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Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials[1]

J. Avouac M.D., L. Gossec M.D. and M. Dougados M.D.*
René Descartes University, Medicine Faculty, APHP Cochin Hospital, Rheumatology B Department, Paris, France

Summary

Objectives: To determine the analgesic effectiveness, the effect on physical function and the safety of opioids in patients with osteoarthritis (OA).

Search strategy: A systematic literature search was performed in electronic databases up to October 2006. A hand search of references was also performed.

Selection criteria: All randomized controlled trials evaluating the efficacy and/or the safety of opioids vs placebo or non-opioid analgesics in patients with OA were selected.

Data collection and analysis: Data were collected using a predetermined form. Statistical analysis determined in each trial the effect size to assess the magnitude of treatment effect and the number needed to harm (NNH) to evaluate opioids safety.

Main results: Eighteen randomized placebo-controlled trials were analyzed, i.e., a total of 3244 participants who received opioids and 1612 who received placebo. The mean trial duration was 13 ± 18 weeks. The pooled effect sizes of all opioids vs placebo for pain intensity and physical function were -0.79 (95% confidence interval, CI, -0.98 to -0.59) and -0.31 (95% CI -0.39 to -0.24), respectively. The NNH was calculated to be 5 vs placebo. The number of studies ($n = 4$) that compared opioids with non-opioid analgesics (paracetamol and non-steroidal anti-inflammatory drugs) was too limited to provide robust data.

Conclusions: Opioids significantly decrease pain intensity and have small benefits on function compared with placebo in patients with OA. Adverse events, although reversible and not life threatening, often cause participants to stop taking the medication and could limit opioid usefulness. Moreover, the long-term efficacy and safety of these drugs for OA is yet to be determined due to the short mean trial duration.

Key words: Osteoarthritis, Opioids, Efficacy, Safety.

Introduction

Osteoarthritis (OA) is a chronic degenerative disease associated with pain, joint stiffness and joint deformities that may cause serious disability and interfere with patients' quality of life[1,2]. It is a common condition concerning worldwide almost 10% of men and 18% of women older than 60[3], and the prevalence increases to around 30% for those ≥70 years old[4].

European League Against Rheumatism (EULAR) guidelines[5,6] state that optimal treatment of knee and hip OA includes both pharmacological and non-pharmacological interventions. Among pharmacological agents, first line recommended treatment is oral paracetamol (paracetamol) followed by non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs are an important component of pharmacological therapy for the management of OA. However, their use is associated with gastrointestinal and renal complications, especially in elderly patients[7,8]. Concerns have also appeared recently regarding the cardio-vascular safety of selective cyclooxygenase 2 (COX-2) inhibitors and traditional non-selective NSAIDs[9]. Furthermore, paracetamol is often insufficient to treat OA-related pain[10]. These limitations provide a rationale for exploring the use of opioids to treat OA-related pain. Moreover, opioid analgesics have been proposed in OA by EULAR guidelines[5,6] in cases of intense pain and have been recommended by the American Pain Society as a safe and effective therapeutic option for the treatment of moderate to severe OA that does not respond to the first line treatment[11]. Nevertheless, their use (especially in the case of strong opioids) in patients with pain unrelated to cancer remains controversial[12] and is debated by the United States Senate and European Parliament[13]. Thus, it appeared useful to study the effectiveness and tolerance of opioids in the treatment of OA.

The objectives of this study were to determine the analgesic effectiveness of opioids for osteoarthritic pain, to assess the effectiveness opioids for improving physical function in patients with OA and to evaluate their safety. To this end, a meta-analysis of published randomized controlled trials (RCTs) reporting the effects of opioids in OA was performed.

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*Address correspondence and reprint requests to: Prof. Maxime Dougados, M.D., Rhumatologie B, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. Tel: 33-158-412562; Fax: 33-1435-49256; E-mail: maxime.dougados@cch.aphp.fr
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Patients and methods

LITERATURE RESEARCH

The objective of the search was to obtain all published RCTs of opioids in OA. Literature search was performed on all articles published between 1966 and August 2006 and expanded on Medline, EMBASE and the Cochrane Controlled Trials Register for RCTs. Papers in English, French and Spanish languages were eligible for inclusion. Search was conducted using the following combination: (''Narcotics'' [Pharmacological Action] OR ''Analgesics, Opioid'' [MeSH]) AND ''Osteoarthritis'' [MAJR]. In addition, reference lists of the papers initially detected were hand searched to identify additional relevant reports.

