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SYSTEMATIC REVIEW

Opioids for Acute Musculoskeletal Pain: A Systematic Review with Meta-Analysis

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Abstract

Objective To evaluate the efficacy of opioids for people with acute musculoskeletal pain against placebo.

Study Design Systematic review and meta-analyses of randomised, placebo-controlled trials of opioid analgesics for acute musculoskeletal pain in any setting. The primary outcomes were pain and disability at the immediate timepoint (< 24 h).

Data Sources Multiple databases were searched from their inception to February 22nd, 2023.

Data Synthesis Continuous outcomes were converted to a 0–100 scale. Dichotomous outcomes were presented as risk differences. Risk of bias and certainty of evidence was assessed.

Results We located 17 trials (1 intravenous and 16 oral route of administration). For adults, high certainty evidence from 11 comparisons shows that oral opioids provide small benefits relative to placebo in the immediate term for pain (mean difference [MD] − 8.8 95% confidence interval [CI] − 12.0 to − 5.6). For disability, the difference is uncertain (MD − 6.2, 95% CI − 17.8 to 5.4). Opioid groups were at higher risk of adverse events (MD 14.3%, 95% CI 8.3–20.4%, very low certainty). There was moderate certainty evidence of a large effect of IV morphine on sciatica pain (MD −42.5, 95% CI − 49.9 to − 35.1, $n = 197$, 1 study). In paediatric populations, moderate certainty evidence from 3 trials shows that oral opioids probably do not provide benefit beyond that of placebo for pain (MD 6.1, 95% CI − 1.7 to 12.8) and there was no evidence for disability. There was low certainty evidence that there may be no difference in adverse events (MD 10.4%, 95% CI − 0.6 to 21.4%).

Discussion Intravenous morphine likely offers benefits, but oral opioids may not provide clinically meaningful benefits.

PROSPERO registration CRD42021249346.

Key Points

High certainty evidence from 16 trials shows oral opioids provide small to no benefits above placebo for acute musculoskeletal pain.

Intravenous morphine likely provides large effects above placebo based on one study of sciatica.

Clinicians should consider that the benefits of prescribing an oral opioid are likely to be small to none, and weigh this against the well-known risks, even when using as a second- or third-line treatment.

Extended author information available on the last page of the article

1 Introduction

Musculoskeletal pain is responsible for the largest disability burden on individuals and the health care system, affecting approximately 1.7 billion people worldwide in 2019 [1]. Many people present to health care services seeking treatment for acute musculoskeletal pain, whether from an injury, a new condition, or an acute flare of a chronic condition. These people are often treated with pain medicines, advice and education, exercise, manual therapy, and occasionally surgery [2].

Opioids are recommended in guidelines for acute musculoskeletal pain when delivered in small doses over short periods of time [3]. Opioids are used frequently for musculoskeletal pain. For example, one study found that two-thirds of adults presenting to the emergency department with back pain receive an opioid medicine [4]. In paediatric populations, the proportion being prescribed opioids for musculoskeletal pain is less than adults but is still substantial

(11% to 22%) [5]. Recommendations to prescribe opioids for acute pain, albeit cautiously, persist despite uncertain evidence of the benefits, and the known harms of opioid use (constipation, dizziness, nausea, somnolence, long-term use, dependence, overdose, etc.). Previous reviews of chronic musculoskeletal pain report that opioids typically provide small or no effect on pain and function compared to placebo [6, 7], and that there were high rates of withdrawal from the studies due to adverse events (AEs) or lack of effect [6]. However, it is not clear if this is the same for acute musculoskeletal pain. One previous review examined opioids for acute musculoskeletal pain [8]; however, they excluded the key diagnosis of low back pain, which is the most prevalent musculoskeletal pain condition [1]. Another examined the efficacy of opioids for musculoskeletal pain in the emergency department (assumed to be acute pain) and found a statistically but not clinically significant benefit of opioids over placebo [9], but the follow-up times in this review were very short (most in the 30- to 120-minute range) and therefore not entirely relevant to other settings like primary care, where the goals are for pain relief for longer periods. A recent placebo-controlled trial of orally administered opioids for acute spinal pain found no or negative effects [10] but has not been systematically reviewed alongside all available evidence.

In order for clinicians to make informed decisions about prescribing opioids for acute musculoskeletal pain, such as fractures, sprains, dislocations, aches and other injuries, we need an unbiased estimate of the benefits and harms of opioids for this population. The gold standard way to measure this is to systematically review randomised trials that compare an opioid to a placebo. Our research question is: are opioids (alone or in combination with other medicines) effective and safe for the management of acute musculoskeletal pain compared with placebo?

2 Methods

We prospectively registered this review on PROSPERO (CRD42021249346). We report this review as per the PRISMA 2020 statement recommendations [11]. A list of post-registration protocol deviations (with justifications) can be found in Appendix 1.

2.1 Identification and Selection of Trials

We searched electronic databases MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform (ICTRP) for eligible randomised controlled trials from their inception until February 22nd, 2023. We also did citation tracking from relevant systematic reviews and included trials.

The search strategy included words describing the study type (e.g., randomised controlled trial, based on the key words recommended by the Cochrane Back and Neck Group in their updated Search Strategies from January 2013) [12], and words describing the target population (e.g., acute musculoskeletal pain, back pain, fracture, sprain, etc.). Words describing the intervention (opioids, oxycodone, morphine, etc.) were determined by the research team by reviewing the strategies used in other similar reviews. See Appendix 2 for search strategies.

