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Title: Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Osteoarthritis: Systematic review and Meta-Analysis

Running title: Opioids for Osteoarthritis

**Keywords:** Osteoarthritis, opioids, systematic review, meta-analysis

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Abstract

**Objective**: Opioids are commonly prescribed for osteoarthritis. Guidelines provide inconsistent recommendations on use of opioids in osteoarthritis and previous reviews are limited in scope, warranting a comprehensive assessment of the evidence. This study evaluated the efficacy and safety of opioids for osteoarthritis.

**Design**: Systematic Review and Meta-Analysis

**Data Sources**: MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL, International Clinical Trials Registries (to October 2020).

**Eligibility Criteria**: Randomised placebo-controlled trials evaluating any opioid analgesic for osteoarthritis.

**Data Extraction and Synthesis**: The primary outcome was pain at the medium term (≥6 weeks but <12 months). Continuous pain and disability outcomes were converted to a 0 to 100 scale. Effects <10 points were considered very small. Dichotomous outcomes were presented as risk ratios. Four authors extracted data and assessed risk of bias. Data were pooled using a random effects model. Quality of evidence was assessed using GRADE.

**Results**: Thirty-six trials (dose range: 10-210 oral morphine milligram equivalent units/day) were included. For the **medium term**, there was low quality evidence from 19 trials (n=8965) of a very small effect of opioids compared to placebo for pain; mean difference (MD) -4.59 (95% CI -7.17, -2.02) and low quality evidence from 16 trials (n=6882) of a very small effect on disability; MD -4.15 (95% CI -6.94, -1.35). Meta-regression didn’t show a significant association of dose with adverse events or pain relief. Opioids increased the risk of adverse events; RR: 1.43 (1.29, 1.59), but evidence was of very low quality. There were no long-term outcomes data.
Conclusions: For people with osteoarthritis, opioids may provide very small effects on pain and disability, and may increase the risk of adverse events.

Registration: CRD42019142813.
Introduction

Osteoarthritis is a leading cause of disability, affecting over 250 million people globally.\textsuperscript{1} Guidelines recommend non-pharmacological strategies such as exercise and maintaining a healthy weight as first-line management;\textsuperscript{2} and simple analgesia such as non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol (acetaminophen).\textsuperscript{2} However there is conflicting advice around the use of opioid analgesics for knee/hip osteoarthritis,\textsuperscript{3,4} which might explain why opioids continue to be commonly prescribed for osteoarthritis, with up to 40% of people with knee osteoarthritis in the USA treated with opioids.\textsuperscript{5}

Previous systematic reviews comparing opioids to placebo for osteoarthritis have a limited scope. For example, one review only evaluated opioid treatment \(\geq 4\) weeks duration.\textsuperscript{6} Another only included opioids administered via the oral route,\textsuperscript{7} did not incorporate GRADE ratings in the abstract or conclusions, and the validity of the opioid dose-response analyses are unclear.\textsuperscript{7,8} Furthermore, some reviews excluded tramadol,\textsuperscript{9} deeming it a non-opioid.

The aim of this review was to provide a comprehensive evaluation of the efficacy and safety of opioid analgesics administered via any route for osteoarthritis, and to explore the association of dose with effects.

METHODS

The protocol was registered prospectively on PROSPERO (CRD420191142813).

Inclusion criteria

Eligible Studies
Randomised controlled trials (RCTs) published in a peer-reviewed journal or clinical trial registry\(^{11}\) comparing an opioid analgesic to placebo, were eligible.

**Participants**

Participants with osteoarthritis of any type (knee ± hip ± hand ± spine) of any duration.

**Intervention**

We considered any dosing regimen of a single ingredient or combination opioid analgesic administered via any route.

**Comparison**

Studies needed to include a placebo comparison to be eligible.

**Exclusions**

We excluded head-to-head trials, that is, those that compared the opioid to different treatment comparators but not to placebo.

**Outcomes**

The primary outcome was pain intensity measured on the visual analogue scale (VAS), numeric rating scale (NRS) or other continuous measure.

Secondary outcomes were disability (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function scale), health-related quality of life (36-item short form health survey (SF-36), patient generated index (PGI) and number and nature of adverse events (AEs).

**Follow up**

Outcomes were grouped by time of follow up: immediate term (<2 weeks after randomisation), short term (≥2 weeks and <6 weeks), medium term (≥6 weeks but <12 months) and long term (≥12 months). Medium term was the primary time point.

