 tablets [375–900]
Chalmers et al., 2021 (C) [USA] [47]	Total knee arthroplasty [major]	8799 Female: 5275 Male: 3524	(I) Oxycodone 5 mg, 42 tablets [315] (Ca) Oxycodone 5 mg, 120 tablets [900] (Cb) Oxycodone 5 mg, 70 tablets [525]
Kukushliev et al., 2023 [USA] [53]	Total hip and total knee arthroplasty [major]	388[g] Female: 21 Male: 366	(I) Not reported—patients were instructed to take outpatient prescription opioids via a patient-specific tapering protocol [292] (C) Oxycodone 5 mg, prescribing 30, 60 or 90 tablets or hydrocodone-acetaminophen 5 mg to be taken at 4–6 h intervals [554]
Padilla et al., 2019 [USA] [49]	Total hip arthroplasty [major]	669 Female: 389 Male: 280	(I) Tramadol 50 mg, every 4–6 h PRN, 12 tablets dispensed [120] (C) Hydrocodone 5 mg, one to two tablets every 6 h PRN, 60 tablets dispensed. Oxycodone 5 mg, every 6–8 h PRN, 12 tablets dispensed [390]
Mussab et al., 2024 [UK] [50]	Total hip and total knee replacement [major]	50 Female: 25 Male: 25	(I) Weak opioid—[Not reported] (C) Strong opioid—[Not reported]
Winkelman et al., 2021 [USA] [57]	Lumbar laminectomy [major]	1031 Female: 348 Male: 683	(I) Not reported—prescribed within 90 days of discharge [315] (C) Not reported—prescribed within 90 days of discharge [450]
Mixed surgery			
Habbouche et al., 2018 [USA] [52]	Mixed surgery [minor to major]	21,960 Female: 14163 Male: 7797	(I) Not reported [371] (C) Not reported [406]
Langnas et al., 2022 [USA] [54]	Inpatient mixed surgery [minor to major+]	37,009[h] Female: 19510 Male: 17495 Non-binary: 3	(I) Not reported [175] (C) Not reported [475]

Table 1 (continued)

Study [country]	Surgery [surgical severity]	Participants randomised (*n*) Sex (*n*)	Intervention (I)/control (C) [total opioid prescribed in OME]
Gynaecology and obstetrics			
Linder et al., 2019 [USA] [56]	Pelvic organ prolapse surgery [intermediate]	96 Female: 96	(I) Not reported [112.5] (C) Not reported—equate to 27 tablets of 5 mg of oxycodone [200]
Endocrine surgery			
Sada et al., 2020 [USA] [55]	Endocrine surgery [minor / intermediate]	754 Not reported	(I) Not reported [50] (C) Not reported [150]
Metabolic and bariatric surgery			
Wilson et al., 2023 [USA] [58]	Bariatric surgery [major]	367 Female: 300 Male: 67	(I) Oxycodone 5 mg, five tablets 37.5 mg [38] (C) Not report (prescriptions for opioids at varying doses and quantities were given prior to discharge on the basis of surgeon preference. Median MED at discharge [180 mg]

[a]A total of seven patients (two patients from the control group, five patients from the intervention group) had their procedures cancelled after randomisation for various reasons unrelated to the trial itself

[b]Not reported, and it is not possible to obtain from the corresponding author, who mentioned that their institutional requirement is to retain raw data for 10 years after publication

[c]There were 116 patients lost to follow-up and not analysed

[d]A total of 163 patients were included (121 patients received standard care, and 42 patients received guideline-base care)

[e]Total study population, $n = 2543$, patient-reported outcomes from questionnaire responses, $n = 1685$ (66.3%), opioid-naïve at admission. $n = 1495$, (89%)

[f]We included 163 patients for analysis

[g]There were 388 patients included, composed of 299 (77%) pre-protocol implementation patients and 89 (23%) post-protocol implementation patients

[h]There were 15,288 patients in the pre-guideline group and 21,721 patients in the post-guideline group

(Table 1). These comprised six gynaecology/obstetrics studies (minor to intermediate surgeries), two orthopaedic studies (major surgeries) and one mixed surgery study (intermediate/minor surgery, with 77% of patients undergoing orthopaedic surgery).

