Oral or transdermal opioids for osteoarthritis of the knee or hip (Review)

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[Intervention Review]

Oral or transdermal opioids for osteoarthritis of the knee or hip

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ABSTRACT

Background

Osteoarthritis is the most common form of joint disease and the leading cause of pain and physical disability in the elderly. Opioids may be a viable treatment option if patients suffer from severe pain or if other analgesics are contraindicated. However, the evidence about their effectiveness and safety is contradictory.

Objectives

To determine the effects on pain and function and the safety of oral or transdermal opioids as compared with placebo or no intervention in patients with osteoarthritis of the hip or knee.

Search strategy

We searched CENTRAL, MEDLINE, EMBASE, and CINAHL (up to 28 July 2008), checked conference proceedings, reference lists, and contacted authors.

Selection criteria

Studies were included if they were randomised or quasi-randomised controlled trials that compared oral or transdermal opioids with placebo or no treatment in patients with osteoarthritis of the knee or hip. Studies of tramadol were excluded. No language restrictions were applied.

Data collection and analysis

We extracted data in duplicate. Standardised mean differences (SMDs) and 95% confidence intervals (CI) were calculated for pain and function, and risk ratios for safety outcomes. Trials were combined using inverse-variance random-effects meta-analysis.

Main results

Ten trials with 2268 participants were included. Oral codeine was studied in three trials, transdermal fentanyl and oral morphine in one trial each, oral oxycodone in four, and oral oxymorphone in two trials. Overall, opioids were more effective than control interventions

in terms of pain relief (SMD -0.36, 95% CI -0.47 to -0.26) and improvement of function (SMD -0.33, 95% CI -0.45 to -0.21). We did not find substantial differences in effects according to type of opioid, analgesic potency (strong or weak), daily dose, duration of treatment or follow up, methodological quality of trials, and type of funding. Adverse events were more frequent in patients receiving opioids compared to control. The pooled risk ratio was 1.55 (95% CI 1.41 to 1.70) for any adverse event (4 trials), 4.05 (95% CI 3.06 to 5.38) for dropouts due to adverse events (10 trials), and 3.35 (95% CI 0.83 to 13.56) for serious adverse events (2 trials). Withdrawal symptoms were more severe after fentanyl treatment compared to placebo (SMD 0.60, 95% CI 0.42 to 0.79; 1 trial).

Authors' conclusions

The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe.

PLAIN LANGUAGE SUMMARY

Opioids for osteoarthritis

This summary of a Cochrane review presents what we know from research about the effect of opioids on osteoarthritis.

The review shows that in people with osteoarthritis:

- Opioids moderately improve pain or physical function.

- Opioids probably cause side effects. However, we do not have precise information about rare but serious side effects.

What is osteoarthritis and what are opioids?

Osteoarthritis (OA) is a disease of the joints, such as your knee or hip. When the joint loses cartilage, the bone grows to try and repair the damage. Instead of making things better, however, the bone grows abnormally and makes things worse. For example, the bone can become misshapen and make the joint painful and unstable. This can affect your physical function or ability to use your knee.

Opioids are powerful pain-relieving substances that are used for the pain of cancer or osteoarthritis. Some examples of opioids are codeine-containing Tylenol® (1, 2, 3 and 4), hydromorphone (Dilaudid), oxycodone (Percocet, Percodan), morphine and others. They can be taken in a pill form, as an injection, or as a patch placed on the painful area.

Best estimate of what happens to people with osteoarthritis who take Opioids

Pain

- People who took opioids rated improvement in their pain to be about 3 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.

- People who took a placebo rated improvement in their pain to be about 2 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.

Another way of saying this is:

- 35 people out of 100 who use opioids respond to treatment (35%).

- 31 people out of 100 who use placebo respond to treatment (31%).

- 4 more people respond to treatment with opioids than with placebo (difference of 4%).

Physical Function

- People who took opioids rated improvement in their physical function to be about 2 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.

- People who took a placebo rated improvement in their physical function to be about 1 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.

Another way of saying this is:

- 29 people out of 100 who use opioids respond to treatment (29%).

- 26 people out of 100 who use placebo respond to treatment (26%).

- 3 more people respond to treatment with opioids than with placebo (difference of 3%).

Side effects

- 23 people out of 100 who used opioids experienced side effects (23%).

- 15 people out of 100 who used a placebo experienced side effects (15%).

- 7 more people experienced side effects with opioids than with placebo (difference of 7%).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Oral or transdermal opioids compared with placebo for osteoarthritis of the knee or hip

Patient or population: Patients with osteoarthritis of the knee or hip
Settings: Various orthopedic or rheumatology clinics
Intervention: Oral or transdermal opioids
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Opioids				
Pain intensity Various pain scales. (median follow-up: 4 weeks)	**-1.8 cm change** on 10 cm VAS[1] 29% improvement	**-2.7 cm change** (Δ -0.9 cm,-1.2 to -0.7)[2] **44% improvement** (Δ 15%, 11% to 20%)[3]	SMD -0.36 (-0.47 to -0.26)	2268 (10)	++++ high	NNT: 25 (95% CI 19 to 34)[4]
Function Various validated function scales. (median follow-up: 4 weeks)	**-1.2 units** on WOMAC (range 0 to 10)[1] 21% improvement	**-1.9 units on WOMAC** (Δ -0.7, -1.0 to -0.5)[5] **34% improvement** (Δ 13%, 9% to 18%)[6]	SMD -0.33 (-0.45 to -0.21)	1794 (7)	++++ high	NNT: 30 (95% CI 22 to 46)[7]
Number of patients experiencing any adverse event (median follow-up: 4 weeks)	150 per 1000 patient-years[8]	233 per 1000 patient-years (212 to 255)	RR 1.55 (1.41 to 1.70)	1080 (4)	+++O moderate[9]	NNH: 12 (95% CI 10 to 16)
Number of patients who withdrew because of adverse events (median follow-up: 4 weeks)	17 per 1000 patient-years[8]	69 per 1000 patient-years (52 to 91)	RR 4.05 (3.06 to 5.38)	2403 (10)	++++ high	NNH: 19 (95% CI 13 to 29)

Number of patients experiencing any serious adverse event (median follow-up: 4 weeks)	4 per 1000 patient-years[8]	13 per 1000 patient-years (3 to 54)	RR 3.35 (0.83 to 13.56)	681 (3)	++00 low[10]	Little evidence of harmful effect [NNH: not statistically significant].
Withdrawal symptoms Short Opiate Withdrawal Scale. (follow-up: 8 weeks)	**0.9 units** (range 0 to 3)	**0.7 units** (△ 0.3, 0.2 to 0.4) **69% increase** (46 to 92%)[11]	SMD 0.60 (0.42 to 0.79)	499 (1)	++00 low[12]	No evidence-based assumption could be made for the calculation of NNH.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference; GRADE: GRADE Working Group grades of evidence (see explanations); NNT: number needed to treat; NNH: number needed to harm.

GRADE Working Group grades of evidence
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++0): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++00): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+000): We are very uncertain about the estimate.
[1] Median reduction as observed across placebo groups in large osteoarthritis trials (see methods section, Nüesch 2009).
[2] Standardised mean differences (SMDs) were back-transformed onto a 10 cm visual analogue scale (VAS) on the basis of a typical pooled SD of 2.5 cm in large trials that assessed pain using a VAS and expressed as change based on an assumed standardised reduction of 0.72 standard deviation units in the control group.
[3] Percentage of improvement was calculated based on median observed pain at baseline across control groups of large osteoarthritis trials of 6.1 cm on 10 cm VAS (Nüesch 2009).
[4] Absolute response risks for pain in the control groups were assumed 31% (see methods section).
[5] Standardised mean differences (SMDs) were back-transformed onto a standardised WOMAC disability score ranging from 0 to 10 on the basis of a typical pooled SD of 2.1 in trials that assessed function using WOMAC disability scores and expressed as change based on an assumed standardised reduction of 0.58 standard deviation units in the control group.
[6] Percentage of improvement was calculated based on median observed WOMAC function scores at baseline across control groups of large osteoarthritis trials of 5.6 units (Nüesch 2009).

[7] Absolute response risks for function in the control groups were assumed 26% (see methods section).
[8] Median control risk across placebo groups in large osteoarthritis trials (see methods section, Nüesch 2009).
[9] Downgraded (1 level) because: 4 out of 10 studies reported this outcome, possibly leading to selective outcome reporting bias.
[10] Downgraded (2 levels) because: 3 out of 10 studies reported this outcome, possibly leading to selective outcome reporting bias, the confidence interval of the pooled estimate is wide and crossed no difference.
[11] Percentage of improvement was calculated based on observed withdrawal symptom scores in the placebo group of 0.39.
[12] Downgraded (2 levels) because the outcome was assessed by a single trial assessing transdermal fentanyl therapy, and 8 weeks follow-up duration considered short for this outcome.

BACKGROUND

Osteoarthritis is the most common form of joint disease and the leading cause of pain and physical disability in the elderly (Altman 1986). It is characterised by focal areas of loss of articular cartilage in synovial joints accompanied by subchondral bone changes, osteophyte formation at the joint margins, thickening of the joint capsule and mild synovitis. Pharmacologic therapy for osteoarthritis, as an alternative or in addition to other therapeutic options, consists mainly of analgesics and nonsteroidal anti-inï¬ammatory drugs (NSAIDs). However, paracetamol may be inadequate to treat more severe, long-term pain in osteoarthritis and chronic NSAID use may cause serious gastrointestinal and cardiovascular adverse events. Opioids could be a viable alternative if patients suffer from severe pain with insufficient response to conventional treatment or if other analgesics are contraindicated (Avouac 2007).