2.2 Eligibility Criteria

We included randomised controlled trials of opioids (alone or in combination) versus placebo, or like regimen minus opioids (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] + opioid vs NSAID alone) where blinding was maintained, for patients with acute musculoskeletal pain. Acute pain is defined as pain that has persisted for equal to or less than 12 weeks. Acute musculoskeletal pain was defined as any pain, sprain or ache of the muscles, ligaments, tendons, bones and joints (including sciatica). This included people with a fracture and were waiting on conservative treatment or surgery. We excluded studies enrolling people in the immediate post-operative phase as this was likely conflated by pain from the incision and trauma of surgery. We included acute flares of chronic pain conditions such as osteoarthritis, but pooled them separately. We excluded studies of people with pregnancy-related musculoskeletal pain. Studies with participants of any age were included. Studies with mixed samples of acute and chronic musculoskeletal pain were included if subgroup results for the acute participants were available. Studies with participants recruited from any setting were included (emergency departments, primary care, etc.).

2.3 Data Extraction

All records identified in the initial search were screened by two independent reviewers for relevance by their title first, and abstract then full text if it was still unclear. Two independent reviewers extracted the following data using a standardised data extraction form: bibliometric data, study characteristics, characteristics of included participants, outcome measures and outcomes. Any disagreements between the two reviewers were resolved by consensus first, then by arbitration by a third, independent reviewer.

2.4 Primary Outcomes

Our dual primary outcomes were pain intensity measured by self-report (e.g., visual analogue scale [VAS]), and disability measured by self-report (e.g., Roland Morris Disability Questionnaire). Our secondary outcome was number (%) of patients reporting an AE and nature of the AE.

We grouped outcomes by the timing of follow-up: immediate term (≤ 24 h or closest to 12 h); short term (> 24 h to 7 days or closest to 4 days); intermediate term (> 7 days to 12 weeks or closest to 6 weeks; and long term (> 12 weeks or closest to 6 months). Our pre-specified primary timepoint was the immediate term.

2.5 Risk of Bias (Certainty) Assessment of the Outcome Measures

We assessed risk of bias using the Cochrane risk of bias 1 tool [13]. A study with an overall low risk of bias was defined as being 'low risk' in at least three of the six domains (domains listed in Appendix 7). We modelled this from a high-quality systematic review of a similar topic [14]. Studies with an 'unclear' or 'high risk' rating in any three or more of six domains were considered overall at high risk of bias.

We rated the certainty of the evidence for each outcome measure using the Grading Recommendations Assessment, Development an Evaluation (GRADE) framework. The domains evaluated by the GRADE framework included study design, risk of bias, inconsistency, indirectness, imprecision and publication bias. See Appendix 4 for further information about how we graded each domain. When reporting the findings, we use the labels "high certainty", "moderate certainty", "low certainty" and "very low certainty". When discussing the findings, we use the terms recommended by the GRADE Working Group for communicating the findings of systematic reviews (e.g., "probably" when discussing moderate certainty evidence, "may" when discussing low certainty evidence, "unclear" when discussing very low certainty evidence) [15].

2.6 Strategy for Data Synthesis

Continuous pain severity and disability outcome measures were converted to a 0–100 scale to improve the comparability of findings between trials. We calculated the mean differences along with 95% confidence intervals (CI) between opioids versus control using a random effects model. Daily morphine milligram equivalent (MME) was calculated by first determining the total daily dose (stated dose for single-dose studies, or by multiplying the stated dose by the number of doses per day for multiple-dose studies) and then multiplying the daily total by the MME multiplier as per the Australian and New Zealand College of Anaesthetists & Faculty of Pain Medicine (ANZCA) opioid dose equivalence calculation table [16]. For studies that described dosing per body weight, we calculated the daily dose based on the mean body weight reported in the trial, or if the trial did not report participant body weight, we used the average body weight reported in a trial with a similar population, or where no similar trial existed, we used a weight of 70 kg for an average adult. When dosage was based on weight, we calculated the daily MME using the group mean weight of study participants. When prescribed dosing was described as a range (e.g., 1–2 tablets every 4–6 h) and no average number of daily tablets were reported, we calculated MME based on the highest allowable dose.

We separated studies according to the age of the population; paediatric (< 18 years) and adults (≥18 years). In the main analysis, we separated studies by route of administration (oral or intravenous [IV]). Effect size was considered small if 5–10 points on a 0–100 scale, moderate if > 10 to 20 points, and large if ≥ 20 points (based on the American College of Physicians guidelines for low back pain) [17]. Dichotomous outcomes (AEs) were calculated as risk differences (absolute) and risk ratios. To avoid duplication error in meta-analysis, we split the sample sizes of groups that were acting as a control to more than one comparator. We used Comprehensive Meta-Analysis Version 4 software for all analyses [18].

2.7 Exploratory Analyses

We conducted post hoc exploratory analyses on the primary outcome (oral opioids for pain in the immediate term) to explore reasons for statistical heterogeneity. We performed subgroup analyses per condition group, per opioid type, and opioid composition (opioids alone vs opioids in combination with simple analgesics). We also performed meta-regression on daily MME against pain outcomes, and a sensitivity analyses removing studies at high risk of bias. We also explored reasons for heterogeneity in the harms outcome by performing subgroup analysis per opioid type and opioid composition, meta regression of total daily MME on risk of harm and sensitivity analysis removing studies at high risk of bias. We performed a post hoc sensitivity analysis on our primary analysis only, excluding one study that examined acute-on-chronic populations.