Eight studies tested oxycodone [24, 27–31, 33, 34], including immediate-release and controlled-release formulations. One study (gynaecology and obstetrics surgery) evaluated hydromorphone [32]. The shortest duration was 2 tablets supplied for 24 h (total dose 30 OME), while the longest duration was 120 tablets supplied for 2 weeks (total dose 1050 OME).

Four studies were scored as having low-risk of bias [27, 28, 32, 34]. All other studies [24, 29–31, 33] had at least three domains with high or uncertain-risk of bias, mainly due to the lack of blinding and selective reporting (eFig. 1 in Supplementary Information).

3.3.1 Pain Outcome

Overall, six studies [24, 28–31, 33] assessed pain intensity. Longer-durations of opioid treatment showed no difference in pain in the medium-term (~ 30 days) (MD 0.06, 95% CI − 1.11 to 1.24, $n = 5402$, 5 studies, $I^2 = 68\%$, low certainty) compared with shorter-durations. Similar results were seen at all other time points with low to moderate certainty evidence (Fig. 3, eTable3 in Supplementary Information).

3.4 Adverse Events Outcome (RCTs)

Significantly fewer adverse events occurred in the lower-dose group than in the higher-dose group (RD − 0.13, 95% CI − 0.20 to − 0.07, $n = 313$, 2 studies, $I^2 = 96\%$, moderate certainty) [25, 26]. This translates to an absolute decrease in risk of 13%. Similarly, significantly fewer participants reported adverse events in the lower-dose opioid group (RD − 0.13, 95% CI − 0.25 to − 0.01, $n = 193$, 1 study, low certainty) [26]. There were no differences

Meta-Analysis of Pain (different daily dose)

Study	Lower-dose mean	Lower-dose SD	Lower-dose sample size, n	Higher-dose mean	Higher-dose SD	Higher-dose sample size, n	weight	Mean Difference IV, Fixed, 95% CI
Immediate-term								
Orthopaedic surgery								
Jenkin et al, 2021	52	18.6	61	44.2	21	59	29.6%	7.80 [0.69, 14.91]
The NO PAin Investigators, 2022	48	28	89	47.5	28	86	21.7%	0.50 [-7.80, 8.80]
General surgery								
Chung et al, 2004	27	13.1	36	23	10.3	33	48.7%	4.00 [-1.54, 9.54]
Overall							100%	4.36 [0.50, 8.23]
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%								
Test for overall effect: Z = 2.21 (P = 0.03)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%								
Short-term								
Orthopaedic surgery								
Jenkin et al, 2021	37.2	23	61	34.1	15.5	59	45.7%	3.10 [-3.90, 10.10]
The NO PAin Investigators, 2022	24.1	19.5	84	30.7	22	78	54.3%	-6.60 [-13.02, -0.18]
Overall							100%	-2.17 [-6.90, 2.57]
Heterogeneity: Chi² = 4.01, df = 1 (P = 0.05); I² = 75%								
Test for overall effect: Z = 0.90 (P = 0.37)								
Test for subgroup differences: Not applicable								
Medium-term								
Orthopaedic surgery								
Jenkin et al, 2021	20.9	18.1	16	25.3	14.6	15	24.4%	-4.40 [-15.94, 7.14]
The NO PAin Investigators, 2022	15.2	18.5	69	19.1	20	64	75.6%	-3.90 [-10.46, 2.66]
Overall							100%	-4.02 [-9.73, 1.68]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Test for subgroup differences: Not applicable								
Long-term								
Orthopaedic surgery								
The NO PAin Investigators, 2022	12.2	18.6	88	14.8	17.3	90	100%	-2.60 [-7.88, 2.68]
Overall							100%	-2.60 [-7.88, 2.68]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Not applicable								