Opioids are potent analgesics that work by targeting mainly spinal and supraspinal opioid receptors. In addition, cellular studies suggest that there are peripheral opioid receptors in inflamed osteoarthritic synovial tissue, which may mediate analgesic effects (Stein 1996). The American College of Rheumatology guidelines on management of osteoarthritis, updated in 2000, suggest that opioids can be used as a last resort in osteoarthritis (ACR OA 2000). English guidelines propose opioids as an alternative if inadequate pain relief is achieved with an NSAID or paracetamol (Eccles 1998). However, the use of strong opioids for the treatment of non-cancer pain remains controversial. Concerns have been expressed about long-term use of opioids for chronic non-cancer pain mainly due to the risks of addiction (Von Korff 2004; Zhang 2008).

OBJECTIVES

We set out to compare oral or transdermal opioids with placebo or a non-intervention control in terms of effects on pain and function, safety, and addiction in patients with knee or hip osteoarthritis (OA); and to explore whether potential variation between trials could be explained by type of opioid, route of administration, biases affecting individual trials, or publication bias.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials with a control group receiving placebo or no intervention.

Types of participants

At least 75% of patients with clinically or radiologically confirmed osteoarthritis of the knee or hip. Trials exclusively including patients with inflammatory arthritis, such as rheumatoid arthritis, were not considered.

Types of interventions

Any type of opioid except tramadol, which is covered in a separate Cochrane Review (Cepeda 2006).

Types of outcome measures

Primary outcomes

The main outcomes were pain and function, as currently recommended for osteoarthritis trials (Altman 1996; Pham 2004). If data on more than one pain scale were provided for a trial, we referred to a previously described hierarchy of pain-related outcomes (Jüni 2006; Reichenbach 2007) and extracted data on the pain scale that was highest on this list:

1. global pain;
2. pain on walking;
3. WOMAC osteoarthritis index pain subscore;
4. composite pain scores other than WOMAC;
5. pain on activities other than walking;
6. rest pain or pain during the night;
7. WOMAC global algofunctional score;
8. Lequesne osteoarthritis index global score;
9. other algofunctional scale;
10. patient's global assessment;
11. physician's global assessment.

If data on more than one function scale were provided for a trial, we extracted data according to the hierarchy:

1. global disability score;
2. walking disability;
3. WOMAC disability subscore;
4. composite disability scores other than WOMAC;
5. disability other than walking;
6. WOMAC global scale;
7. Lequesne osteoarthritis index global score;
8. other algofunctional scale;
9. patient's global assessment;
10. physician's global assessment.

If pain or function outcomes were reported at several time points, we extracted the measure at the end of the treatment period.

Secondary outcomes

Secondary outcomes were the number of patients experiencing any adverse event, patients who withdrew because of adverse events, patients experiencing any serious adverse events, and patients experiencing symptoms of opioid dependence such as craving or physical withdrawal symptoms. Serious adverse events were defined as events resulting in hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events, or death.

Search methods for identification of studies

Electronic searches

We searched the electronic databases CENTRAL (*The Cochrane Library*) (http://mrw.interscience.wiley.com/cochrane/), MEDLINE and EMBASE through the Ovid platform (www.ovid.com), and CINAHL through EBSCOhost (all from implementation to July 28 2008) using truncated variations of preparation names including brand names combined with truncated variations of terms related to osteoarthritis, all as text words. A validated methodologic filter for controlled clinical trials was applied (Dickersin 1994). The specific search algorithms are displayed in Appendix 1 and Appendix 2.

Searching other sources

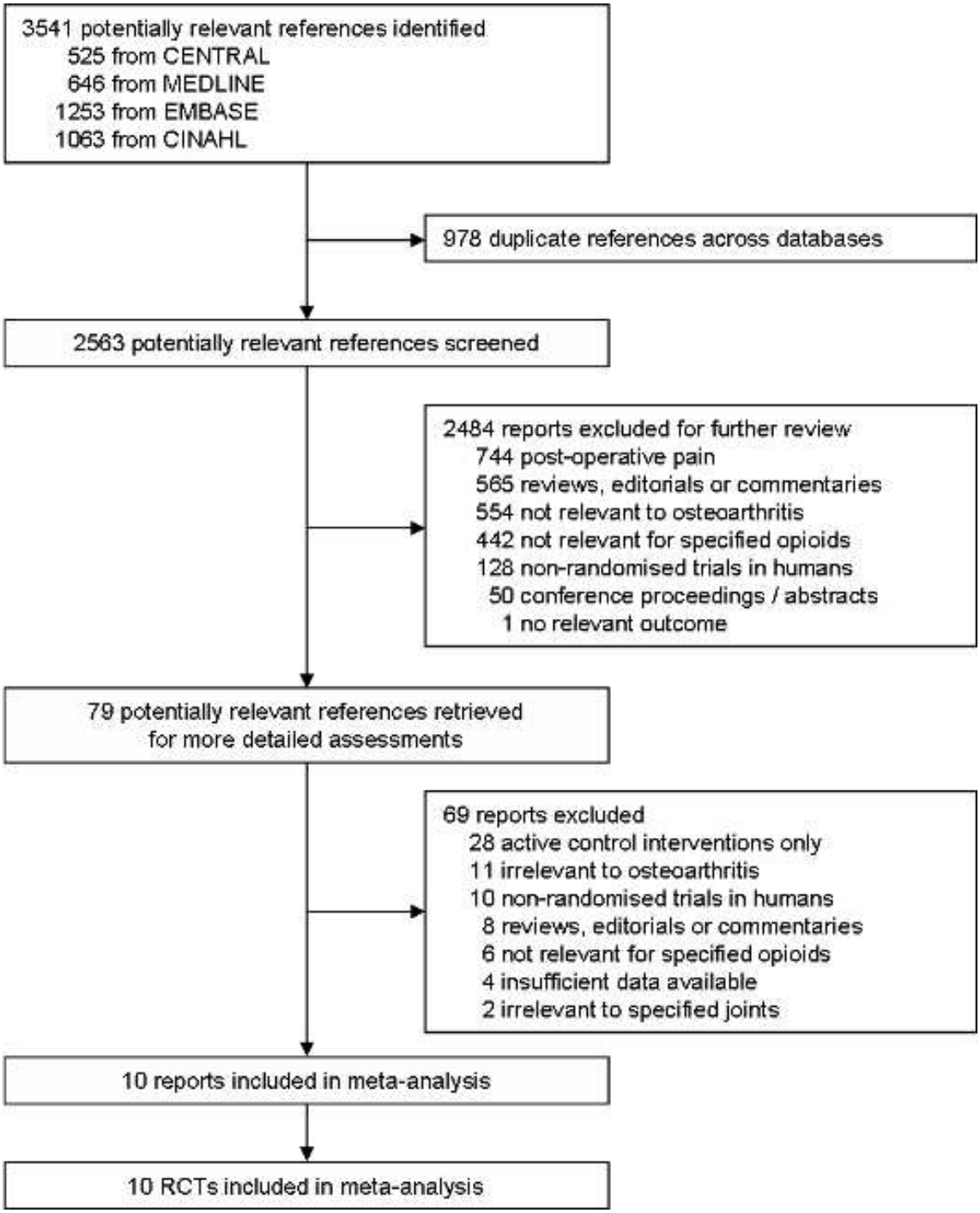
We manually searched conference proceedings, used Science Citation Index to retrieve reports citing relevant articles, contacted content experts and trialists, and screened reference lists of all obtained articles. Finally, we searched several clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com, www.actr.org.au, www.umin.ac.jp/ctr) to identify ongoing trials. The last update of the manual search was on July 28, 2008.

Data collection and analysis

Selection of studies

Two review authors independently evaluated all titles and abstracts for eligibility (EN, AR) (see Figure 1). Disagreements were resolved by discussion. No language restrictions were applied. If multiple reports described the same trial, we considered all.

Figure 1. Study flow chart



Data collection

Two review authors (EN, AR) extracted trial information independently using a standardised, piloted extraction form accompanied by a codebook. Disagreements were resolved by discussion. We extracted both the generic and trade name of the experimental intervention, the type of control used, dosage, frequency, route of administration, duration of treatment, patient characteristics (gender, average age and duration of symptoms, types of joints affected), types of measures used and pain and function-related outcomes, trial design, trial size, duration of follow up, type and source of financial support, and publication status. When necessary, means and measures of dispersion were approximated from figures in the reports. For crossover trials, we extracted data from the first period only. Whenever possible, we used results from an intention-to-treat analysis. If effect sizes could not be calculated, we contacted the authors for additional data.