3 Results

The search retrieved 15,144 articles, 17 of which (reporting 17 studies) were found to be eligible for inclusion [19–36]. All studies were of parallel design. Four studies were not included in the meta-analysis as they provided outcomes

in formats that were not able to be pooled. See Figure 1 for PRISMA flow diagram. See Appendix 5 for a list of excluded studies and reasons. See Table 1 for study characteristics. See Appendix 6 for individual results. The studies were from 6 countries (USA = 11, Australia = 2, Canada = 2, China = 1, New Zealand = 1, Turkey = 1).

3.1 Participants

There were 14 adult studies with a total of 3124 participants. The mean age of participants across studies was 46.1 years (SD = 12.3, $n = 9$ studies). The lowest study mean age was 29.9 [19] and the highest study mean was 69.6 [35]. The mean proportion of female participants across studies was 51.4% ($n = 13$ studies). The mean duration of pain upon admission to the study ranged from 120 min to up to 12 weeks. The mean pain intensity of participants at baseline was 69 out of 100 and ranged from 56 to 83. Four studies were categorised as 'mixed presentations' [22–24, 37], five studies were categorised as 'spinal pain including sciatica' [10, 20, 27, 31, 33, 35], two studies were categorised as 'an acute flare of osteoarthritis' [32, 34], and two studies were categorised as 'soft tissue injury' [19, 25]. Three of the 14 studies investigated populations with acute flares of chronic pain conditions [31, 32, 34]. All studies investigated oral opioids except for one, which investigated an intravenous opioid [33].

There were 3 paediatric studies enrolling a total of 427 participants [26, 28, 29] [Table 1]. The mean age of participants across studies was 11.5 years (SD = 2.9). The mean proportion of female participants across studies was 42.2%. The mean duration of pain upon admission to the study was not reported numerically but was defined as acute [28], < 24 h [26], and < 72 h [29]. The mean pain intensity of participants at baseline was 61.6/100 and ranged from 59 to 65. Two studies were categorised as 'mixed presentations' (combining fractures, sprains, contusions, etc.) [28, 29], and one study was categorised as 'bony injuries' [26]. All three studies examined acute pain conditions (not acute flares of chronic conditions).

3.2 Interventions

Adult studies tested seven types of opioid analgesics, with 5 studies with multiple arms testing different opioids (all orally administered unless stated: oxycodone = 6 trials, tramadol = 5 trials, codeine = 3 studies, butorphanol = 1 study, hydrocodone = 1 study, IV morphine = 1 study, and tapentadol = 1 study). Six studies delivered the opioid intervention as a single ingredient and eight used a combination of an opioid with a non-opioid. There were two types of controls (placebo alone = 9 and like regimen minus opioids where blinding was maintained = 5). Five trials had more than two arms [22, 24, 25, 33, 35]. Ten of 14 studies followed-up participants for longer than 1 day, and follow-up ranged from 30 min to 12 months in duration.

Paediatric studies tested three types of oral opioid analgesics (oxycodone, morphine and codeine). All three studies delivered the opioid orally and in combination with an NSAID. All three controls were NSAIDs with placebo. All three studies followed participants up for 120 min.

3.3 Risk of Bias

All three paediatric studies were rated as low risk of bias [26, 28, 29]. Eight of the 14 adult studies were scored as being at low risk of bias [10, 19, 20, 23, 25, 26, 33, 34]. All other studies had at least three domains that were high or uncertain risk of bias (see Appendix 7 for individual domain ratings for each study). The most frequent reasons for downgrading were high loss to follow-up and lack of prospective registration to confirm there was no selective reporting.

3.4 Outcomes

3.4.1 Pain

For adults, oral opioids provided a small effect compared to placebo at our primary timepoint (immediate term) (MD − 8.8, 95% CI − 12.0 to − 5.6, $n = 1385$, 7 studies, high certainty, includes studies testing codeine, immediate-release oxycodone, modified-release oxycodone, tramadol, and hydrocodone) (Fig. 2, Table 2). At our secondary timepoints, opioids provided a small effect in the short term (MD − 9.2, 95% C − 13.9 to − 4.4, $n = 1676$, 5 studies, moderate certainty, includes studies testing tramadol, butorphanol, hydrocodone and modified-release oxycodone), no effect in the intermediate term (MD − 9.0, 95% CI − 30.4 to 12.4, $n = 305$, 3 studies, moderate certainty, studies testing modified-release oxycodone and tramadol), and a small negative effect in the long term (6 months) (MD 8.0, 95% CI 2.6–13.4, $n = 247$, 1 study, moderate certainty, study testing modified-release oxycodone) [Appendix 8].

A single study investigated single dose of IV morphine with a daily MME of 21.0 and found moderate certainty evidence of a large effect (MD − 42.5, 95% CI − 49.9 to − 35.1, $n = 197$) for sciatica pain at the immediate timepoint.

For paediatric patients, there is moderate certainty evidence that opioids did not provide greater pain relief compared with placebo at our primary timepoint (immediate term) (MD 6.1, 95% CI − 1.7 to 13.8, $n = 236$, 3 studies, moderate certainty, studies testing morphine, oxycodone and codeine) (Fig. 2, Table 2). There were no paediatric studies