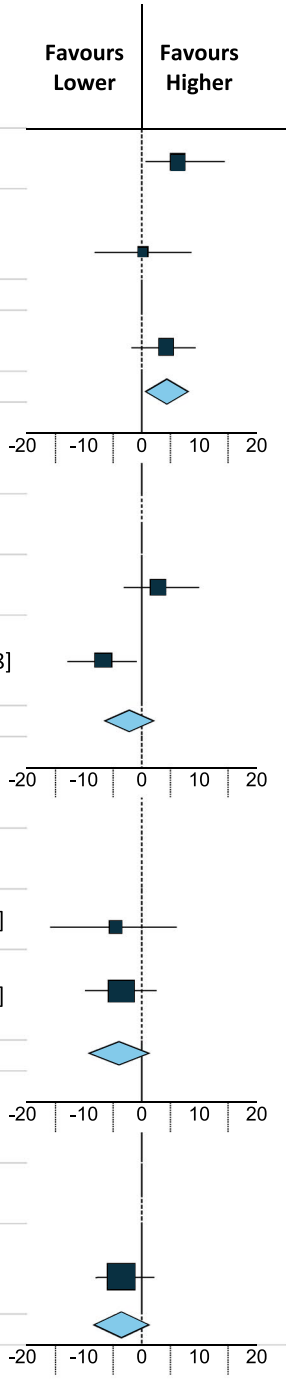

Fig. 2 Meta-analysis of pain (different daily dose)

Meta-Analysis of Pain (different treatment duration)

Study	Shorter-duration mean	SD	sample size, n	Longer-duration mean	SD	sample size, n	weight	Mean Difference IV, Fixed, 95% CI
Immediate-term								
Orthopaedic surgery								
Fleischman et al, 2019	50.5	20.9	77	52.7	24.1	79	31.2%	-2.20 [-9.27, 4.87]
Hannon et al, 2019	43	20.9	161	40	24.1	143	58.1%	3.00 [-2.10, 8.10]
Mixed surgery								
Stessel et al, 2014	24.12	25	33	11.9	21.9	33	11.7%	12.13 [0.79, 23.47]
Overall							100%	2.50 [-1.38, 6.39]
Heterogeneity: Chi² = 4.50, df = 2 (P = 0.11); I² = 56%								
Test for overall effect: Z = 1.26 (P = 0.21)								
Test for subgroup differences: Chi² = 3.14, df = 1 (P = 0.08), I² = 68.1%								
Short-term								
Orthopaedic surgery								
Fleischman et al, 2019	32.7	20.9	77	32.7	24.1	79	3.6%	0.00 [-7.07, 7.07]
Hannon et al, 2019	41	20.9	161	39	24.1	143	6.9%	2.00 [-3.10, 7.10]
Gynaecology & obstetrics								
Davidson et al, 2020	36	22.2	56	45	26.7	50	2.0%	-9.00 [-18.41, 0.41]
Smid et al, 2024	40	29.6	2539	40	22.2	2578	87.4%	0.00 [-1.38, 1.38]
Overall							100%	-0.04 [-1.39, 1.30]
Heterogeneity: Chi² = 4.10, df = 3 (P = 0.25); I² = 27%								
Test for overall effect: Z = 0.06 (P = 0.95).								
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%								
Medium-term								
Orthopaedic surgery								
Fleischman et al, 2019	18.6	20.9	76	18.9	24.1	77	2.7%	-0.30 [-7.45, 6.85]
Hannon et al, 2019	22	20.9	161	22	24.1	143	5.3%	0.00 [-5.10, 5.10]
Gynaecology & obstetrics								
Davidson et al, 2020	4.3	12.6	51	10	15.6	45	4.2%	-5.70 [-11.42, 0.02]
Smid et al, 2024	20	22.2	2339	20	22.2	2338	84.7%	0.00 [-1.27, 1.27]
Osmundson et al, 2018	40	22.2	87	30	22.2	85	3.1%	10.00 [3.36, 16.64]
Overall							100%	0.06 [-1.11, 1.24]
Heterogeneity: Chi² = 12.53, df = 4 (P = 0.01); I² = 68%								
Test for overall effect: Z = 0.11 (P = 0.91).								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%								
Long-term								
Gynaecology & obstetrics								
Davidson et al, 2020	0.1	7.4	51	0.1	5.3	38	2.3%	0.00 [-0.42, 0.42]
Smid et al, 2024	0.1	22.2	1858	0.1	22.2	1859	97.7%	0.00 [-0.06, 0.06]
Overall							100%	0.00 [-0.06, 0.06]
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