Quality assessment

Two review authors (EN, AR) independently assessed randomisation, blinding, and adequacy of analyses (Jüni 2001). Disagreements were resolved by consensus. Two components of randomisation were assessed: generation of allocation sequences and concealment of allocation. Generation of sequences was considered adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate include random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards, and drawing lots. Trials using an unpredictable allocation sequence were considered randomised; trials using potentially predictable allocation mechanisms, such as alternation or the allocation of patients according to date of birth, were considered quasi-randomised. Concealment of allocation was considered adequate if patients and investigators responsible for patient selection were unable to suspect before allocation which treatment was next. Methods considered adequate include central randomisation; pharmacy-controlled randomisation using identical prenumbered containers; and sequentially numbered, sealed, opaque envelopes. Blinding of patients was considered adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used. Analyses were considered adequate if all randomised patients were included in the analysis according to the intention-to-treat principle. We further assessed the reporting of primary outcomes, sample size calculations, and funding source. Finally, we used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2008), defined as the extent of confidence into the estimates of treatment benefits and harms.

Data synthesis

Continuous outcomes were summarised using standardised mean differences (SMD), with the differences in mean values at the end of treatment across treatment groups divided by the pooled standard deviation. If differences in mean values at the end of the treatment were unavailable, differences in mean changes were used. If some of the required data were unavailable we used approximations, as previously described (Reichenbach 2007). An SMD of -0.20 standard deviation units can be considered a small difference between the experimental and control groups, an SMD of -0.50 a moderate difference, and -0.80 a large difference (Cohen 1988; Jüni 2006). SMDs can also be interpreted in terms of the percent of overlap of the experimental group's scores with scores of the control group. An SMD of -0.20 indicates an overlap in the distribution of pain or function scores in about 85% of cases, an SMD of -0.50 in approximately 67%, and an SMD of -0.80 in about 53% of cases (Cohen 1988; Jüni 2006). On the basis of a median pooled SD of 2.5 cm, found in large-scale osteoarthritis trials that assessed pain using a 10 cm visual analogue scale (VAS) (Nüesch 2009), SMDs of -0.20, -0.50, and -0.80 correspond to approximate differences in pain scores between experimental and control groups of 0.5, 1.25 and 2.0 cm on a 10 cm VAS. SMDs for function were back transformed to a standardised WOMAC disability score (Bellamy 1995) ranging from 0 to 10 on the basis of a median pooled SD of 2.1 units observed in large-scale osteoarthritis trials (Nüesch 2009). Binary outcomes were expressed as relative risks.

We used standard inverse-variance random-effects meta-analysis to combine the trials (DerSimonian 1986). We quantified heterogeneity between trials using the I^2 statistic (Higgins 2003), which describes the percentage of variation across trials that is attributable to heterogeneity rather than to chance. I^2 values of 25%, 50%, and 75% may be interpreted as low, moderate, and high between-trial heterogeneity, although its interpretation depends on the size and number of trials included (Rücker 2008). The association between trial size and treatment effects was investigated in funnel plots, plotting effect sizes on the vertical axis against their standard errors on the horizontal axis. We assessed asymmetry by the asymmetry coefficient, the difference in effect size per unit increase in standard error (Sterne 2001) which is mainly a surrogate for sample size, and used uni-variable, meta-regression analysis to predict treatment effects in trials as large as the largest trials included in the meta-analysis using the standard error as the explanatory variable (Shang 2005). We then performed analyses of the primary outcomes, pain and function, stratified by the following trial characteristics: type of opioid, analgesic potency (strong versus weak), route of administration (oral versus transdermal), type of control (placebo versus no intervention), concealment of allocation (adequate versus inadequate or unclear), blinding of patients (adequate versus inadequate or unclear), analysis in accordance with the intention-to-treat principle (yes versus no or unclear), trial size, funding, and duration of treatment. Fentanyl, morphine, oxycodone, and oxymorphone were classified as strong opioids, codeine and dextropropoxyphene as weak opioids. A cut off of 200 allocated patients was used to distinguish between small-scale and large-scale trials. A sample size of 2 x 100 patients will yield more than 80% power to detect a small to moderate SMD of -0.40 at a two-sided P of 0.05, which corresponds to a difference of 1 cm on

a 10 cm VAS between the experimental and control intervention. A cut off of one month was used to distinguish between short-term and long-term trials. Uni-variable, random-effects meta-regression models were used to determine whether treatment effects were affected by these factors (Thompson 1999). In addition, the following two continuous variables at trial level were included in uni-variable meta-regression: daily morphine equivalence dosage and treatment duration. Morphine equivalence doses were calculated as previously described (Loeser 2001; Schug 2006): 10 mg oral morphine was considered equivalent to 65 mg oral codeine, 2 μg/hour transdermal fentanyl, 7.5 mg oral oxycodone, and 10 mg oral oxymorphone.

We converted SMDs of pain intensity and function to odds ratios (Chinn 2000) to derive numbers needed to treat (NNT) to cause one additional treatment response on pain or function as compared with placebo, and numbers needed to harm (NNH) to cause one additional adverse outcome. We defined treatment response as a 50% improvement in scores (Clegg 2006). With a median standardised pain intensity at baseline of 2.4 standard deviation units, observed in large osteoarthritis trials (Nüesch 2009), this corresponds to an average decrease in scores of 1.2 standard deviation units. Based on the median standardised decrease in pain scores of 0.72 standard deviation units (Nüesch 2009), we calculated that a median of 31% of patients in the placebo group would achieve an improvement of pain scores of 50% or more. This percentage was used as the control group response rate to calculate NNTs for treatment response on pain. Based on the median standardised WOMAC function score at baseline of 2.7 standard deviation units and the median standardised decrease in function scores of 0.58 standard deviation units (Nüesch 2009), 26% of patients in the placebo group would achieve a reduction in function of 50% or more. Again, this percentage was used as the control group response rate to calculate NNTs for treatment response on function. The median risks of 150 patients with adverse events per 1000 patient-years, 4 patients with serious adverse events per 1000 patient-years, and 17 dropouts due to adverse events per 1000 patient-years as observed in placebo groups in large osteoarthritis trials (Nüesch 2009) were used to calculate NNHs for safety outcomes. All P-values are two-sided. Analyses were performed using RevMan version 5 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen) and STATA version 10.1 (StataCorp, College Station, Texas).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

We identified 2563 potentially relevant references through our electronic searches (Figure 1); 2484 references were excluded after screening titles and abstracts and 79 potentially relevant references were retrieved for full-text assessment. Ten randomised controlled trials were included in the review. Checking reference lists and handsearching of conference proceedings did not yield any additional trials.

Three trials evaluated weak opioids. All three compared codeine with placebo (Kjaersgaard-Andersen 1990; Quiding 1992; Peloso 2000), one of these with paracetamol 3000 mg daily as analgesic co-intervention administered in both the experimental and control groups (Kjaersgaard-Andersen 1990) and another with ibuprofen 1200 mg daily administered in both groups (Quiding 1992). Strong opioids were compared to placebo in seven trials. Morphine was used in one trial (Caldwell 2002), oxymorphone in two (Matsumoto 2005; Kivitz 2006), oxycodone in four (Chindalore 2005; Markenson 2005; Matsumoto 2005; Zautra 2005), and transdermal fentanyl in one trial (Langford 2006). Fentanyl was the only opioid applied by a transdermal route, all others were given orally. Opioids were administered at a median daily dose of 51 mg morphine equivalents (range 13 to 160 mg).

The median treatment duration was four weeks (range 3 days to 3 months). Trials randomised a median number of 161 patients (range 27 to 491 patients). Nine trials (90%) were multicentre parallel-group trials, one was a multicentre crossover trial (Quiding 1992). Two trials exclusively included patients with hip osteoarthritis (Kjaersgaard-Andersen 1990; Quiding 1992), one trial included only patients with knee osteoarthritis (Zautra 2005), and six trials included a mixed population of both knee and hip osteoarthritis (Peloso 2000; Chindalore 2005; Markenson 2005; Matsumoto 2005; Kivitz 2006; Langford 2006). In six studies only patients with insufficient analgesic response to paracetamol, NSAIDs, or previous opioids treatment were included (Caldwell 2002; Chindalore 2005; Kivitz 2006; Langford 2006; Markenson 2005; Matsumoto 2005). The three trials assessing codeine included patients with a need for analgesic treatment but without any requirement of previous insufficient treatment response (Kjaersgaard-Andersen 1990; Quiding 1992; Peloso 2000); one trial did not provide information about eligibility criteria concerning the previous analgesic therapy (Zautra 2005).