INCLUSION CRITERIA

Study design

RCTs of opioids vs placebo or non-opioid analgesics. Comparisons between different opioids were excluded.

Study population

Patients with OA as defined by the authors. In all cases, the patients fulfilled American College of Rheumatology[14,15] classification criteria for OA and/or were diagnosed by X-ray. Articles reporting opioid use for post-operative pain after joint replacement for knee or hip OA were excluded.

Intervention

Any opioid administered via an oral or transdermal route as a treatment for OA-related pain. For this analysis, opioids were classified as weak (codeine, propoxyphene and tramadol) or strong (oxycodone, oxytrex, oxymorphone, fentanyl and morphine sulfate).

Outcome measures

Articles were analyzed if an evaluation of pain and/or functional status and/or safety was available. If an article reported no interpretable results for all three outcome measures (pain, function and safety), it was not analyzed. Efficacy was assessed by the change in overall pain intensity and/or physical functional status between baseline and the end of the study, in both active and control groups.

Pain intensity was extracted from the studies, as available, by a 100 mm visual analogic scale (VAS), the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) Index Pain intensity scores or by a daily four (or five) point Likert scale. Physical function was assessed by the WOMAC subscale for physical function[16].

In order to evaluate safety, data were extracted from each study in both active and control groups regarding the number of treatment discontinuations due to adverse effects. Data were also analyzed regarding the number of the following arbitrarily predefined adverse events in both groups: epigastric pain, nausea, vomiting, constipation, dry mouth, dizziness, somnolence and headache.

METHODOLOGICAL QUALITY

The articles that fulfilled the inclusion criteria underwent quality appraisal. We used, to assess the quality of RCTs, the impact factor of the journal in which the trial was published, it was checked whether the statistics used intention-to-treat analysis and the Jadad scale was applied[17], which contains two questions for randomization and masking and one question evaluating the reporting of withdrawals and dropouts. Each question entails a yes or no response option. In total, 5 points can be awarded, with higher scores indicating superior quality. Data were also extracted regarding funding sources for the studies.

DATA EXTRACTION IN INCLUDED STUDIES

Data extraction was performed by one reviewer (J.A.), on the full texts, not blinded to author and journal, using a predefined extraction sheet, available from the authors. Informations extracted included first author, publication year, mean age/height/weight/body mass index (BMI) of participants, sex proportion, trial duration, type of opioid, type of comparator, drug dose, number of patients in active and control group, and the outcome measures used to assess efficacy and safety *a priori* defined.

STATISTICAL ANALYSIS

To measure the magnitude of the treatment effect for pain intensity and physical function, the effect size was calculated. The effect size is a standard way to determine the degree of improvement (or otherwise) of a particular therapy after any placebo effect has been accounted for. The effect size is calculated as the ratio of the treatment effect (mean differences in treatment group minus differences in placebo group) to the pooled standard deviation of these differences[18]. This calculation entails the use of means, for both baseline and final data (or baseline and change during study) with a measure of variability such as standard deviation (SD). Every effort was made to calculate the effect size in all studies. If the SD was given in only one group it was used as baseline SD for both groups. However, if no measure of variability was given the effect size could not be extrapolated. By convention, an effect size < 0.2 is usually considered as trivial; $>0.2-0.5$ as small; $>0.5-0.8$ as moderate; $> 0.8-1.2$ as important and >1.2 as very important[19]. Minus or plus signs indicate direction of difference, not magnitude of difference.

Primary analyses examined pooled effect size of opioids vs controls for pain intensity and physical function. Sensitivity analyses were calculated within subgroups of studies decided a priori (type of opioids, type of scale for pain intensity and methodological quality) to assess the robustness of the main conclusions. Quality was analyzed as a binary variable: studies scoring 3 or more on the Jadad scale were considered to be of high quality; 2 or less, of low quality. A sensitivity analysis was also performed with the upper limit for low quality changed to 3.