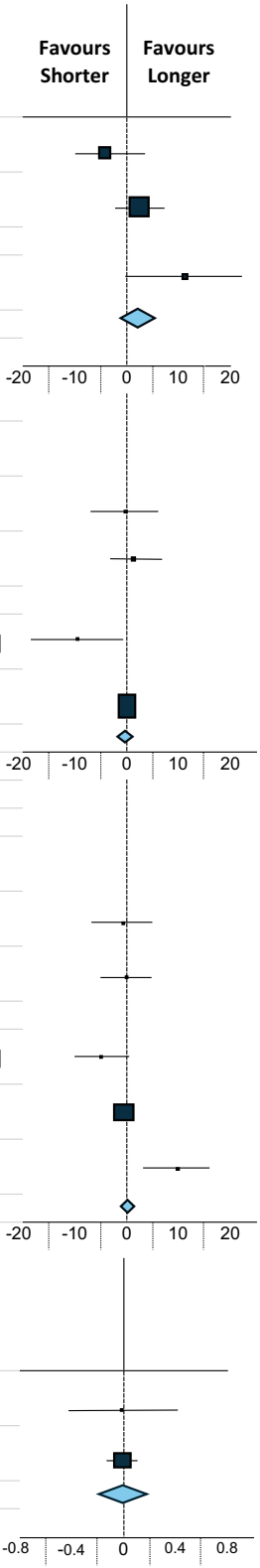

Fig. 3 Meta-analysis of pain (different treatment duration)

between lower-doses and higher-doses in terms of serious adverse events (RD 0.01, 95% CI −0.02 to 0.05, $n = 262$, 2 studies, $I^2 = 0\%$, moderate certainty) [23, 26] (Fig. 4, eTable4 in Supplementary Information).

No differences were found in the number of adverse events in studies comparing different durations (RD −0.01, 95% CI −0.03 to 0.01, $n = 5744$, 3 studies, low certainty) [24, 29, 34]. Only one study [31] assessed number of participants with adverse events, which found a higher number in the shorter-duration group who experienced oxycodone side effects (RD 0.04, 95% CI 0.00 to 0.07, $n = 418$, low certainty). Another study [29] reported serious adverse events, with fewer adverse events reported in the longer-duration group compared to the shorter-duration group (RD 0.02, 95% CI 0.01–0.03, $n = 5520$, low certainty) (Fig. 4, eTable 4 in Supplementary Information).

3.5 Other Outcomes (RCTs)

There was significantly less opioid used (OME) in the lower-dose and shorter-duration groups from short-term to long-term. In general, studies did not find a between-group difference in physical function, quality of life, rates of continued opioid use and hospital readmission (see eTable 4 and eForest plots in Supplementary Information for all other outcomes).

3.6 Results of Non-RCTs

The 24 non-RCTs included a total of 118,849 participants, with mean ages ranging from 59 to 67 years old. The majority (~60% of studies) were orthopaedic surgeries. In total, seven studies [35–41] investigated different daily doses, while five studies [42–46] investigated different durations. Overall, 12 studies [47–58] provided both different durations and doses, or the information was unclear.

Most studies had risk of bias issues, 3 studies with a critical risk of bias, 16 studies with a serious risk of bias and 5 with a moderate risk of bias (eTable 5 in Supplementary Information).

3.6.1 Pain Outcome

Two studies of orthopaedic surgeries assessed pain intensity in the immediate term. An arthroscopic shoulder surgery study [36] found that higher daily doses of extended and immediate-release oxycodone (~120 OME) were more effective in reducing pain compared to the lower daily doses of tramadol (80 OME). In contrast another study [49], on hip arthroplasty, found no significant differences between the higher-doses of hydrocodone and oxycodone (390 OME) versus the lower-dose of tramadol (120 OME). None of the included studies with different durations assessed pain in the medium-term. Overall, no differences in pain were found between higher doses compared with lower doses at other timepoints from short-term to long-term. However, one study reported that individuals on shorter-duration and lower-dose opioid therapy experienced less pain than those on longer-duration or higher-dose opioid therapy in the long term at day 41 and day 42 after discharge [57].

3.6.2 Adverse Events Outcome

Overall, fewer adverse events were reported in both the lower-opioid treatment group and the shorter-duration group.

All secondary outcomes are provided in eOutcomes and eTable 6 in Supplementary Information.

4 Discussion

Our findings indicate that higher-doses of opioids provide a slight reduction in pain intensity in the immediate-term post discharge, but probably not at other time points, following minor, intermediate and major surgeries. Longer-duration opioid treatment following minor to major surgeries may not confer benefits in reducing pain over shorter-duration opioid treatment in the medium term, and is probably not more effective in reducing pain at other time points. Higher doses significantly increased adverse events. No benefits of higher doses or longer durations were found for physical function or quality of life.