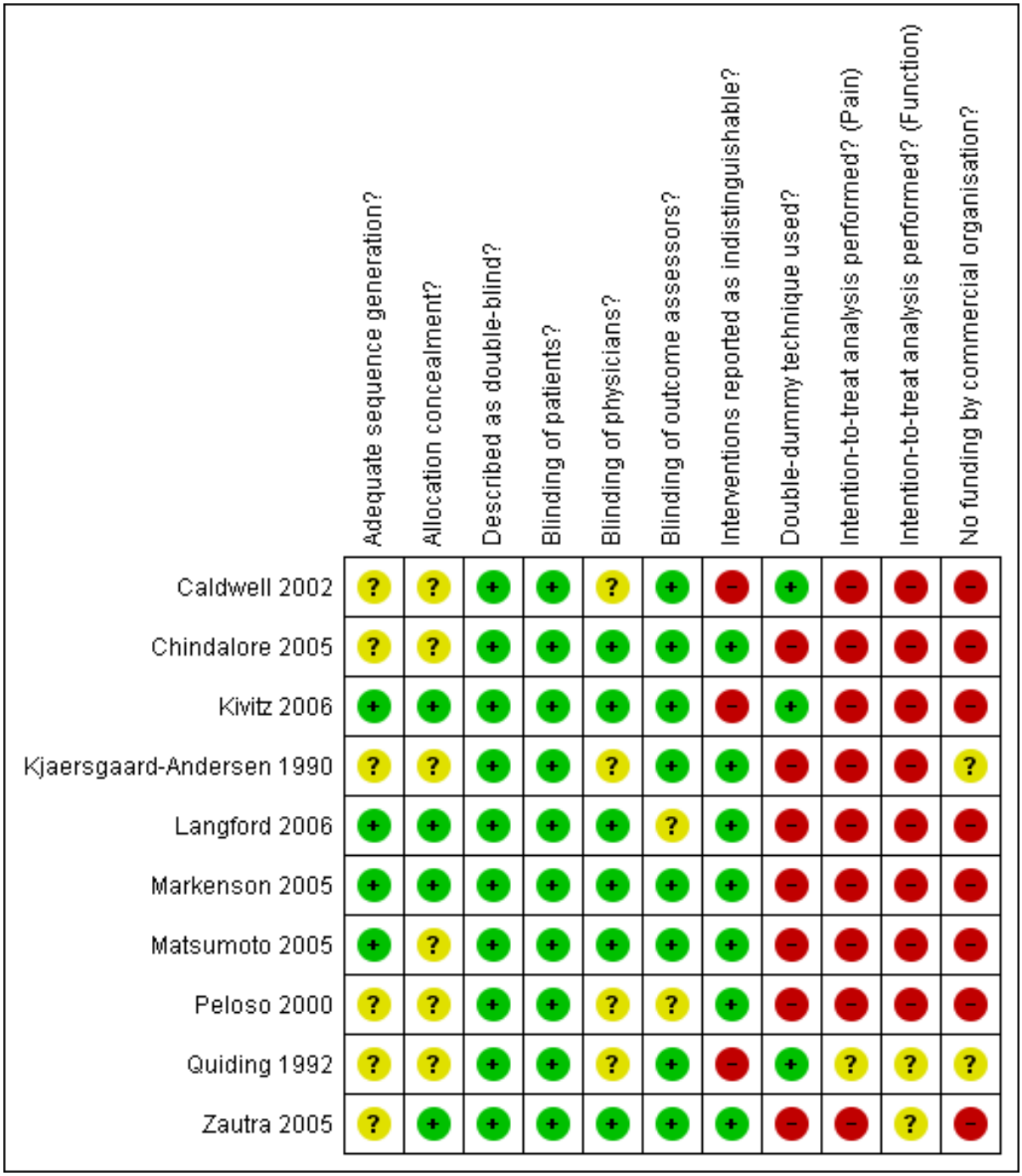
The Characteristics of excluded studies table displays the reasons why trials were not considered in this systematic review. Typical reasons were more than 25% of patients with rheumatoid arthritis in the sample, the use of active control interventions, or the use of crossover designs without providing sufficient information on the first phase.

Risk of bias in included studies

Figure 2 summarises the methodological characteristics and sources of funding of included trials. Three trials (30%) reported both adequate sequence generation and adequate allocation concealment (Markenson 2005; Kivitz 2006; Langford 2006); one trial reported only adequate sequence generation (Matsumoto

2005); and one trial reported adequate concealment but remained unclear about the generation of allocation sequence (Zautra 2005). In the remaining five trials, low quality of reporting hampered any judgment regarding sequence generation and concealment of allocation. All 10 trials were described as double blind. Seven trials reported the use of indistinguishable interventions to blind patients whereas the other three trials used double-dummy techniques (Quiding 1992; Caldwell 2002; Kivitz 2006). However, only six trials explicitly reported adequate blinding of physicians (Chindalore 2005; Markenson 2005; Matsumoto 2005; Zautra 2005; Kivitz 2006; Langford 2006). Seven trials described their analysis to be according to the intention-to-treat principle (Peloso 2000; Chindalore 2005; Markenson 2005; Matsumoto 2005; Zautra 2005; Kivitz 2006; Langford 2006), but none were considered to have an intention-to-treat analysis of pain and function outcomes at end of treatment according to our criteria. Exclusion of patients from the analysis of pain outcomes ranged from 0.3% to 52% in the experimental groups and from 2% to 33% in the control groups. For four trials no information was available on the proportion of excluded patients (Quiding 1992; Caldwell 2002; Markenson 2005; Langford 2006). For the analysis of function outcomes, exclusion of patients ranged from 1% to 48% in the experimental groups and from 2% to 37% in the control groups; in two trials no information was available on the proportion of excluded patients (Caldwell 2002; Markenson 2005).

Figure 2. Methodological characteristics and source of funding of included trials. (+) indicates low risk of bias, (?) unclear and (-) a high risk of bias on a specific item.



Nine trials (90%) reported a primary outcome (Kjaersgaard-Andersen 1990; Peloso 2000; Caldwell 2002; Chindalore 2005; Markenson 2005; Matsumoto 2005; Zautra 2005; Kivitz 2006; Langford 2006) of which five explicitly reported it to be pre-specified in the protocol (Peloso 2000; Caldwell 2002; Markenson 2005; Matsumoto 2005; Langford 2006) and six trials reported a sample size calculation for this primary outcome (Kjaersgaard-Andersen 1990; Peloso 2000; Markenson 2005; Matsumoto 2005; Kivitz 2006; Langford 2006). Eight trials received financial support from a commercial organisation (Peloso 2000; Caldwell 2002; Chindalore 2005; Markenson 2005; Matsumoto 2005; Zautra 2005; Kivitz 2006; Langford 2006) whereas no trial was explicitly supported by a non-profit organisation. For the effectiveness outcomes pain and function, the quality of the evidence (Guyatt 2008) was classified as high in view of the low risk of bias in the included trials and the low heterogeneity between trials (Summary of findings for the main comparison). For adverse event and serious adverse event outcomes, the quality of the evidence (Guyatt 2008) was classified as moderate to low because of the small number of trials reporting the outcomes and the small number of serious adverse events which resulted in imprecise estimates (Summary of findings for the main comparison).

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Knee or hip pain

Ten trials including 1541 patients in experimental groups and 727 patients in control groups contributed to the analyses of knee or hip pain. Figure 3 presents results of the analysis, overall and stratified according to type of opioid. In the overall analysis, combined oral and transdermal opioids were more effective in pain reduction than control interventions (SMD -0.36, 95% CI -0.47 to -0.26), which corresponds to a difference in pain scores of 0.9 cm on a 10 cm VAS between opioids and placebo. This corresponds to a difference in improvement of 15% (95% CI 11% to 20%) between opioids and placebo (Summary of findings for the main comparison). The estimated difference in the percentage of treatment responders of 4% between opioids and placebo translates into an NNT to cause one additional treatment response on pain of 25 (95% CI 19 to 34) (Summary of findings for the main comparison). An I^2 of 18% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.27). A visual inspection of the funnel plot suggested slight asymmetry (asymmetry coefficient -1.66, 95% CI -3.74 to 0.43) and the test for asymmetry indicated limited evidence for asymmetry (P = 0.10) (Figure 4). Benefits were moderate for codeine (SMD -0.51, 95% CI -1.01 to -0.01; 3 trials), small to moderate for oxycodone (SMD -0.42, 95% CI -0.65 to -0.20; 4 trials) and oxymorphone (SMD -0.39, 95% CI -0.58 to -0.21; 2 trials), and small for morphine (SMD -0.32, 95% CI -0.59 to -0.06; 1 trial) and transdermal fentanyl (SMD -0.22, 95% CI -0.42 to -0.03; 1 trial). The confidence intervals were wide and a test for interaction between benefit and type of opioid was non-significant (P = 0.89). Table 1 presents the results of stratified analyses. We found little evidence for an association of SMDs with analgesic potency, route of administration, type of control intervention, treatment duration, use of analgesic co-interventions, concealment of allocation, or sample size. All the trials had blinded patients adequately, none had performed analyses according to the intention-to-treat principle. Therefore, we could not evaluate the impact of these characteristics. Fourteen comparisons from 10 trials contributed to the analysis of a linear association between equivalence dose and treatment benefit (Figure 5). We found little evidence for a linear association between daily equivalence doses and pain reduction (P = 0.47).

Figure 3. Forest plot of 10 trials comparing the effects of any type of opioids and control (placebo or no intervention) on knee or hip pain. Values on x-axis denote standardised mean differences. The plot is stratified according to type of opioids. Matsumoto 2005 contributed with two comparisons and the standard error was inflated and the number of patients in the placebo group was halfed to avoid duplicate counting of patients when including both comparisons in the overall meta-analysis. Data relating to the 3, 3, 3, and 2 active intervention arms in Caldwell 2002, Chindalore 2005, Kivitz 2006, and Matsumoto 2005, respectively, were pooled.