**Electronic searches**
We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL, PsycINFO for eligible RCTs (without language restrictions) from inception to October 2020 (Supplementary Table 1). We additionally searched the WHO clinical trials registry for unpublished trials,\textsuperscript{10} as excluding these may overestimate treatment effect.\textsuperscript{11} We screened reference lists to identify additional RCTs (Figure 1).

**Study Selection**

Three reviewers (CAS/WA/GZ) independently screened titles and abstracts and inspected the full report of potentially eligible RCTs to determine eligibility. Disagreements were resolved by consensus. Trials involving patients with a range of pain conditions were included if results for participants with osteoarthritis could be separately extracted.

**Data extraction and management**

Pair of reviewers independently extracted study and participant characteristics and outcome data and assessed risk of bias using the Cochrane Collaboration’s tool.\textsuperscript{12} Each of the seven items were judged to be of ‘high’, ‘low’, or ‘unclear’ risk of bias. Disagreements were resolved by consensus.

**Measures of treatment effect**

Analyses were carried out in R version 4.0.3\textsuperscript{13} and R Studio version 1.2.1093.\textsuperscript{14} Continuous outcomes were converted to a common 0-100 scale.

We present results as mean differences (MD) rather than standardised mean differences (SMD), so that outcomes are expressed in points on a 0-100 scale rather than proportions of a standard deviation (SD).

We considered between group treatment effects in the range 0-9 points as very small, 10-19 points as small, 20-29 points as moderate and ≥ 30 points as large. Where mean and mean change scores were available, we present the mean scores and SD if groups were similar at
baseline. For dichotomous outcomes we report the relative risk (RR) and 95% Confidence Interval (CI).

**Adverse events**

We collected data on the nature and number of adverse events and the number of participants receiving an opioid who withdrew because of adverse events, lack of efficacy, or were lost to follow-up, in both the run-in phase (for enriched trial designs) and trial phase.

**Missing data**

Missing data were estimated using the methods described in the Cochrane Handbook.\(^{12}\)

**Assessment of heterogeneity and reporting bias**

We assessed clinical heterogeneity by considering characteristics of participants, interventions, outcome measures and timing of outcome measurement. We assessed statistical heterogeneity by visual inspection of forest plots and the \(I^2\) statistic.

**Data Synthesis**

We used a random effects meta-analysis model with data pooled using restricted maximum likelihood estimation. Three level mixed effects models, fitted using “metafor” version 3.0-1\(^{15}\) accounted for the dependence of effect sizes coming from the same study/comparator group, and assumed a compound symmetry covariance structure.

We evaluated the association of opioid dose with treatment effects on pain and adverse events at medium term follow-up with meta-regression using the same three level models. The doses of single ingredient opioid analgesic trials were first converted to oral morphine equivalent doses\(^{16}\) and log transformed for the meta-regression.

The pooled effect of single-ingredient opioid analgesics was presented in the primary analysis. We conducted a separate analysis to calculate treatment effect sizes for placebo-controlled
trials evaluating combination opioid analgesics containing a simple analgesic (paracetamol or non-steroidal anti-inflammatory drug).

**Overall quality of evidence**

We used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to evaluate the overall quality of evidence. Quality of evidence was downgraded a level for each of four factors:

- limitation in study design when more than a quarter of the studies included in an analysis were considered at high risk of bias. A study was considered high risk when one or more domains were judged as high risk,

- inconsistency of results (if statistical heterogeneity between trials was large [$I^2 > 50\%$]),

- imprecision (when the width of the confidence intervals was > 10 points for continuous outcomes or crossed the line of no effect for dichotomous outcomes) and

- publication bias (assessed using funnel plot analysis/ Egger's regression test for 10 or more studies).

Overall quality of evidence was defined as high, moderate, low quality, and very low quality. Definitions for the certainty of evidence ratings are provided in Supplementary table 2.

**Sensitivity analyses**

We conducted sensitivity analyses to investigate the effects of the following on treatment effect:

- Opioid formulation (modified release preparations versus immediate release preparations)

- Enrichment versus non enrichment design

- Industry funding versus no industry funding
- Tramadol versus non-tramadol opioids

**Meta-regression**

A regression of the log-transformed morphine milligram equivalent (MME) dose on pain relief and adverse events was carried out for the medium term.

**Protocol amendments**

We carried out sensitivity (instead of sub-group) analysis of immediate release vs modified release preparations and enrichment versus non-enrichment design. We had not originally planned to carry out the sensitivity analysis on tramadol, but decided this would be important to explore given that tramadol, is recommended in some guidelines for treatment of osteoarthritis.4

The sensitivity analysis exploring the effects of industry funding (versus non-industry funded trials), peer review publication (versus non-published trials) and use of rescue medication (versus no rescue medication) was also additional.