Statistical heterogeneity was tested by Q test (χ^2)[20]. All meta-analyses were carried out with use of fixed-effects model, or random-effects model in case of significant heterogeneity. The number needed to harm (NNH) was used to assess the safety of opioids. The NNH is an epidemiological measure (defined as the inverse of the absolute risk increase) which reflects the number of patients who, if they received opioids, would lead to one additional patient being harmed, compared with control patients. The NNH is calculated as 1/absolute risk increase, the latter defined as (experimental event rate-control event rate). Harm was

primarily defined by the discontinuation of the study drug because of toxicity and secondarily by the occurrence of one or more of the *a priori* defined adverse events. In this second case, the NNH is the number of patients to treat to observe the occurrence of one extra adverse event in the treatment group, compared to the control group. The advantage of the NNH is that it reflects an absolute risk increase, and because it is related to the control event rate, it reflects the true baseline or underlying risk of the study population[21]. For rational decision making in daily clinical practice, absolute measures such as NNH may be more meaningful than relative measures[22]. Because of the large confidence intervals (CIs) around the opioid adverse event rates, CIs were not reported for the NNH, as proposed by McQuay and Moore[23].

Results

INCLUDED STUDIES

The results of the article selection process are reported in Fig. 1. From the 175 articles identified, 22 (Refs.[13,24–44]) were included since they reported RCTs comparing efficacy and/or safety of opioids vs placebo or non-opioid analgesics and presented interpretable data. All RCTs were parallel in design, except one[41], which had a cross-over design. Nine studies concerned strong opioids (oxymorphone, oxycodone, oxytrex, fentanyl and morphine sulfate) and 13 weak opioids (tramadol, tramadol/paracetamol, codeine and propoxyphene). All studies were funded by the pharmaceutical industry with one exception[42]. The comparators were placebo in 18 studies, paracetamol in two studies and NSAIDs (diclofenac and suprofen) in two studies. In view of the limited number of studies that evaluated opioids against other active medications (paracetamol and NSAIDs) which did not allow us to present robust data, data presented here concern only the comparison between opioids and placebo.

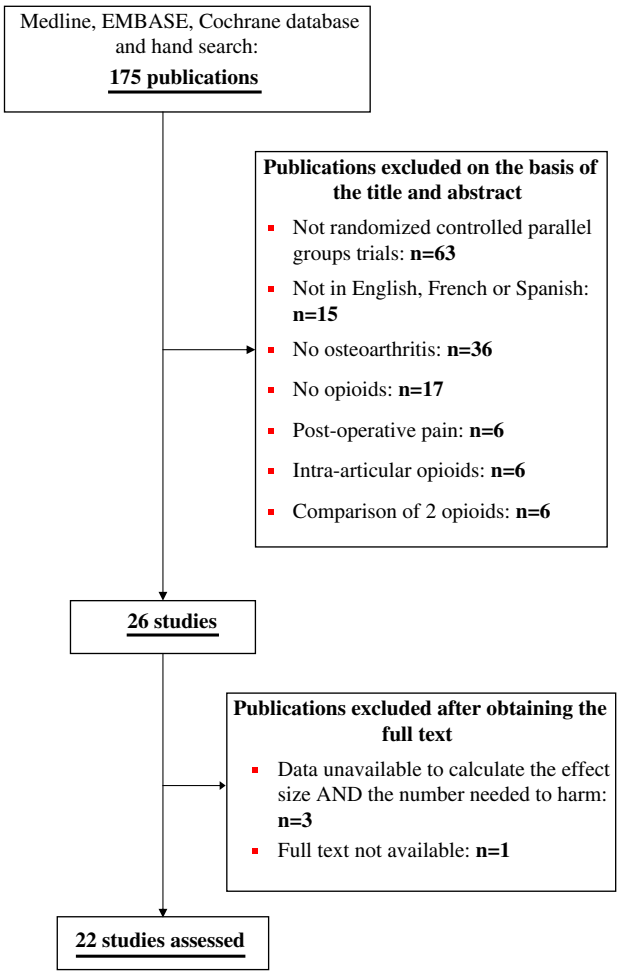

Fig. 1. Articles reporting the efficacy and/or the safety of opioids in osteoarthritis: screening process.

QUALITY OF STUDIES

The methodological quality was satisfactory: the mean ± SD impact factor of the journals in which were published the different trials was 3.5 ± 1.5 (range 1.1–7.3) and the mean ± SD Jadad score was 3.7 ± 0.6 (range: 2–5). All but one (95%)[31] of these trials used intention-to-treat analyses.