This is, to our knowledge, the first review to examine the comparative effectiveness and safety of different opioid regimens prescribed at surgical discharge. Another meta-analysis [11] found that opioids are not more effective than non-opioids for minor and moderate surgeries. Our review complements this finding by demonstrating that higher doses/longer durations of opioids are not superior to lower doses/shorter durations for pain management, even after major surgeries. Although there was a slight difference favouring higher-doses in the immediate-term, the effect size is likely clinically unimportant and the benefit reduces quickly with time. Both reviews highlight adverse events associated with opioids. When considering the findings of these two reviews together, it suggests that non-opioids should be preferred for minor and moderate surgeries. For major surgeries where opioids are used, lower-doses and shorter-durations can be used without compromising outcomes.

Patients are often prescribed more opioids than necessary for adequate pain management following surgery (minor to major) [59]. If patients are provided smaller quantities or dosages, they are less likely to transition to longer-term opioid use, thereby reducing the ongoing risk of opioid-related

Meta Analysis of Adverse Events, Number of Participants with Adverse Events, and Serious Adverse Events (different daily dose) and (different treatment duration)

Study	Lower/ shorter Events	sample size, n	Higher /longer Events	sample size, n	weight	Risk Difference M-H, Fixed, 95% CI
Different daily dose						
Number of adverse events						
Jenkin et al, 2021 (day7)	19	61	37	59	33.2%	-0.32 [-0.49, -0.15]
Jenkin et al, 2021 (day21)	1	29	6	21	13.5%	-0.25 [-0.46, -0.05]
The NO PAin Investigators, 2022	3	95	2	98	53.4%	0.01 [-0.03, 0.06]
Total (95% CI)					100%	-0.13 [-0.20, -0.07]
Heterogeneity: $Chi^2 = 45.08$, df = 2 ($P < 0.00001$); $I^2 = 96\%$						
Test for overall effect: Z = 3.88 (P = 0.0001)						
Number of participants with adverse events						
The NO PAin Investigators, 2022	18	95	31	98	100%	-0.13 [-0.25, -0.01]
Total (95% CI)					100%	-0.13 [-0.25, -0.01]
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
Serious adverse events						
Chung et al, 2004	2	36	1	33	26.3%	0.03 [-0.07, 0.12]
The NO PAin Investigators, 2022	1	95	0	98	73.7%	0.01 [-0.02, 0.04]
Total (95% CI)					100%	0.01 [-0.02, 0.05]
Heterogeneity: $Chi^2 = 0.12$, df = 1 ($P = 0.73$); $I^2 = 0\%$						
Test for overall effect: Z = 0.86 (P = 0.39)						
Different treatment duration						
Number of adverse events						
Smid, 2024	421	2748	447	2772	97.3%	-0.01 [-0.02, 0.01]
Stessel et al, 2014	43	35	59	35	-	Not estimated
Serna-Gallegos et al, 2024	8	76	4	78	2.7%	0.05 [-0.03, 0.14]
Total (95% CI)						-0.01 [-0.03, 0.01]
Heterogeneity: $Chi^2 = 1.98$, df = 1 ($P = 0.16$); $I^2 = 50\%$						
Test for overall effect: Z = 0.66 (P = 0.44)						
Number of participants with adverse events						
Hannon et al, 2019	10	200	3	218	100%	0.04 [0.00, 0.07]
Total (95% CI)					100%	0.04 [0.00, 0.07]
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
Serious adverse events						
Smid, 2024	146	2748	103	2772	100%	0.02 [0.01, 0.03]
Total (95% CI)					100%	0.02 [0.01, 0.03]
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						