**RESULTS**

A total of 2286 titles was retrieved from the electronic searches and citation tracking, of which 36 English language RCTs were eligible (Figure 1). Characteristics of included studies are presented in Supplementary Table 3 and reasons for study exclusion are presented in Supplementary Table 4. A summary of results and sensitivity analyses is presented in Supplementary Table 5.

**Participants and drop out**

Trials typically included people with pain of ≥40 on a 0-100 pain scale. The median pain score at baseline was 72.0 (interquartile range [(IQR)] 61.7 to 75.8) on a 0-100 pain scale.

In the opioid treated arm a median of 41.9% participants (IQR 32.6% to 51.9%) discontinued the study during the trial phase. In the placebo arm, the median drop-out rate was 39.5% (IQR
24.1% to 48.2%). Common reasons for discontinuation in the opioid arm included adverse events (median 23.5% IQR 14.6% to 30.3%), lack of efficacy (median 7.8% IQR 3.8% to 11.3%), or other reasons (loss to follow up, protocol violation) (median 6.8% IQR 3.6% to 12%) (Supplementary Table 6, Supplementary Figure 1).

**Treatment regimens**

The studies evaluated oral or transdermal formulations of opioid analgesics (predominantly modified release formulations) for osteoarthritis, primarily of the knee, hip, or both. There were five studies that evaluated transdermal buprenorphine or fentanyl.\(^{36,38,45,50,53}\)

Treatment duration ranged from 1 day (combination ibuprofen 200 mg/codeine 30 mg for hip osteoarthritis) to 12 weeks, with 15 studies\(^{20-24,26,27,30,31,33,35,37,41,43,47}\) reporting a treatment duration of \(\leq 4\) weeks, typically involving a regular (as opposed to when required) treatment regimen. The opioid analgesics evaluated included: oxycodone, tapentadol, hydromorphone, codeine, buprenorphine, fentanyl, oxymorphone, tramadol and the combination of tramadol + acetaminophen (paracetamol), oxycodone + acetaminophen and ibuprofen + codeine. The dose ranged from 10 to 210 MME per day.

**Trial conduct**

All but two studies\(^{27,30}\) were assessed as high risk of bias (Supplementary Table 7). Maximum follow-up was 16 weeks, but typically was 12 weeks. Treatment duration was usually the same as the follow up period. No trial provided long-term follow up data. Four trials\(^{38,39,46,49}\) employed an enrichment trial design, whereby patients who completed an open label run-in phase and were able to tolerate and respond to the medicine were randomised to the trial phase.

**Treatment effects**
Complete data extraction describing treatment effects on pain for all time points are presented in Supplementary Table 8. Results for the primary outcome are shown in Figure 2.

Pain

Immediate term

There was moderate quality evidence from 13 trials\textsuperscript{21,23,24,26,28,30,31,34,36,44,50,52,55} (n=5320, dose range 10-126 MME/daily) of a very small effect on pain with a MD -4.90 (-6.46, -3.34).

Short-term

There was moderate quality evidence from 19 trials\textsuperscript{22,23,24,26,28,30-37,43,44,47,50,52,55} (n=6949, dose range 10-210 MME/daily) of a very small effect of opioids with a MD -6.38 (-8.45, -4.30).

Medium term

There was low quality evidence from 19 trials\textsuperscript{25,28,32,34,36,38,39,40,42,44,45,46,48,50,51,52,53,54,55} (n=8965, dose range 10-126 MME/daily) of a very small effect of opioids with a MD -4.59 (-7.17, -2.02).

Disability

Immediate term

There was moderate quality evidence from 3 trials\textsuperscript{26,34,48} (n=2105, dose range 10-40 MME/daily) of a very small effect of opioids with a MD -4.11 (-6.92, -1.30) (Supplementary Table 9).

Short term

There was moderate quality evidence from 8 trials\textsuperscript{23,26,32,33,34,35,48,52} (n=3394, dose range 10-210 MME/daily) of a very small effect of opioids with a MD -5.84 (-7.90, -3.79).