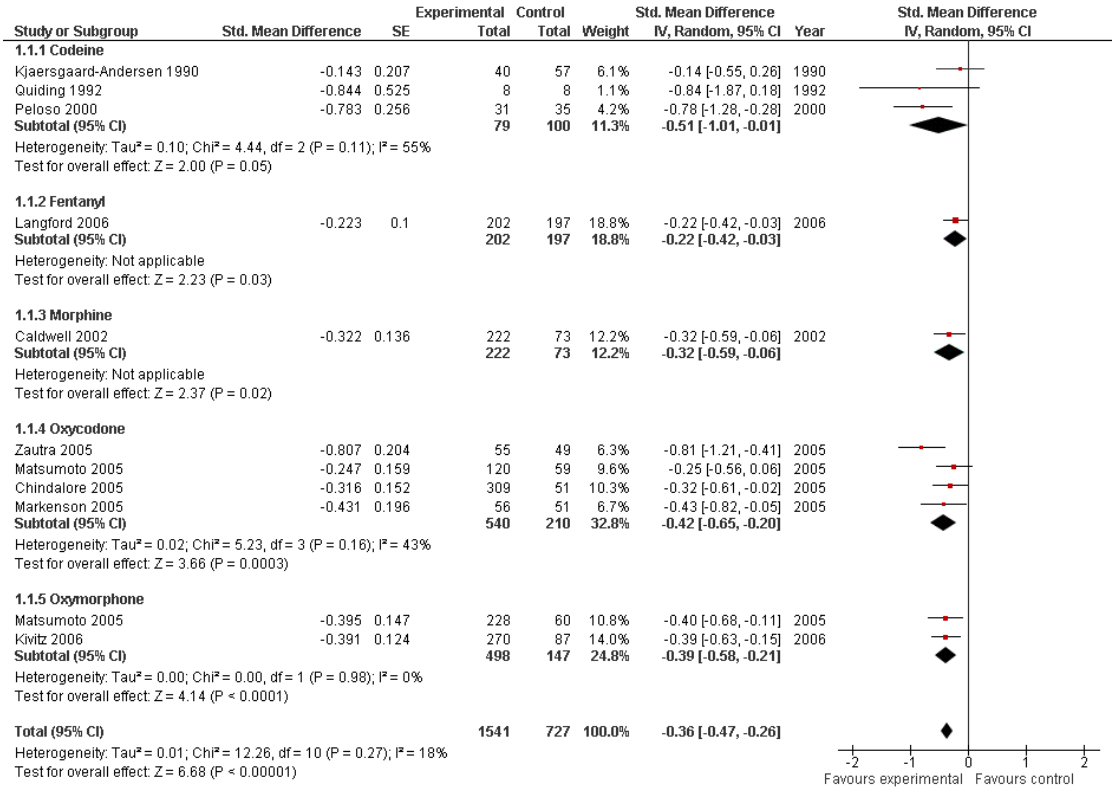


Figure 4. Funnel plot for effects on knee or hip pain.
Numbers on x-axis refer to standardised mean differences (SMDs), on y-axis to standard errors of SMDs.

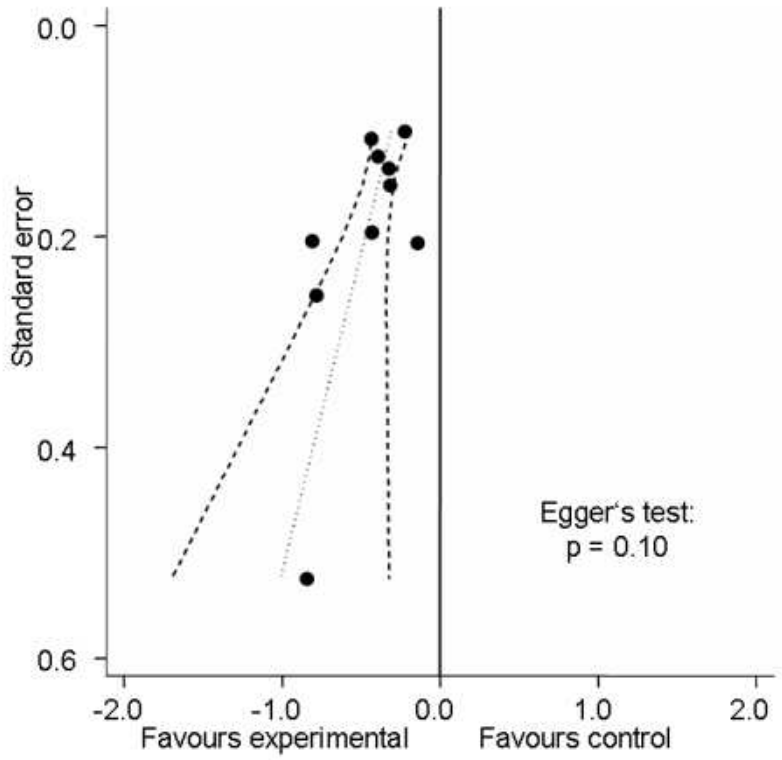


Figure 5. Standardised mean differences of knee or hip pain (y-axis) are plotted against total daily dose of morphine equivalents (x-axis). The size of the circles is proportional to the random-effects weights that were used in the meta-regression. The dotted line indicates predicted treatment effects (regression line) from univariable meta-regression by using daily morphine equivalence doses the explanatory variable, and dashed lines represent the 95% CIs.

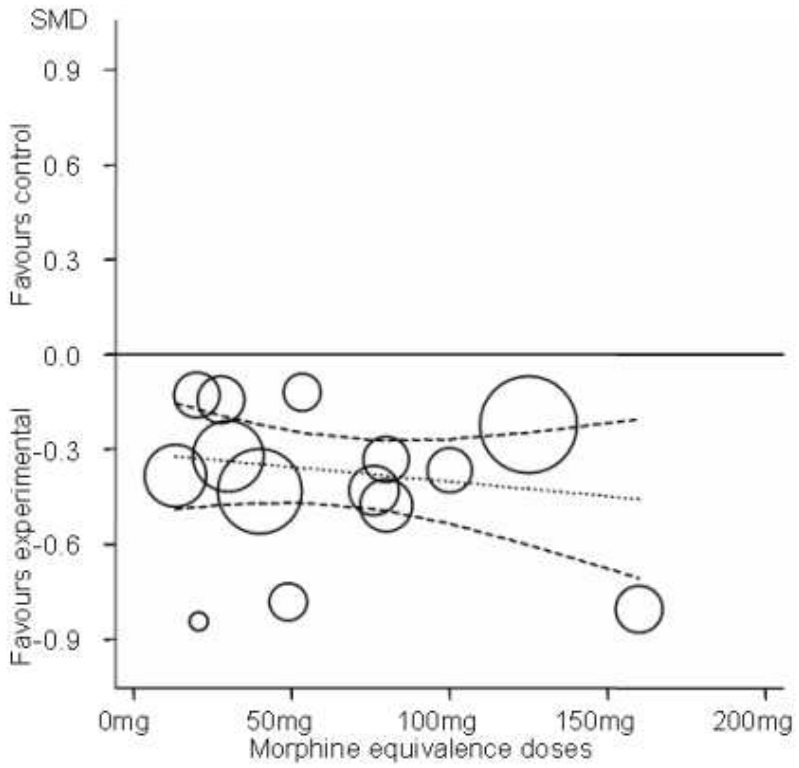


Table 1. Stratified analyses: pain

Variable	Number of studies	N of patients opioids	N of patients control	Pain intensity SMD (95% CI)	Hetero-geneity I^2 (%)	P-value*
All trials	10	1541	727	-0.36 (-0.47 to -0.26)	18%	
Analgesic potency						0.74
Weak	3	79	100	-0.51 (-1.01 to -0.01)	55%	
Strong	7	1462	627	-0.38 (-0.49 to -0.26)	19%	
Route of administration						0.14
Oral	9	1339	530	-0.42 (-0.54 to -0.31)	12%	
Transdermal	1	202	197	-0.22 (-0.42 to -0.03)	N/A	
Allocation concealment						0.96
Adequate	4	583	384	-0.42 (-0.64 to -0.20)	56%	
Inadequate or unclear	6	958	343	-0.38 (-0.52 to -0.25)	3%	
Type of control intervention						0.53
Placebo	8	1493	662	-0.40 (-0.52 to -0.28)	30%	
No intervention	2	48	65	-0.33 (-0.93 to 0.28)	35%	

Table 1. Stratified analyses: pain (*Continued*)

Number of patients randomised						0.15
> 200	5	1351	527	-0.33 (-0.44 to -0.23)	0%	
≤ 200	5	190	200	-0.55 (-0.83 to -0.27)	42%	
Duration of treatment						0.23
> 1 month	2	258	248	-0.27 (-0.44 to -0.09)	0%	
≤ 1 month	8	1283	479	-0.43 (-0.56 to -0.29)	23%	
Use of analgesic co-interventions						0.66
Similar between groups	3	289	283	-0.41 (-0.71 to -0.11)	56%	
Unclear	7	1252	444	-0.40 (-0.53 to -0.28)	14%	

*P-value for interaction

Function

Seven studies including 1172 patients in experimental groups and 622 patients in control groups contributed to the analysis of function. Improvement of function was larger in opioid treated patients compared to control groups (SMD -0.33, 95% CI -0.45 to -0.12) (Figure 6), which corresponds to a difference in function scores of 0.7 units between opioids and placebo on a standardised WOMAC disability scale ranging from 0 to 10. This corresponds to a difference in improvement of 13% (95% CI 9% to 18%) between opioids and placebo (Summary of findings for the main comparison). The estimated difference in the percentage of treatment responders between patients allocated to opioids and patients allocated to placebo of 3% translated into an NNT to cause one additional treatment response on function of 30 (95% CI 22 to 46) (Summary of findings for the main comparison). An I^2 of 24% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.24). We found a moderate benefit for codeine (SMD -0.42, 95% CI -0.74 to -0.10; 2 trials) and oxycodone (SMD -0.44, 95% CI -1.12 to 0.24; 2 trials) and small effects for oxymorphone (SMD -0.32, 95% CI -0.50 to -0.13; 2 trials), morphine (SMD -0.29, 95% CI -0.56 to -0.03; 1 trial) and transdermal fentanyl (SMD -0.28, 95% CI -0.48 to -0.09; 1 trial). As was the case for pain, confidence intervals of estimates were wide and a test for interaction between benefit and type of opioid was non-significant (P = 0.98). Heterogeneity between the two trials that studied effects of oxycodone was high with an I^2 estimate of 86% (P for heterogeneity < 0.001), but low for the other types of opioid. The funnel plot (Figure 7) appeared somewhat asymmetrical (asymmetry coefficient -2.49, 95% CI -5.75 to 0.77, P for asymmetry = 0.07). Table 2 presents the results of the stratified analyses. Again, we found little evidence for an association of SMDs with analgesic potency, route of administration,

type of control intervention, treatment duration, use of analgesic co-interventions, and allocation concealment. Adequately powered trials with more than 200 randomised patients tended to show smaller improvements of function (P for interaction = 0.09). Ten comparisons from seven trials contributed to the analysis of a linear association between equivalence dose and treatment benefit for function (Figure 8). We found no evidence for an association between daily equivalence doses and improvement of function (P = 0.82).