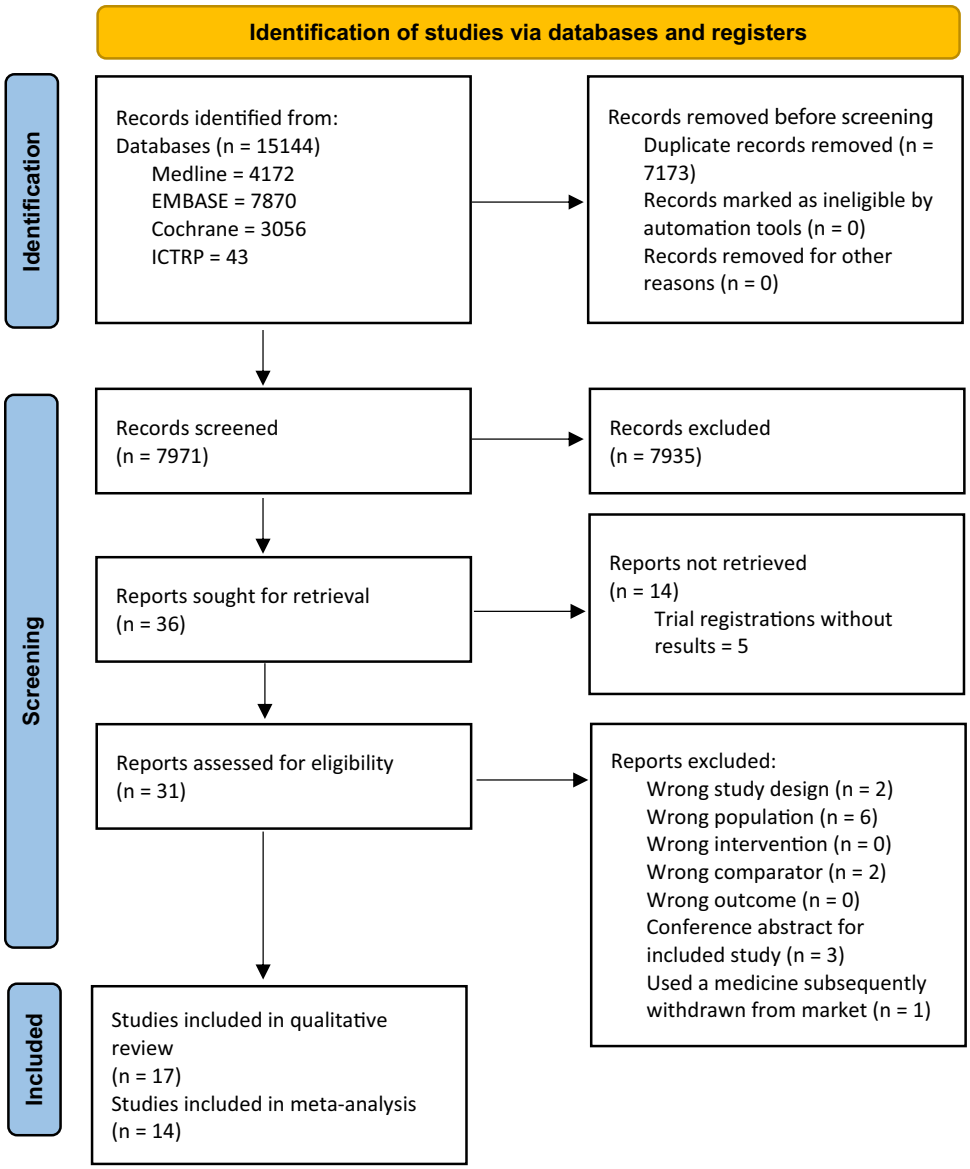

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram

providing evidence for the pain outcome at our secondary timepoints of short-, intermediate-, and long-term.

3.4.2 Pain Exploratory Analyses

Exploratory subgroup analyses were conducted on the studies investigating oral opioids at the primary timepoint (immediate) to explore effect modifiers [Appendix 9]. When separated by condition group, opioids had a small effect on mixed musculoskeletal pain (7 comparisons, $n = 397$, $I^2 = 0\%$), and soft tissue injuries (2 comparisons, $n = 595$, $I^2 = 0\%$) in the immediate term. There may be no effect on spinal pain (2 comparisons, $n = 393$, $I^2 = 87\%$); however, this estimate is of low certainty and the heterogeneity remains very high. When separated by opioid type, all oral opioids had small-to-moderate effects except hydrocodone which showed no effect in a single study of ankle sprains. Studies investigating opioids alone had a moderate effect compared to studies investigating opioids in combination with simple analgesics which had a small effect, but the actual difference between the two mean estimates was only 4 points (7.7 vs 11.9). Meta-regression of the effect of daily MME on pain scores showed that MME was not a significant treatment effect modifier ($p = 0.224$) [Appendix 9]. A sensitivity analysis removing all studies at high risk of bias found a smaller effect compared to the main analysis (MD −4.6, 95% CI −8.7 to −0.4, $n = 488$, 3 studies, high certainty).

We performed a post hoc sensitivity analysis on our primary analysis only, excluding one study that examined acute-on-chronic populations. Of the 3 included studies that examined acute-on-chronic conditions [31, 32, 34], only 1 [31] reported a result relevant to our primary timepoint