STUDY POPULATION

This systematic review included 4856 OA patients. The mean age of these patients was 61.6 ± 3 years, 66% were women and their mean BMI was 33 ± 2 kg/m^2. The characteristics of OA patients are detailed in Table I.

Table I
Characteristics of OA patients included in 18 RCTs of opioids compared to placebo

	All patients	Active intervention group (opioids)	Placebo group
Number of patients	4856	3244	1612
Mean age (years) ± SD (median, range)	61.6 ± 3 (62, 54–70)	61 ± 5 (62, 54–70)	62 ± 3 (62, 54–67)
Female sex, %	66	64	68
Number and % of patients with			
Knee OA	2868(59)	1880 (58)	988 (61)
Hip OA	943 (19)	596 (18)	347 (22)
Spine OA	137 (3)	85 (3)	52 (3)
Other localization	40 (1)	25 (1)	15 (1)
Not specified	868 (18)	658 (20)	210 (13)
Height (cm) mean ± SD (median, range)	168.6 ± 1.3 (169,165–171)	169.0 ± 1.2 (169, 167–171)	168.0 ± 1.5 (168, 165–169)
Mean weight (kg) ± SD (median, range)	91.5 ± 6 (94, 74.6–99)	92.6 ± 6 (94, 74.7–99)	89.5 ± 7 (93.5, 74.6–97.3)
Mean BMI (kg/m^2) ± SD (median, range)	33 ± 2 (33, 28–35)	33 ± 2 (33, 28–35)	32 ± 2 (33, 28–35)

EFFICACY OF OPIOIDS VS PLACEBO

Of the 18 placebo-controlled studies analyzed, 13 provided the required data on pain intensity for 2438 participants who received the active treatment and for 1295 who received placebo. Six studies concerned strong opioids (oxycodone in four studies, fentanyl and morphine sulfate in one study) and seven, weak opioids (tramadol in four studies, tramadol/paracetamol in two studies and codeine in one study). The mean trial duration was 13 ± 18 weeks (median 12 weeks, range 1.4−72 weeks).

The effect sizes for pain intensity and physical function for each of the 13 studies are provided in Tables II and III.

The pooled effect size of all opioids for pain intensity was −0.79 (95% CI −0.98 to −0.59). The heterogeneity was substantial ($Q = 198.5$ for 20 degrees of freedom, df; $P < 0.0001$). In the assessment of heterogeneity, sensitivity analyses showed no changes in the conclusions with the type of opioids, the type of scale used to measure pain intensity (VAS or Likert scale) and methodological quality of the study (Table IV).

Five placebo-controlled studies evaluated effects of opioids on physical function from 1429 participants receiving the active treatment (tramadol/paracetamol in two studies, morphine sulfate, tramadol and codeine in one study each) and from 595 receiving placebo. The mean trial duration was 7 ± 5 weeks (median: 4 weeks, range 1.4−13 weeks).

The pooled effect size of all opioids for physical function was −0.31 (95% CI −0.39 to −0.24). These results were homogenous ($Q = 6.8$ for 9 df; $P = 0.66$).

SAFETY OF OPIOIDS VS PLACEBO

All the 18 studies provided suitable data to assess opioid safety. The most frequent adverse events reported with opioids were nausea (30%), constipation (23%), dizziness (20%), somnolence (18%) and vomiting (13%).

The average treatment discontinuation rate for toxicity was 25% (818/3244) in the opioid group (516/1650, 31% for strong opioids and 302/1594, 19% for weak opioids) and 7% (116/1612) in the placebo group. Thus, the NNH for all class of opioids vs placebo was 5; for strong and weak opioids it was 4 and 9, respectively.

The NNHs vs placebo calculated for each adverse event (a priori defined) are provided in Table V.

Discussion

This meta-analysis suggests that in OA opioids are more effective than placebo to reduce pain intensity and improve physical function. These results are consistent with published data[8,45]. However, the benefits on physical function are small (effect size < 0.5), and may not be clinically relevant. This may be explained by the mechanism of action of opioids (they do not have anti- inflammatory effects)[30] and the short follow-up periods, as three trials out of five analyzing effects on physical function were short (from 1.4 to 4 weeks) to estimate the efficacy of opioids on function[34,35,37]. Moreover, opioids may also influence the effects on physical function because of side effects such as dizzines and drowsiness.