Figure 6. Forest plot of 7 trials comparing the effects of any type of opioids and control (placebo or no intervention) on function. Values on x-axis denote standardised mean differences. The plot is stratified according to type of opioids. Matsumoto 2005 contributed with two comparisons and the standard error was inflated and the number of patients in the placebo group was halved to avoid duplicate counting of patients when including both comparisons in the overall meta-analysis. Data relating to the 3, 3, and 2 active intervention arms in Caldwell 2002, Kivitz 2006, and Matsumoto 2005, respectively, were pooled.

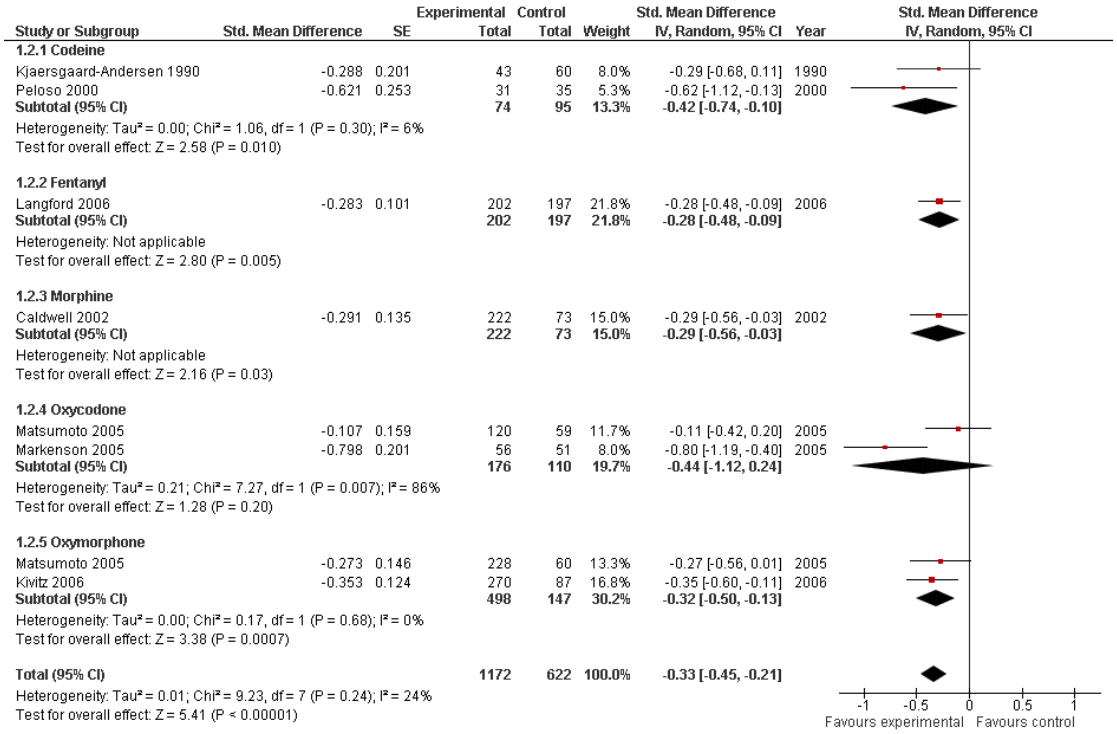


Figure 7. Funnel plot for effects on functioning of the knee or hip.
Numbers on x-axis refer to standardised mean differences (SMDs), on y-axis to standard errors of SMDs

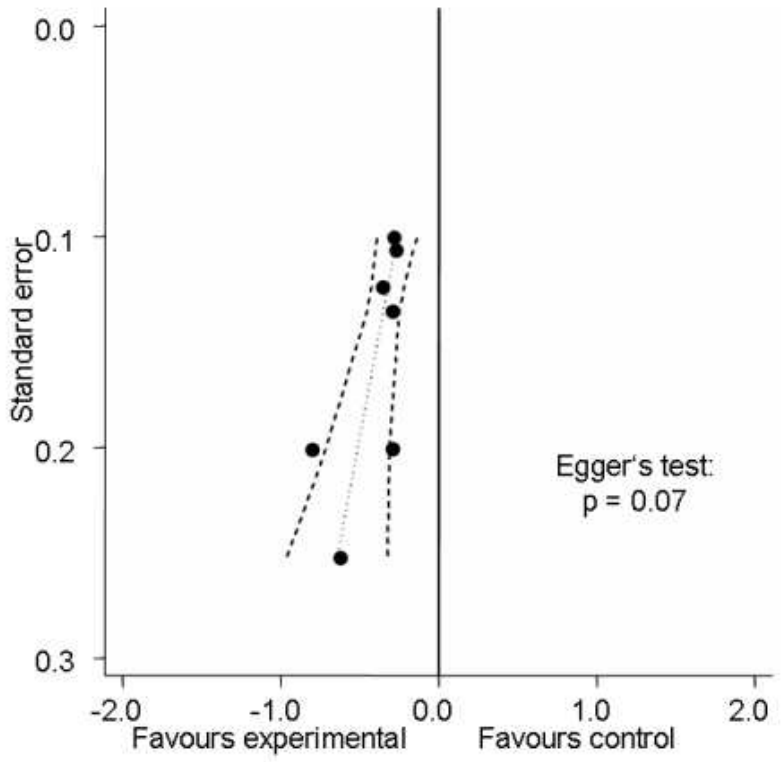


Figure 8. Standardised mean differences of function (y-axis) are plotted against total daily dose of morphine equivalents (x-axis). The size of the circles is proportional to the random-effects weights that were used in the meta-regression. The dotted line indicates predicted treatment effects (regression line) from uni-variable meta-regression by using daily morphine equivalence doses the explanatory variable, and dashed lines represent the 95% CIs.

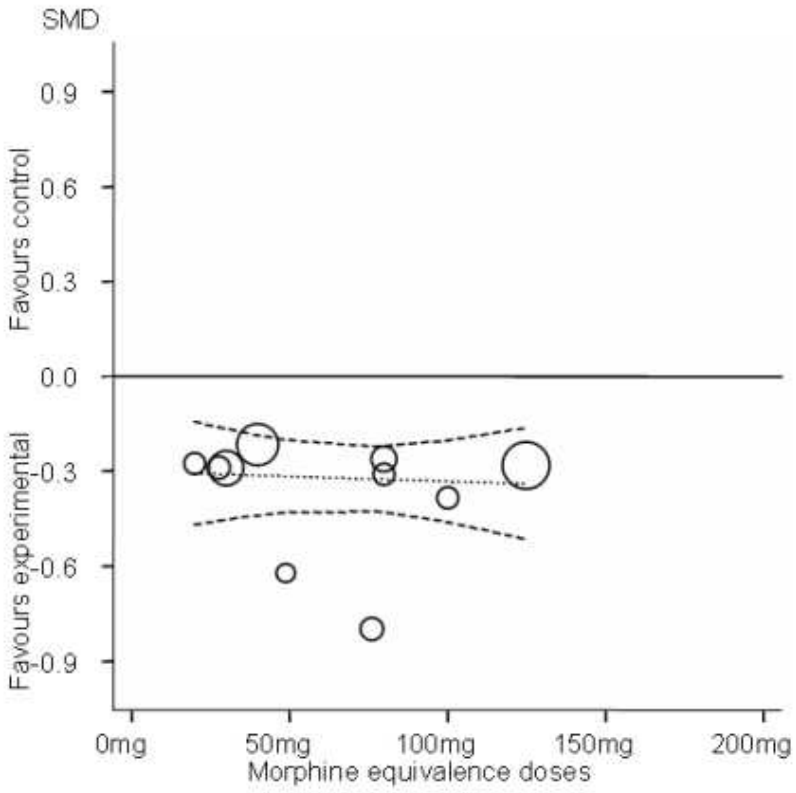


Table 2. Stratified analyses: function

Variable	Number of studies	N of patients opioids	N of patients control	Function SMD (95% CI)	Hetero-geneity I^2 (%)	P-value*
All trials	7	1172	622	-0.33 (-0.45 to -0.21)	24%	
Analgesic potency						0.68