Table 1 Study characteristics

Study	*N*	Condition	Formulation	Intervention	Control	Daily MME	Maximum follow- up
Adult (aged 18 + years)							
Ekman 2006 [19]	361	Acute ankle sprain	Oral tablets, assumed to be IR	Tramadol, 50 mg, 4 per day for 7 days	Placebo	40.0	7 d
Friedman 2015 [20]	215	Acute low back pain	Oral tablets, assumed to be IR	Naproxen 500 mg, oxycodone 5 mg, acetaminophen 325 mg, 3–6 per day for 10 days	Naproxen 500 mg, placebo	22.5 to 45.0	3 mo
Friedman 2021 [21]	154	MSK pain refractory to ibuprofen	Oral capsules, assumed to be IR	Oxycodone 10 mg, acetaminophen 650 mg, single dose	Acetaminophen 650mg	15.0	2 h
Gilbert 1978 [22]	73	Moderate or severe MSK pain	Oral capsules, assumed to be IR	(i) Butorphanol tartrate 4 mg* (ii) Butorphanol tartrate 8 mg* (iii) Codeine phosphate 60 mg 4–6 doses per day to a maximum of 12 doses	Placebo	(i) 40.8–61.2 (ii) 81.8–122.4 (iii) 31.2–46.8	72 h
Gong 2019 [23]	119	Acute MSK injuries	Oral capsules, assumed to be IR	Paracetamol 1 g, ibuprofen 400 mg, codeine 60 mg, single dose	Paracetamol 1 g, placebo	7.8	120 min
Graudins 2016 [24]	182	Limb injuries	Oral tablets, assumed to be IR	(i) Paracetamol 1 g, Ibuprofen 400 mg, Codeine 30 mg (ii) 1g paracetamol, 400 mg ibuprofen, 10 mg oxycodone Single doses	Paracetamol 1 g, Ibuprofen 400 mg, placebo	(i) 3.9 (ii) 15.0	90 min
Hewitt 2007 [25]	603	Ankle sprain	Oral capsules, assumed to be IR	(i) Tramadol 37.5 mg or 75 mg, acetaminophen 650 mg (ii) Hydrocodone 7.5 mg, acetaminophen 650 mg every 4 h for up to 5 days	Placebo	(i) 45.0–90.0 (average tablets per day was 4.3 = 48.4 MME) (ii) 45.0^ (average tablets per day was 4.6 = 34.5 MME)	5 d
Lasko 2012 [27]	277	Acute low back pain	Oral tablets, modified-release	Tramadol 75 mg and paracetamol 650 mg twice daily 1–2 tablets every 10–12 h for 2.5 days	Placebo	30.0–60.0	2.5 d
Jones 2023 [10]	347	Acute spinal pain	Oral tablets, modified release	Oxycodone 5 mg with naloxone 2.5 mg, titrated up to 10 mg oxycodone/5 mg naloxone 1 or 2 tablets as per individual prescription, every 12 h, for up to 6 weeks or until recovery	Placebo	15.0–30.0 (average tablets taken per day was 2 = 15.0 MME)	12 mo
Ma 2008 [31]	116	Acute flare of chronic neck pain (>6 months)	Oral tablets, modified release	Oxycodone 5mg 1–2 tablets every 12 h for up to 4 weeks	Placebo	15.0–30.0	28 d

Table 1 (continued)

Study	*N*	Condition	Formulation	Intervention	Control	Daily MME	Maximum follow- up
Roth 1998 [32]	42	People with OA who were on a stable NSAID regimen who experienced a sudden increase in pain requiring supplemental analgesics, who tolerated tramadol in the open-label phase	Oral capsules, assumed to be IR	Tramadol hydrochloride 50–100 mg in addition to their stable NSAID routine, taken every 4–6 h as needed for up to 13 days	Placebo	40.0–120.0 (average tablets taken per day was 5 = 50.0 MME)	14 d
Serinken 2016 [33]	300	Sciatica	IV infusion	Morphine 0.1 mg/kg, single dose	Placebo	21.0 (calculated based on weight of 70 kg)	30 min
Silverfield 2002 [34]	308	Acute flare of OA	Oral tablets, assumed to be IR	(i) Tramadol 37.5 mg and acetaminophen 325 mg (ii) Tramadol 75 mg and acetaminophen 650 mg 1 or 2 tablets every 6 h for up to 10 days	Placebo	(i) 30.0 (ii) 60.0	10 d
Vorsanger 2013 [35]	108	Vertebral compression fracture	Oral capsules, IR	(i) Tapentadol 50 mg then 50 or 75 mg every 4–6 h as needed (ii) Oxycodone 5 mg then 5 or 10 mg every 4–6 h as needed every 4–6 h as needed for up to 10 days)	Placebo	(i) 60.0–127.5 (ii) 30.0–82.5	10 d
Paediatric (< 18 y)							
Koller 2007 [26]	44	Orthopaedic injuries	Combined oral liquid	Oxycodone 0.1 mg/kg max 10 mg + ibuprofen 10 mg/kg max 800 mg, single dose	Ibuprofen 10 mg/kg max 800 mg + placebo	17.4 (calculated based on weight of 58 kg)	120 min
Le May 2017 [28]	300	MSK injury	Combined oral liquid	0.2 mg/kg oral morphine plus 10 mg/kg ibuprofen, single dose	Ibuprofen 10 mg/kg plus placebo morphine	34.8 (calculated based on weight of 58 kg)	120 min
Le May 2013 [29]	83	Limb injury	Separate codeine liquid and chewable ibuprofen tablets	Codeine 1 mg/kg and ibuprofen 10 mg/kg, single dose	Ibuprofen 10 mg/kg and placebo	7.5 (calculated based on weight of 58 kg)	120 min

ANZCA Australian and New Zealand College of Anaesthetists & Faculty of Pain Medicine, *IR* immediate-release, *MME* morphine milligram equivalent, *MSK* musculoskeletal, *OA* osteoarthritis
*Butorphanol is not reported in ANZCA table. We used a multiplier of ×15 for parenteral administration as per Nielsen et al. [39]. However, this study uses butorphanol orally and oral bioavailability is thought to be approximately 17% compared to intravenous administration. To arrive at a daily MME estimate, we multiplied the grams per dose of butorphanol by the number of doses per day, multiplied by 15, and then multiplied by 0.17

^Hydrocodone not on ANZCA table. Used multiplier of 1 as per Nielsen et al. [39]