Opioid benefits may be limited by the occurrence of adverse events. The NNH of all class of opioids vs placebo for major adverse events indicates that, of every five patients who received opioid therapy, one discontinued the medication because of the occurrence of an adverse event. This was particularly important for strong opioids with an NNH of 4, vs 9 for weak opioids. Moreover, five of the *a priori* defined side effects (nausea, somnolence, dizziness, vomiting and constipation) were very frequent, with NNHs ranging from 4 to 9. These data emphasize the fact that adverse events need to be considered when treating OA patients with opioids.

This meta-analysis did not permit us to assess how opioids compare with other available pharmacological treatments (paracetamol and NSAIDs) because of the limited number of studies. Additional efficacy and safety monitoring investigations are needed.

This analysis had some limitations that merit considerations. Because of the absence of subgroup analyses in the articles reviewed, it was not possible to conduct subgroup analysis using meta-regressions to assess potential effect modification by type of patient (sex, age, BMI), disease duration or trial duration. Thus, we were limited in our ability to fully and clearly assess heterogeneity in opioids analgesic effectiveness.

Chronic pain is a long-term disorder. The studies included in this meta-analysis had various follow-up periods; most trials were not long enough to estimate the efficacy of opioids in chronic pain, the potential for opioid tolerance, or long-range adverse effects.

Another limitation of these results is the handling of missing data: one of the studies did not perform intention-to-treat analysis[31], while others performed intention-to-treat analysis with the last-value-carried-forward method[32,37]. Serious flaws still prevailed as all randomized patients were not included in the intention-to-treat analysis in one of these trials[30], and the best case scenario used for intention-to-treat analysis limits the validity of results, even if the quality of study was generally satisfactory.

Potential publication bias introduced into the process of locating and selecting studies for inclusion cannot be excluded because studies with significant results are more likely to be published than studies without significant results[46].

With the exception of one study, all the rest were industry funded and there is evidence suggesting that industry funded studies could overestimate treatment effects[47].

This systematic review emphasized some implications for practice and future research. The evaluation of the long-term effectiveness/safety of opioids for the treatment of OA is important: these agents are increasingly used to treat OA despite a lack of strong supporting evidence for their long-term effectiveness, and despite concerns about their tolerability and long-term safety. However, published data are relatively scarce for such a frequent disease. In particular, well designed equivalence RCTs that compare head to head the effectiveness and safety profiles of opioids and paracetamol or NSAIDs are warranted, in order to guide clinicians in selecting the best treatment approach.

Furthermore, additional trials are desirable in OA for other-than-oral routes of administration; for example, we found only one randomized placebo-controlled trial of transdermal route.

Finally, these results suggest that, when compared to placebo, opioids are superior for improving pain (with an advantage for strong opioids) and have small benefits on physical function in OA patients.

The number of studies ($n = 4$) that compared opioids with non-opioid analgesics (paracetamol and NSAIDs) was too limited to provide robust data.

Table II
Characteristics of controlled trials comparing strong opioids with placebo for pain intensity and physical function in patients with OA