Table 2. Stratified analyses: function (*Continued*)

Weak	2	74	95	-0.42 (-0.74 to -0.10)	6%	
Strong	5	1098	527	-0.35 (-0.48 to -0.21)	34%	
Route of administration						0.58
Oral	6	970	425	-0.38 (-0.53 to -0.23)	28%	
Transdermal	1	202	197	-0.28 (-0.48 to -0.09)	N/A	
Allocation concealment						0.60
Adequate	3	528	335	-0.43 (-0.68 to -0.18)	62%	
Inadequate or unclear	4	644	287	-0.31 (-0.45 to -0.16)	0%	
Type of control intervention						0.83
Placebo	6	1129	562	-0.36 (-0.50 to -0.23)	32%	
No intervention	1	43	60	-0.29 (-0.68 to 0.11)	N/A	
Number of patients randomised						0.09
> 200	4	1042	476	-0.29 (-0.41 to -0.18)	0%	
≤ 200	3	130	146	-0.56 (-0.88 to -0.25)	39%	
Duration of treatment						0.55

Table 2. Stratified analyses: function (*Continued*)

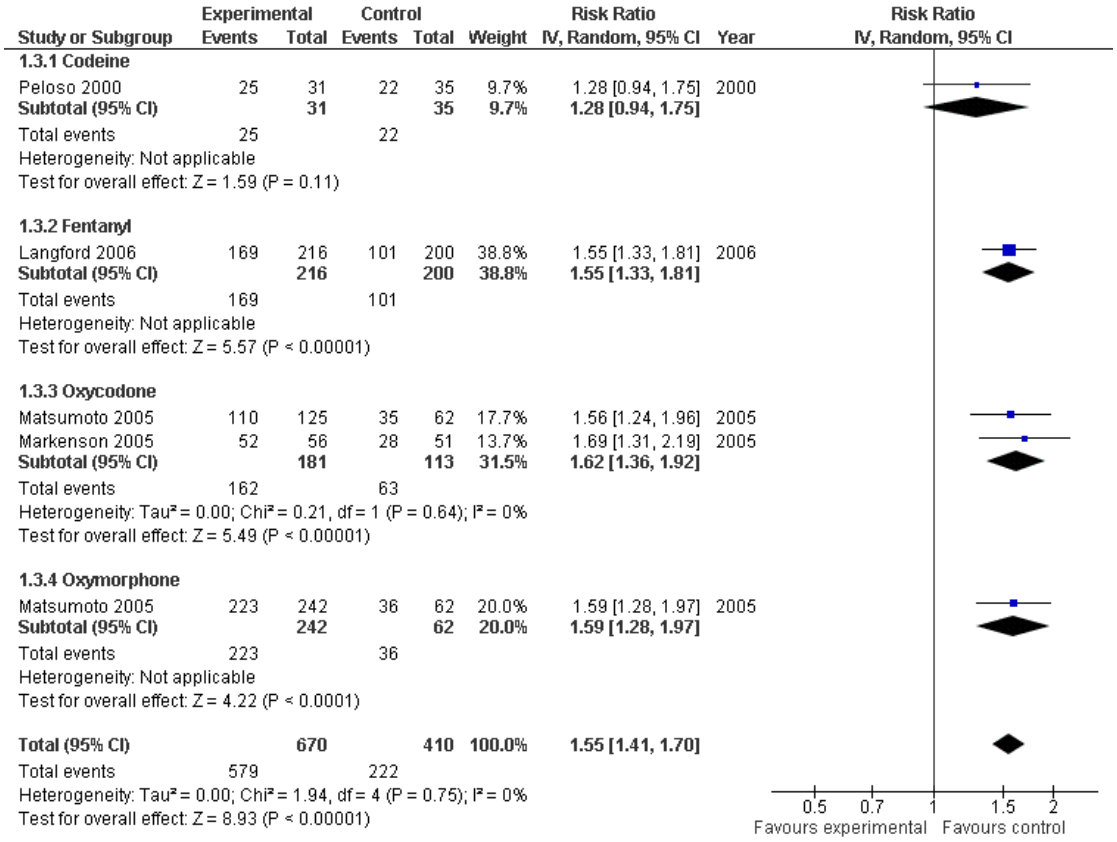
> 1 month	2	258	248	-0.51 (-1.01 to -0.01)	81%	
≤ 1 month	5	914	374	-0.32 (-0.44 to -0.19)	0%	
Use of analgesic co-interventions						0.29
Similar between groups	3	289	283	-0.53 (-0.88 to -0.18)	67%	
Unclear	4	883	339	-0.30 (-0.43 to -0.17)	0%	

*P-value for interaction

Secondary outcomes

Four trials reported the occurrence of any adverse event in 579 out of 670 patients in experimental groups and 222 of 410 patients in control groups (Figure 9). Patients were 55% more likely to experience adverse events in experimental groups compared to placebo (RR 1.55, 95% CI 1.41 to 1.70). The NNH to cause one additional patient to experience an adverse event, as compared to placebo, was 12 (95% CI 10 to 16) (Summary of findings for the main comparison). Results were consistent between different studies (I^2 = 0%, P for heterogeneity = 0.75) and different types of opioids (P for interaction = 0.95). Due to the low number of trials, we did not perform an analysis of the association between equivalence dose and log relative risk for this outcome.

Figure 9. Forest plot of 4 trials comparing patients experiencing any adverse event between any opioid and control (placebo or no intervention). Values on x-axis denote risks ratios. The plot is stratified according to type of opioid. Matsumoto 2005 contributed with two comparisons and the number of patients in the placebo group was halved to avoid duplicate counting of patients when including both comparisons in the overall meta-analysis.



Ten trials with 2403 patients contributed to the meta-analysis of patients withdrawn or dropped out because of adverse events (Figure 10). Patients receiving opioid therapy were four times as likely as patients receiving placebo to be withdrawn or drop out due to adverse events (RR 4.05, 95% CI 3.06 to 5.38), with little between trial heterogeneity (I^2 = 8%, P for heterogeneity = 0.37). The NNH to cause one additional dropout or withdrawal due to adverse events compared with placebo was 19 (95% CI 13 to 29) (Summary of findings for the main comparison). We found the highest pooled risk ratio for oxycodone versus placebo (RR 7.75, 95% CI 3.76 to 15.97) and the lowest pooled RR for transdermal fentanyl versus placebo (RR 2.63, 95% CI 1.64 to 4.23) but confidence intervals were wide and a test for interaction between type of opioids and relative risk of being withdrawn or dropping out because of adverse events negative gave a P for interaction of 0.38. Fourteen comparisons in 10 trials contributed to the analysis of the association between equivalence dose and log relative risk (Figure 11). We found little evidence for a relationship (P = 0.76).

Figure 10. Forest plot of 10 trials comparing patients withdrawn or dropped out because of adverse events between any opioid and control (placebo or no intervention). Values on x-axis denote risks ratios. The plot is stratified according to type of opioid. Matsumoto 2005 contributed with two comparisons and the number of patients in the placebo group was halved to avoid duplicate counting of patients when including both comparisons in the overall meta-analysis. The risk ratio in one trial could not be estimated because no withdrawals or dropouts because of adverse events occurred in either group.