When prescribed dosing was described as a range (e.g., 1–2 tablets every 4–6 h) and no average number of daily tablets were reported, we calculated MME based on the highest allowable dose

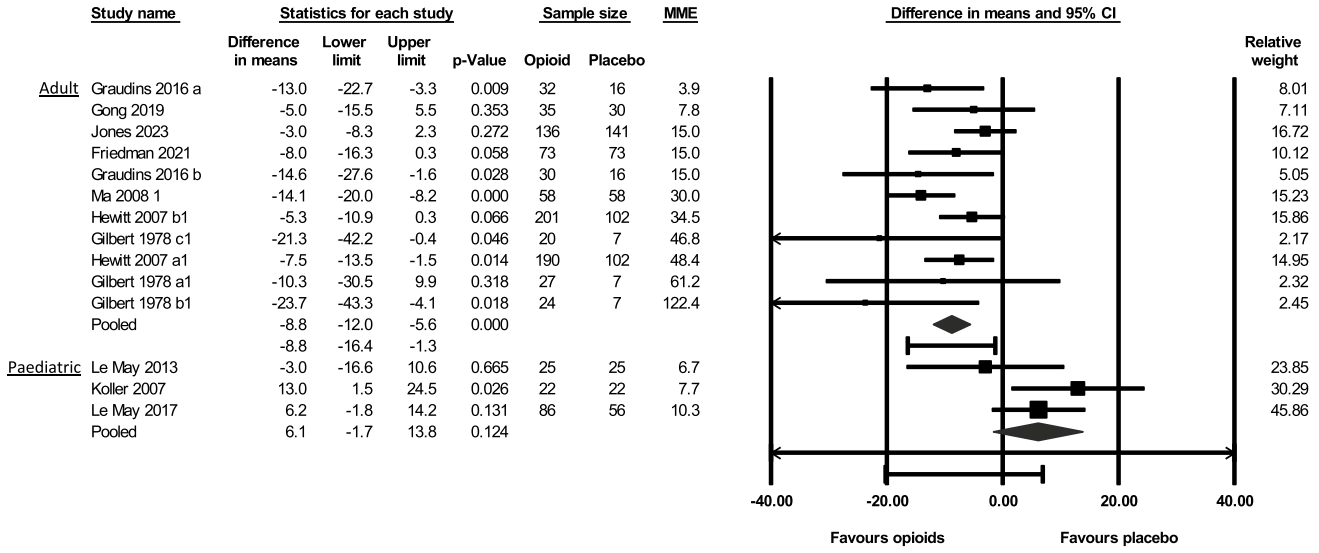

Fig. 2 Pain outcomes for oral opioids at primary (immediate) timepoint, sorted by daily morphine milligram equivalent (MME) dose. Graudins a—oxycodone, Graudins b—codeine, Hewitt a—tramadol, Hewitt b—hydrocodone, Gilbert a—butorphanol tartrate 4 mg, Gilbert b—butorphanol 8 mg, Gilbert c—codeine

(immediate term). The pooled estimate excluding Ma 2008 [31] was not substantially different from the primary analysis (MD − 7.4, 95% CI − 10.3 to − 4.4, n = 1269, 10 comparisons from 6 studies, I^2 = 11%, high certainty). The individual result from Ma 2008 [31] was more favourable but of low certainty (MD − 14.1, 95% CI − 20.0 to − 8.2, n = 116, testing modified-release oxycodone for acute-on-chronic neck pain).

3.4.3 Disability

For adults, there was no difference between opioid and placebo groups at the primary timepoint (immediate term) (MD − 6.2, 95% CI − 17.8 to 5.4, n = 208, 2 studies, very low certainty) (Fig. 3). At our secondary timepoints, opioids provided no effect in the short term (MD − 5.8, 95% CI − 13.7 to 2.1, n = 416, 2 studies, moderate certainty), intermediate term (MD − 7.5, 95% CI − 30.7 to 15.7, n = 478, 3 studies, low certainty) or the long term (MD −15.0, 95% CI − 51.1 to 21.2, n = 208, 2 studies, very low certainty). No paediatric studies reported disability.

There were insufficient studies to conduct subgroup analysis or meta-regression on the disability outcome.

3.4.4 Harms

For adults, oral opioid groups were at more risk of harm compared to placebo groups (RD 14.3%, 95% CI 8.3–20.4%, n = 2649, 11 studies, very low certainty) [Appendix 10]. The risk ratio was 1.69 (95% CI 1.35 to 2.09). A single study investigating IV opioids found no difference (RD 4%, 95% CI − 0.3 to 8.3%) (RR 8.9, 95% CI 0.5–163.3).

For paediatrics, there was no evidence for a difference in risk of experiencing an AE, although there was a trend towards opioid groups being more at risk of harms (risk difference [RD] 10.4%, 95% CI [− 0.6 to 21.4%], n = 393, 3 studies, low certainty) (Fig. 3). The risk ratio was 2.8 (95% CI 1.5–53). One of the three studies is unclear about whether the reported harms are number of events or number of people reporting at least one AE. Excluding this study, the pooled risk difference for the remaining two studies (which state number of people reporting at least one AE) was not substantially different (RD 8.5%, 95% CI − 3.6 to 20.6%, n = 349, low certainty).

The reporting of harms was too inconsistent to analyse by the nature of the harm. Studies that identified the nature of the harm reported common opioid-related AEs, including somnolence, dizziness, vomiting and confusion.