Author, Reference	Jadad score	Opioid	Dose	Trial duration (weeks)	Number of patients, intervention/placebo	Outcome measure	Effect size (95% CI)
Langford[13]	4	Fentanyl TD	25–100 μg/h	6	202/197	Pain intensity VAS (0–100 mm)	−0.37 (−0.57 to −0.17)
Chindalore[26]	4	Oxytrex bid Oxytrex qid Oxycodone	10–40 mg/day 10–40 mg/day 10–40 mg/day	3	310/52	Pain intensity VAS (0–100 mm)	−1.09 (−1.45 to −0.73) −0.29 (−0.63 to +0.05) −0.15 (−0.49 to +0.18)
Markenson[28]	4	Oxycodone CR	10 mg/day	13	56/51	Pain intensity VAS (0–100 mm)	−1.49 (−1.92 to −1.05)
Zautra[29]	4	Oxycodone CR	10–120 mg/day	13	55/49	Pain intensity VAS (0–100 mm)	−0.75 (−1.15 to −0.34)
Cadwell[34]	4	Morphine sulfate QAM Morphine sulfate QPM Morphine sulfate CR	30 mg/day 30 mg/day 30 mg/day	4	222/73	Pain intensity VAS (0–100 mm)	−0.74 (−1.07 to −0.40) −0.55 (−0.89 to −0.22) −0.57 (−0.90 to −0.24)
						WOMAC physical function	−0.34 (−0.67 to −0.01) −0.33 (−0.66 to −0.03) −0.25 (−0.58 to +0.07)
Roth[38]	3	Oxycodone 10 mg Oxycodone 20 mg	20 mg/day 40 mg/day	2	88/45	Four point scale for pain intensity	−1.98 (−2.50 to −1.46) −4.96 (−5.82 to −4.09)
Kinitz[24]	4	Oxymorphone ER	20 mg/day 40 then 80 mg/day 40 then 100 mg/day	2	279/91	Pain intensity VAS (0–100 mm)	Insufficient data to calculate the effect size
Matsumoto[27]	4	Oxycodone ER Oxycodone ER Oxycodone CR	20 mg/day 40 mg/day 40 mg/day	4	367/124	Pain intensity VAS (0–100 mm)	Insufficient data to calculate the effect size
Cadwell[39]	4	Oxycodone Oxycodone/paracetamol	20–60 mg/day 5/325–60/4000 mg/day	4	71/36	Four point scale for pain intensity	Insufficient data to calculate the effect size

CR: controlled release, ER: extended release, QAM: once daily in the morning, QPM: once daily in the evening, bid: twice a day, qid: four times a day.

Table III
Characteristics of controlled trials comparing weak opioids with placebo for pain intensity and physical function in patients with OA

Author, Reference	Jadad score	Opioid	Dose	Trial duration (weeks)	Number of patients intervention/placebo	Outcome measure	Effect size (95% CI)
Gana[25]	4	Tramadol ER	100 mg/day 200 mg/day 300 mg/day 400 mg/day	12	806/205	Pain intensity VAS (0−100 mm)	−0.37 (−0.57 to −0.17) −0.48 (−0.68 to −0.28) −0.50 (−0.70 to −0.30) −0.37 (−0.57 to −0.17)
						WOMAC Physical function	−0.29 (−0.48 to −0.09) −0.36 (−0.56 to −0.16) −0.30 (−0.50 to −0.10) −0.28 (−0.48 to −0.09)
Emkey[30]	3	Tramadol/paracetamol	37.7/325−300/2600 mg/day	13	153/154	Pain intensity VAS (0−100 mm) WOMAC Physical function	−0.49 (−0.72 to −0.26) −0.20 (−0.42 to +0.03)
Malonne[31]	3	Tramadol ER	200 mg/day	2	111/119	Pain intensity VAS (0−100 mm)	−0.58 (−0.85 to −0.32)
Babul[32]	4	Tramadol ER	100−400 mg/day	12	124/122	Pain intensity VAS (0−100 mm)	−0.93 (−1.19 to −0.66)
Silverfield[35]	5	Tramadol/paracetamol	37.5/325−300/2600 mg/day	1.4	197/111	Four point scale for pain intensity WOMAC Physical function	−0.60 (−0.83 to −0.36) −0.31 (−0.54 to −0.07)
Fleischmann[36]	3	Tramadol	50−400 mg/day	13	63/66	Five point scale for pain intensity	−0.36 (−0.7 1to −0.01)
Peloso[37]	4	Codeine	100 mg/day	4	51/52	Pain intensity VAS (0−100 mm)	−1.22 (−1.65 to −0.79)
						WOMAC Physical function	−0.78 (−1.19 to −0.37)
Rozenthal[33]	4	Tramadol/paracetamol	168/1500 mg/day	1.5	69/44	Four point scale for pain intensity	Insufficient data to calculate the effect size
Roth[40]	2	Tramadol	50−400 mg	2	20/21	Time to exit study because of therapeutic failure	Insufficient data o calculate the effect size

CR: controlled release, ER: extended release, QAM: once daily in the morning, QPM: once daily in the evening, bid: twice a day, qid: four times a day.