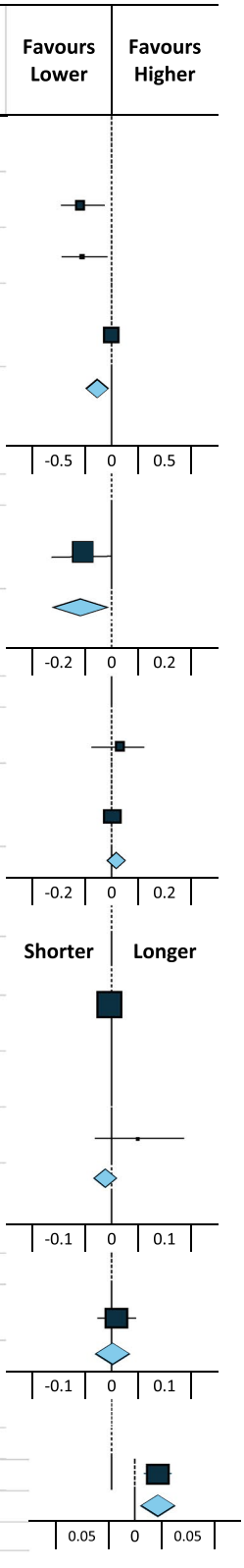

Fig. 4 Meta-analysis of adverse events, number of participants with adverse events and serious adverse events (different daily dose and different treatment duration)

harms and side effects [60–62]. Studies [63–65] suggest that using fewer opioids reduces healthcare utilization, lowers costs and decreases the circulation of surplus opioids in the community, thereby preventing potential misuse and reducing reservoirs of unused opioid analgesics.

Opioids remain a mainstay analgesic for pain management after major surgeries [66] and the results of our review can enable a reduction in opioid overprescribing by demonstrating that lower-doses and shorter-durations can effectively manage pain and decrease the occurrence of adverse events. However, determining the lowest effective dose and shortest duration might be complex and dependent on individual patient context, including surgical severity, co-morbidities and concomitant medicine use. A limitation of this review is that it cannot provide guidance on what the lowest-dose or shortest-duration should be owing to the range of surgical procedures included and the varied regimens used by the studies. According to an Australian guideline [67], discharge opioid regimens should be determined based on the patient's use over the immediate preceding 24-h period and be prescribed for short-term use only, ideally less than 1 week in most cases [68]. Additionally, American guidelines [69] recommend that if opioids are used continuously for more than 3 days but for less than 1 week, clinicians should consider reducing the daily dosage by 50% over 2 days to decrease side effects.

A limitation of this review is the low number of RCTs and limited types of surgery involved, so the results may not be generalisable to all types of surgery. Another limitation is that there was heterogeneity in doses and durations across studies. We did not pre-specify the definitions of high or low opioid dose or long or short treatment durations owing to the lack of consensus in this area and the broad surgical types included in the review. Furthermore, half of the RCTs lacked blinding, resulting in a high-risk of bias and therefore low to moderate GRADE ratings. The majority of included studies were from North America, where opioid overuse is a major problem, but we lacked studies from most other countries, including lower and middle income countries [7]. These limitations highlight evidence gaps for future studies in this area.

5 Conclusions

Findings from this meta-analysis suggest that higher-doses and longer-durations of opioid treatment are probably not more effective in reducing pain after surgical discharge from short term to long term, but higher-doses of opioids provide a slight reduction in pain intensity in the immediate-term. Higher doses of opioids may significantly increase adverse events. Evidence from this meta-analysis largely relied on data from orthopaedic, and gynaecology and obstetrics surgeries. Our findings suggest that clinicians may choose to prescribe lower doses of opioids or shorter durations of opioids without compromising pain control, even in the case of major surgery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-025-01165-9.

Declarations

Conflict of interest Masoud Jamshidi, Caitlin MP Jones, Aili V Langford, Asad E Patanwala, Chang Liu, Ian A Harris, Janney Wale, Mark Horsley, Sam Adie, Deanne Jenkin and Chung-Wei Christine Lin have no conflicts of interest that are directly relevant to the content of this article.

Availability of data and material All data generated or analysed during this study are included in this published article (and its supplementary information files).

Ethical approval Not applicable.

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Consent to participate Not applicable.

Consent for publication Not applicable

Code availability Not applicable.

Author contributions C.-W. C.L. was involved in conceptualisation, supervision, interpretation and critical revision of the manuscript; M.J. was involved in conceptualisation, searching, screening, extraction, analysis and writing the first draft of manuscript; C.M.P.J. and A.V.L. were involved in interpretation, searching, screening, extraction, analysis and critical revision of the manuscript; A.E.P. was involved in conceptualisation and critical revision of the manuscript; C.L., I.A.H., M.H. and S.A. were involved in critical revision of the manuscript; J.W. was involved as a consumer representative and in the critical revision of the manuscript; D.E.J. was involved in updating the screening, extraction, analysis and critical revision of the manuscript. All authors have approved the final version of the manuscript.

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