3.4.5 Harms Exploratory Analyses

Subgroup analyses by opioid type did not reduce the statistical heterogeneity [Appendix 11]. When analysing by opioids alone (not in combination with simple analgesics), the pooled outcome estimate did not change substantially but I^2 value reduced to 32%. Sensitivity analysis removing all studies at high risk of bias did not substantially change the estimate of risk difference, but it reduced I^2 to 34%. Total daily MME was not a significant effect modifier for risk of

Table 2 Outcomes and GRADE ratings

Findings					Certainty of evidence assessment (GRADE)					
Comparator	Time point	Studies (comparisons/ unique studies)	Point estimate (intervention vs control) and 95% CI	Number of participants (*n*)	Risk of bias	Inconsistency (I^2 value)	Indirectness	Imprecision	Publication bias (Egger 2-tail *p* value)	Overall rating
Primary outcome—mean difference (out of 100-points)										
Adults—oral opioids										
Pain (0– 100)	Immediate	11/7	−8.8 (−12.0 to − 5.6)	1385	No	No (32%)	No	No	No (0.2)	High
	Short	9/6	− 9.2 (− 13.9 to −4.4)	1676	No	Yes (83%)	No	No	No (0.4)	Mod
	Intermediate	3/3	− 9.0 (− 30.4 to 12.4)	305	No	Yes (89%)	No	Yes	No (0.5)	Low
	Long	1/1	8.0 (2.6 to 13.4)	247	No	No (0%)	Yes	No	No (NA)	Mod
Disability (0–100)	Immediate	4/2	− 6.2 (− 17.8 to 5.4)	208	Yes	No (47%)	Yes	Yes	Yes (0.02)	Very low
	Short	5/2	− 5.8 (− 13.7 to 2.1)	416	Yes	No (35%)	No	No	No (0.09)	Mod
	Intermediate	3/3	− 8.9 (− 30.4 to 12.7)	459	No	Yes (96%)	No	Yes	No (0.4)	Low
	Long	0/0	–	–	–	–	–	–	–	–
Adverse events (risk difference %)	N/A	16 /11	14.3%, (8.3–20.4%)	2649	No	Yes (68%)	No	No	Yes (0.00)	Low
Adults—IV opioids										
Pain (0–100)	Immediate	1/1	− 42.5 (− 49.9 to − 35.1)	197	No	No (0%)	Yes	No	NA	Mod
Paediatrics—oral opioids										
Pain (0–100)	Immediate	3/3	6.1 (− 1.7 to 13.8)	236	Yes	No (36%)	No	No	No (0.8)	Mod
	Short	0/0	–	0	–	–	–	–	–	–
	Intermediate	0/0	–	0	–	–	–	–	–	–
	Long	0/0	–	0	–	–	–	–	–	–
Disability (0–100)	Immediate	0/0	–	0	–	–	–	–	–	–
	Short	0/0	–	0	–	–	–	–	–	–
	Intermediate	0/0	–	0	–	–	–	–	–	–
	Long	0/0	–	0	–	–	–	–	–	–
Adverse events (risk difference %)	N/A	3/3	10.4% (−0.6% to 21.4%)	393	No	Yes (70%)	No	Yes	No (0.6)	Low

CI confidence interval, *IV* intravenous

See Appendix 3 for further details on how decisions were made to downgrade in each domain

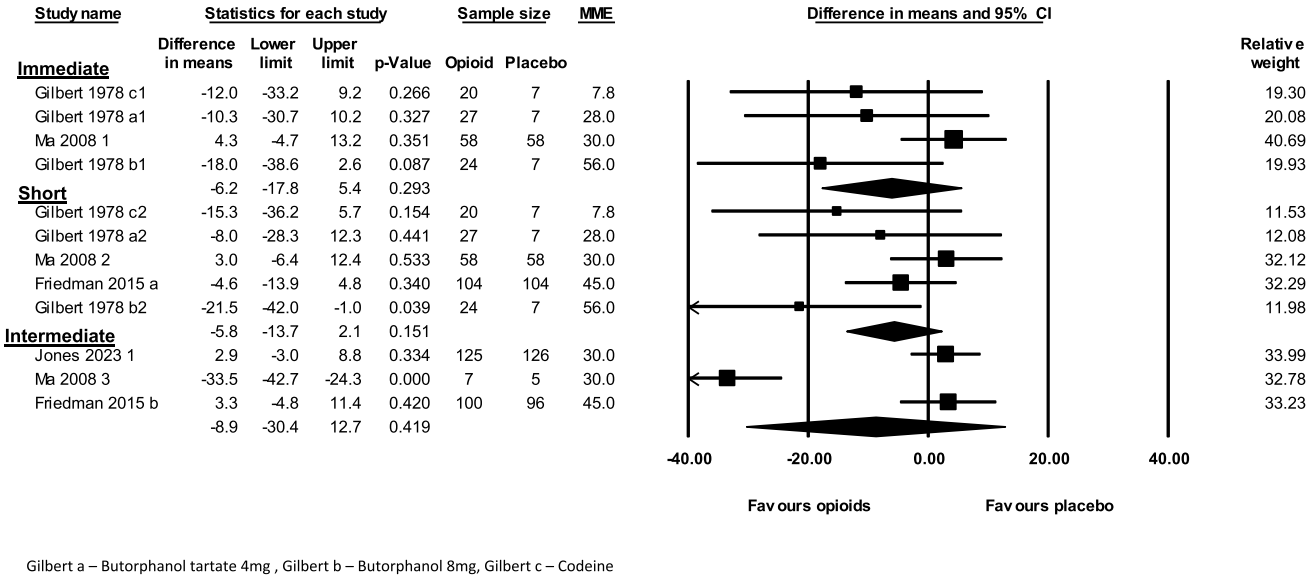

Fig. 3 Adult disability outcomes at primary (immediate) timepoint, as well as secondary timepoints (short and intermediate), sorted by daily morphine milligram equivalent (MME) dose in adults. Gilbert a—butorphanol tartrate 4 mg, Gilbert b—butorphanol 8 mg, Gilbert c—codeine

harm. The risk of harm increased by 1.7% for every 10 MME increase in daily dose ($p = 0.07$) [Appendix 12].