Table IV
Sensitivity analyses of opioids vs placebo for pain intensity

Characteristics	No of studies	Fixed-effects model		Random-effects model		Q (*P* value)
		Effect size	95% CI	Effect size	95% CI	
All studies	13	−0.58	−0.64 to −0.52	−0.79	−0.98 to −0.59	198.5 ($P < 0.0001$)
Type of opioids						
Strong	6	−0.69	−0.79 to −0.60	−1.08	−1.52 to −0.65	165.8 ($P < 0.0001$)
Weak	7	−0.52	−0.60 to −0.45	−0.56	−0.69 to −0.43	26.1 ($P < 0.002$)
Oxycodone	4	−0.93	−1.08 to −0.78	−1.46		144.8 ($P < 0.0001$)
Fentanyl	1	−0.37	−0.57 to −0.17			NA
Morphine sulfate	1	−0.62	−0.81 to −0.43		−2.23 to −0.69	0.70 ($P = 0.7$)
Tramadol and tramadol/paracetamol	6	−0.50	−0.58 to −0.43	−0.51		15.3 ($P = 0.053$)
Codeine	1	−1.22	−1.65 to −0.79		−0.62 to −0.41	NA
Type of scale						
VAS	9	−0.53	−0.59 to −0.46	−0.58	−0.70 to −0.45	55.4 ($P < 0.0001$)
Likert score	4	−0.79	−0.96 to −0.62	−1.01	−1.61 to −0.41	33.2 ($P < 0.0001$)
High methodological quality (cut-off 3)						
High quality (4 and 5)	9	−0.53	−0.60 to −0.47	−0.59	−0.72 to −0.46	57.5 ($P < 0.0001$)
Low quality (1, 2 and 3)	4	−0.62	−0.77 to −0.47	−0.81	−1.31 to −0.31	30.7 ($P < 0.0001$)

Adverse events, although reversible and not life threatening, often caused participants to stop taking the medication and could limit opioids usefulness.

Future trials of opioids for OA compared with non-opioid analgesics are warranted. They should consistently have well-defined methods and follow-up periods adequate in length. More attention should be paid to factors affecting methodological rigor, such as success of blinding, avoidance of dropouts, and adequate intention-to-treat analysis.

Table V
NNH calculation for adverse events reported for opioids vs placebo

Adverse event (AE)	Opioids	No (%) of AE in OA patients treated with opioids in studies where the AE was reported	No (%) of AE in OA patients treated with placebo in studies where the AE was reported	NNH
Epigastric pain	All class	19/698 (3)	5/447 (1)	50
	Weak	4/388 (1)	3/395 (0.8)	500
	Strong	15/310 (5)	2/52 (4)	50
Nausea	All class	950/3138 (30)	145/1511 (9.5)	5
	Weak	315/1543 (20)	49/842 (6)	7
	Strong	635/1595 (40)	96/669 (14)	4
Vomiting	All class	408/3075 (13)	32/1445 (2)	9
	Weak	118/1480 (8)	15/776 (2)	17
	Strong	290/1595 (18)	17/669 (2)	6
Constipation	All class	733/3189 (23)	88/1563 (5.6)	4
	Weak	275/1594 (17)	36/894 (4)	8
	Strong	458/1595 (29)	52/669 (8)	5
Dry mouth	All class	213/2532 (8)	19/1041 (2)	17
	Weak	69/1214 (6)	5/621 (1)	22
	Strong	144/1318 (11)	14/420 (3)	12
Dizziness	All class	633/3189 (20)	83/1563 (5)	7
	Weak	278/1594 (17)	45/894 (5)	8
	Strong	355/1595 (22)	38669 (6)	6
Somnolence	All class	549/3126 (18)	55/1497 (4)	8
	Weak	166/1531 (11)	16/828 (2)	11
	Strong	383/1595 (24)	39/669 (6)	6
Headache	All class	343/2649 (13)	128/1255 (10)	33
	Weak	145/1155 (12.5)	52/653 (8)	22
	Strong	198/1494 (13)	76/602 (13)	Infinite
	NNH for overall adverse events			5
	Discontinuation rate for adverse events (opioids/placebo)			25% / 7%

No: number, AE: adverse event, OA: osteoarthritis, NNH: calculation of the number of patients which need to be treated by opioids to observe one supplementary treatment discontinuation due to an AE in the opioid arm, compared to the placebo arm.

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