Medium term

There was low quality evidence from 16 trials\textsuperscript{25,28,32,34,36,40,42,44,45,46,48,50,51,52,53,55} (n=6882, dose range 10-126 MME/daily) of a very small effect of opioids with a MD -4.15 (-6.94, -1.35).
QOL

In general, there was no significant effect of opioids on the SF-36 mental component score at any time point. There was a very small effect of opioids on the SF-36 physical component score in the short term (2 trials,33,35 n=824) with a MD 3.05 (95% CI 1.13, 4.97) and medium term (5 trials,34,36,44,48,52 n=3525) with a MD 0.70 (95% CI 0.04, 1.37). One study32 (n=107) showed a favourable effect of opioids (76 MME/day) in the medium term on the PGI; MD 11.5 (2.37, 20.63) (Supplementary Table 10).

WOMAC Osteoarthritis Index (composite score)

There was no significant effect of opioid on the WOMAC total (composite score) at any time point (Supplementary Table 11).

Adverse events

There was very low-quality evidence from 16 studies28,32,34,36,38,40,42,44,45,46,48,50,51,52,53,55 (n=8482) that opioids over the dose range 10 to 126 MME/daily increased the risk of adverse events compared with placebo; with a RR 1.43 (1.29, 1.59) at medium follow-up. There was a 49.8% incidence of AEs in placebo compared with 72.4% with opioids; 1560/3133 vs 3871/5349 respectively. Gastrointestinal AEs were the most common (e.g. nausea, vomiting, constipation, diarrhoea). Other common side effects included dry mouth, fatigue, pruritus, somnolence, dizziness and headache (for details see Supplementary Tables 12 and 13). Rates of adverse events with tramadol were similar to adverse events reported for all opioid drugs; RR 1.4 (1.3 to 1.6). There was no statistically significant association between opioid dose and AEs in the medium term. All MME conversions for the drugs evaluated are presented in Supplementary Table 14.

Meta-regression
The meta-regression (19 trials, n=8965) revealed no association of log MME dose with effects on pain at medium term follow-up; with a regression co-efficient of 0.92 (95%CI -6.58 to 8.41). There was no significant association of log MME dose with adverse events at medium term follow-up (16 trials, n=8482, regression co-efficient 0.08 95% CI -0.17 to 0.33). All dose regimens within the dose range evaluated were associated with a similar risk of adverse events at this time point (see Figure 3). However this finding was based on very low-quality evidence.

**Sensitivity analysis – medium term**

Results from the sensitivity analyses are summarised in Supplementary Table 5.

**Combination opioid + simple analgesic vs placebo**

Four studies evaluated the combination of opioid + simple analgesic vs placebo. There was moderate-quality evidence that the combination of ibuprofen 200 mg + codeine 30 mg (six doses daily) has small benefit on pain for hip osteoarthritis; with a MD, $-19.0$; 95% CI, $-31.2$ to $-6.8$.

There was low-quality evidence that the combination tramadol + acetaminophen provides very small pain relief in the short and medium term. There was low-quality evidence from one trial that the combination oxycodone IR 5 mg + acetaminophen 325 mg four times daily provides small pain relief in the short term; with a MD $-17.00$ ($-30.28$, $-3.72$).

**Discussion**

This review provides moderate to low-quality evidence that opioids provide very small effects on pain and function measured at a range of time points up to 3 months follow-up. Opioids may increase the risk of experiencing an adverse event in the medium term, but this finding was based on very low quality evidence. In general the incidence of adverse events such as gastrointestinal and central nervous system effects was higher with opioids. Meta-regression
did not show a significant association between dose (ranging from 10-126 MME/daily) and effect on pain or incidence of adverse events at medium term follow up. The use of an enrichment design and high withdrawal rates during main trial phase mean that effect estimates are based upon approximately half of the participants originally entering these trials.

Strengths and weaknesses of this review

This review included a total of 36 trials of opioid analgesics administered via any route, making it the largest and most comprehensive review of opioids for osteoarthritis to date. The most recent review in this area located half as many trials (18 trials). Previous reviews have excluded studies on tramadol, evaluated only oral preparations, or only included treatment regimens which exceed one month, and therefore do not provide a complete clinical picture. Often these reviews expressed results for continuous pain and function outcomes as standardised mean differences, whereas we present weighted mean differences on a common 0-100 scale to facilitate easier interpretation of the findings by clinicians and patients. There are three possible reasons for the high heterogeneity observed with some effects. Firstly the opioid regimen ranged from 1 day to 12 weeks duration with doses ranging from 10 to 210 MME per day. The second potential cause is trial quality. All but two trials were at high risk of bias. Lastly some trials used an enrichment design which may provide more optimistic estimates of effect as only the participants who respond to and tolerate the medicine in the run-in phase enter the main trial.