4 Discussion

4.1 Summary of Findings

In adult studies, oral opioids provided a small effect compared to placebo for pain (high certainty) in the immediate term. There was low to very low certainty evidence of small benefits for pain in the short and intermediate term for musculoskeletal pain. Only one study reported outcomes in the long term and found a small negative effect of modified-release oxycodone for spinal pain. In contrast, one trial evaluated IV morphine and found moderate certainty evidence of a large effect on sciatica pain at immediate-term follow-up. When separated by condition in further exploratory analysis of the primary analysis (immediate term), the result was reasonably consistent across all condition categories. There was no effect for disability in the short term (moderate certainty), or immediate and long term (both very low certainty). We found very low certainty evidence of a 14% absolute increase in risk for opioids groups in the adult studies, where the maximum follow-up was 12 months. Meta regression showed that increased daily doses of opioids (MMEs) were not associated with greater effects on pain scores.

In paediatric studies, there was no difference between oral opioids and placebo in reducing pain in the immediate term for musculoskeletal pain (fractures or soft tissue injuries) (moderate certainty). There were no data for pain or disability for timepoints beyond 24 h. We found no difference in risk of experiencing an AE in paediatric studies (possibly due to maximum follow-up time being 120 min). For both adults and paediatric populations, clinicians should carefully consider that the benefits may be small-to-none, and that the harms are uncertain, when making decisions about using opioids to treat acute musculoskeletal pain.

4.2 Strengths and Limitations

This is the first systematic review of opioids versus placebo for acute musculoskeletal pain which included all musculoskeletal conditions (including low back pain). These findings provide up-to-date, clinically relevant information to clinicians and policy makers. Four out of five of the pain outcome timepoints (including oral and IV) had moderate or high certainty evidence. A limitation is the lack of data to inform paediatric outcomes. All but one disability outcome was of low or very low certainty, and AE outcomes were both low certainty. Also, more than half of the included studies were at high risk of bias, mainly due to unclear/poor reporting of randomisation and allocation concealment practices, and high rates of losses to follow-up. There was also a low rate of prospective registration, meaning we could not determine whether there was selective reporting. Although, sensitivity analyses confirmed these studies at high risk of bias were not inflating the results.

4.3 Interpretation

In addition to this evidence for opioids versus placebo, recent trials and reviews comparing opioids with non-opioid analgesics show that oral opioids do not provide superior pain-relieving effects in acute pain and are associated with increased AEs. A review of analgesics for musculoskeletal pain in the emergency department found that NSAIDs had equal benefits to opioids (including oral, IV and intramuscular routes), but less risk of harm [9]. The same review found that paracetamol was only slightly less effective than opioids, again with less risk of harm, and may also be considered in place of an opioid [9]. Another review of oral opioids for post-surgical pain (prescribed at discharge) found there were no benefits over some non-opioid analgesics such as NSAIDs [38]. These results are likely relevant to those with acute musculoskeletal pain in any setting, therefore clinicians may consider NSAIDs before opioids if there are no contraindications, even when rapid pain relief is required.

More studies are needed to properly assess whether opioids have a benefit above placebo and/or non-opioid analgesics in paediatric populations at all timepoints. Although the rates of prescribing in paediatric populations are lower than that of adult populations, there is some concern (based on limited data) that a prescription of an opioid during adolescent years may increase the risk of opioid misuse by 33% in later years [5]. It is important that opioids are only prescribed to paediatric populations when there is genuine clinical benefit to avoid contributing to the opioid overuse problems. Further investigation into whether people (paediatrics and adults) receiving an opioid are at higher of risk of ongoing use, misuse, and dependence in the long term compared to groups who were not prescribed an opioid for their acute pain would be beneficial. While we did not set out to collect these outcomes, we note that only one study reported them, finding that the opioid group was at higher risk of misuse at 12-months after a short course of opioids (up to 6 weeks) [10]. Another aspect worthy of investigation is whether the rates of prescription of other analgesics such as pregabalin or ketamine, which may be equally as harmful, are increasing in place of opioids.

5 Conclusion

There was moderate certainty evidence of no effect of oral opioids in paediatric populations for acute musculoskeletal pain in the immediate term, and no data at other timepoints. In adult populations, there was low to high certainty evidence that oral opioids provide small benefits in the shorter term ($\leq$ 7 days) but not in the longer term. Intravenous opioids provided large effects on pain in the immediate term. There was very low certainty evidence of a 14% absolute higher risk of experiencing an AE in adults. Clinicians should carefully weigh up the short-term small-to-no benefits of oral opioids (low-to-moderate certainty) against the uncertain evidence on safety.

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Declarations

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Conflicts of interest Authors CJ, AL, CM, CAS, RD, and CL all declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Availability of data and materials No original data collected in this project.

Ethics approval Not applicable.

Author contributions CJ, AL, CAS, CM and CL jointly conceived the protocol. CJ and AL performed screening and data extraction, with arbitration from CL when required. RD joined after the first draft was written to provide a prescriber's perspective. CJ drafted the manuscript and all authors provided critical revisions.

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