Meaning and implications for clinicians, policy makers and patients

This is the first review of osteoarthritis to demonstrate that single ingredient opioids, in the range of doses evaluated (10-210 MME daily), provide very small effects at all time points and that opioid dose may not be associated with pain relief for the medium term. This refutes
conventional thinking that higher doses yield greater benefit and should discourage the
practice of initiating patients with severe osteoarthritis pain on “stronger” opioid analgesics
(which have larger MME dose equivalence). Given that single ingredient opioids have very
small benefits for the range of doses evaluated, and on average are not likely to be clinically
worthwhile, this raises the question as to whether they should be initiated for the
management of osteoarthritis at all. The data would also suggest the association between
dose and risk of adverse events for the medium term is unclear.

However, combination medicines containing a low dose opioid and simple analgesic may
provide an synergistic effect. For example, the combination ibuprofen and low dose codeine
and the combination of low dose oxycodone (5 mg immediate release) and acetaminophen
may provide up to large benefits for pain (> 30 points on 0-100 pain scale) as suggested by
the 95% CI, however this is based on a small number of studies. For some people, the time-
limited use of these combination analgesics may be a plausible treatment option in
osteoarthritis, however these findings need confirmation in more robust studies.

Research demonstrates that the first month following opioid initiation is critical in the risk of
persistent use and that long-acting opioid preparation is a risk factor for persistent use.56

Recent data shows that up to 25% of patients with osteoarthritis who are initiated on opioid
analgesics continue to use opioids 1 year later.57 Another concern is that osteoarthritis, being
a chronic disease, is commonly treated with modified release preparations of opioid
analgesics (evidenced by this review where most studies evaluated modified release
preparations). Modified release preparations are taken regularly so that there is less ‘swing’
between peak and trough concentrations, and therefore provide more steady pain relief.

Because of the nature in which modified release medicines are normally taken (“regularly to
control pain”58 as opposed to when required) this may make it very difficult for patients
initiated on these preparations to cease them, in light of what is known about initial exposure and duration of use contributing to persistent use.\textsuperscript{56}

Existing guidelines provide inconsistent recommendations around the use of opioids for osteoarthritis. Our review findings raise questions about the use of opioids for osteoarthritis. Based on our findings, opioids provide comparable pain relief to paracetamol (acetaminophen) for osteoarthritis, and almost half as much pain relief as NSAIDs (all be it based on indirect comparisons).\textsuperscript{59} This challenges conventional thinking that simpler analgesics are less effective than opioids for common musculoskeletal conditions.

\textit{Directions for future research}

Future research should focus on evaluating alternate pain management strategies, as well as opioid sparing and tapering strategies for people with osteoarthritis who are currently using opioids. Furthermore, most studies were carried out in the US, and it is difficult to ascertain whether there may be ethnic, cultural differences or health services arrangements that modify treatment effect.

\textbf{Conclusion}

Opioids may provide very small benefits in patients with osteoarthritis and may increase the risk of adverse events. The association between opioid dose, pain relief and risk of adverse events requires further investigation.

\textbf{Contributors}

XXX, XX, XX, XX and XX designed the review protocol. XXX, XX, XX developed the search strategy and performed study selection. XXX, XX, XX, XX and extracted data. XXX, XX, XX, and XXX carried out risk of bias assessments. XXX and XX analysed the data. XXX, XX drafted the manuscript and all authors contributed to the drafting of the review and revised it critically.
for important intellectual content. All authors approved the final version of the article. All authors had access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. XXX and XX are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Competing interests declaration**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; support from the following organisations that may have an interest in the submitted work in the previous three years:

XXXX

**Patient consent**

Not applicable.

**Ethical approval**

Not required.

**Data sharing**

No additional data is available.

**Transparency**

The lead authors (the manuscript’s guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
Figure Legends

**Figure 1**: Summary of search strategy

**Figure 2**: Effects of opioids on pain (0-100 pain scale) in the medium term. Negative results favour opioids.

**Figure 3**: 3a) Meta-regression of the log transformed morphine milligram equivalent (MME) dose on pain treatment effect (0-100 pain scale) for the medium term; regression equation $Y = -6.0 + 0.92 \times \log \text{MME dose}$. 3b) Meta-regression of the log transformed MME dose on adverse events for the medium term; regression equation $Y = 0.23 + 0.08 \times \log \text{MME dose}$. Note that circles represent the number of eligible comparisons across the included trials and are therefore greater than the total number of trials for each outcome. The circles are proportional to sample size; there is one circle per treatment comparison. Results are not statistically significant. Dashed line is a 95% confidence interval.
References