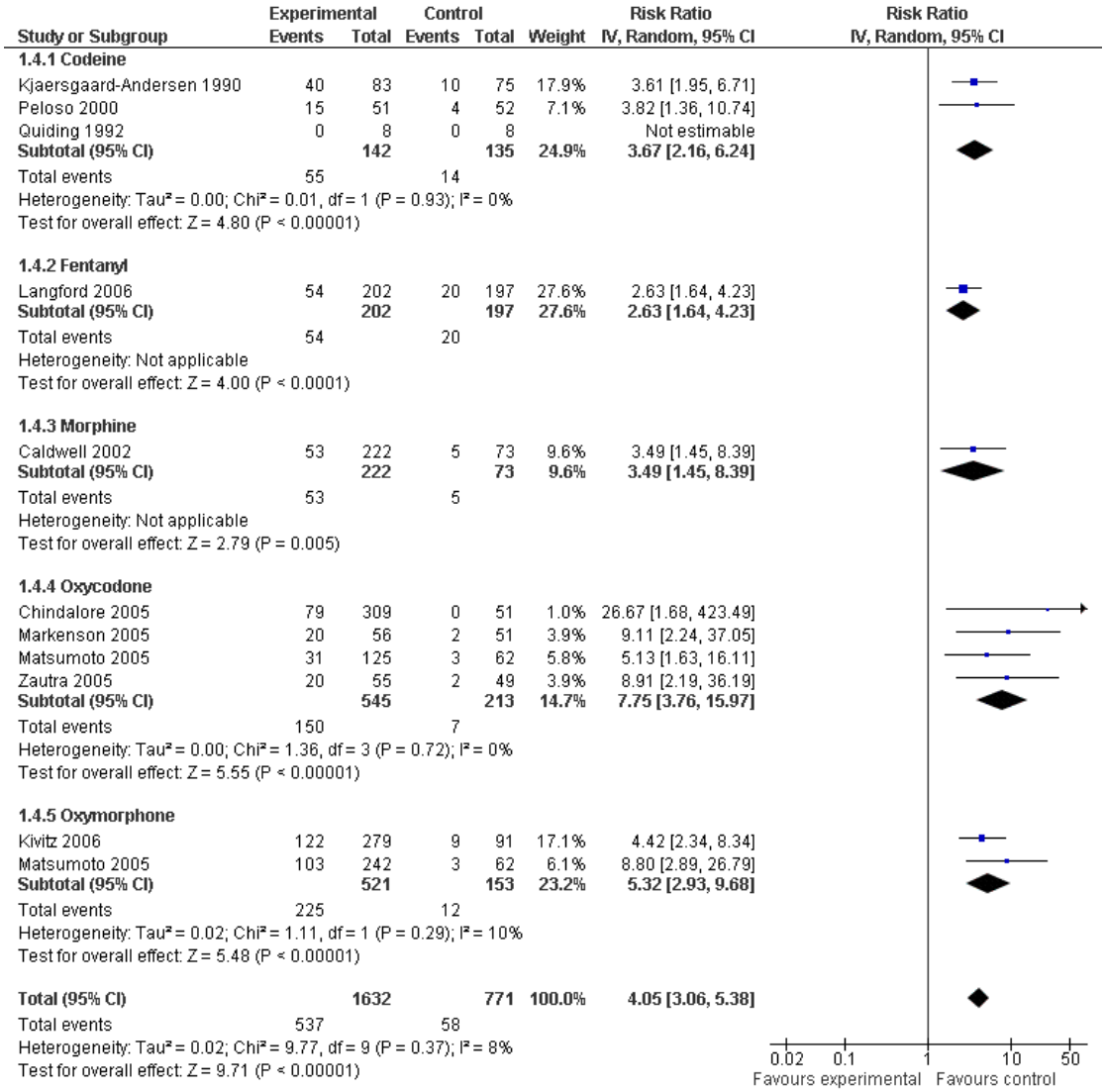
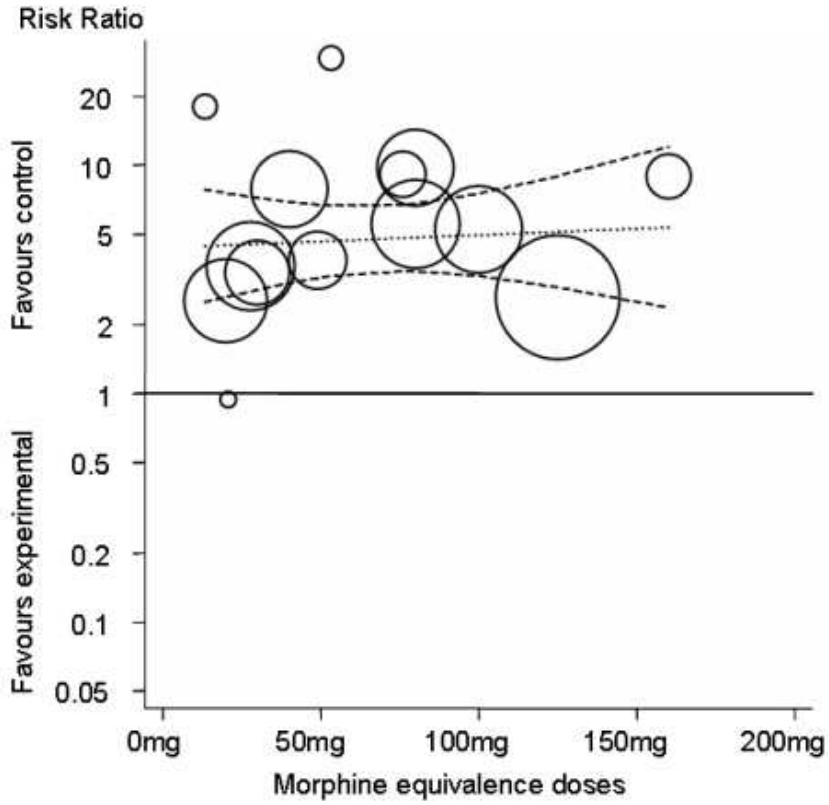
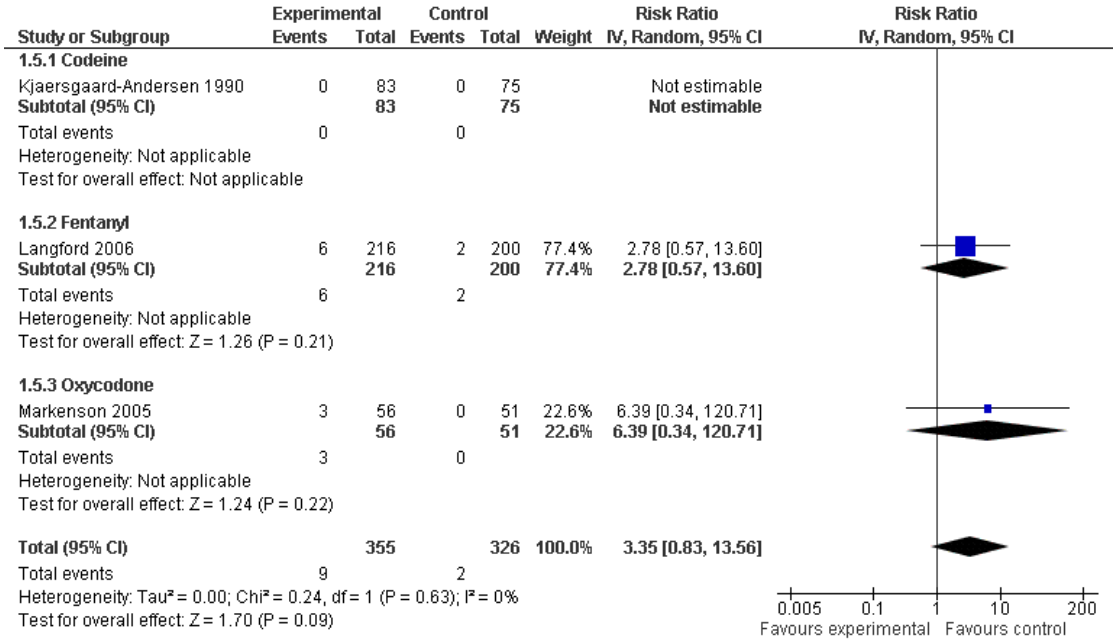


Figure 11. Risk ratios of patients withdrawn or dropped out because of adverse events between opioids and control groups (y-axis) are plotted against total daily dose of morphine equivalents (x-axis). The size of the circles is proportional to the random-effects weights that were used in the meta-regression. The dotted line indicates predicted treatment effects (regression line) from uni-variable meta-regression by using daily morphine equivalence doses the explanatory variable, and dashed lines represent the 95% CIs.



Three trials with 681 patients contributed to the analysis of patients experiencing any serious adverse event (Figure 12). Of the three trials, one trial reported that no patient experienced a serious adverse event (Kjaersgaard-Andersen 1990). Overall data from the remaining two trials indicated that patients receiving opioids tended be more likely to experience a serious adverse event (RR 3.35, 95% CI 0.83 to 13.56). Due to the low number of trials and events, we neither performed an analysis of the association between equivalence dose and log relative risk for this outcome, nor a calculation of NNH to cause one additional patient to experience a serious adverse event compared with placebo. Only one trial contributed to the meta-analysis of symptoms of opioid dependency (Langford 2006). The study assessed opiate withdrawal symptoms after eight weeks of transdermal fentanyl therapy, using the Short Opiate Withdrawal Scale questionnaire (Gossop 1990; Langford 2006). Patients in the fentanyl group reported more severe withdrawal symptoms compared with the placebo group with an SMD of 0.60 (95% CI 0.42 to 0.79), which corresponds to a mean difference on the Short Opiate Withdrawal Scale of 0.27; the scale ranges from 0 to 3.

Figure 12. Forest plot of 3 trials comparing patients experiencing any adverse event between any opioid and control (placebo or no intervention). Values on x-axis denote risks ratios. The plot is stratified according to type of opioid. The risk ratio in one trial could not be estimated because no serious adverse event occurred in either group.



DISCUSSION

Summary of main results

In our systematic review and meta-analysis we found oral or transdermal opioids more effective than placebo in terms of pain relief and improvement of function in osteoarthritis patients. However, benefits were only small to moderate. The occurrence of adverse events often caused patients to stop taking the opioids, which is likely to limit the usefulness of opioids in the long term. The potentially higher risk of serious adverse events and substance addiction might further limit their use. The reporting of safety outcomes was incomplete and adverse events were reported in four trials, and serious adverse events in three trials only.

Quality of the evidence

Most of the trials were funded by the pharmaceutical industry and we did not have enough data to explore whether the type of funding was associated with the estimated treatment effects. The effectiveness of opioids may drop after chronic use as the effects of opioids are mediated through opioids receptors. Our analysis of this characteristic was hampered by the low number of studies (two only) reporting opioid use for more than four weeks. The relatively low dose of morphine equivalents (median daily dose 51 mg) administered in the included trials might provide an explanation of the small benefits observed as compared with other studies (Maier 2002). Our ability to provide a reliable assessment of dose dependency might have been hampered by the generally low morphine equivalent doses used and the lack of individual participant data.

Data on risks of addiction due to opioids therapy is scarce, and currently available trials are not designed to evaluate these issues. There is a clear need for additional randomised trials and observational studies using longer follow-up times to address the risks of substance dependence associated with different opioids. In this systematic review only one trial reported measures of the severity of withdrawal symptoms (Langford 2006). Similar to previous systematic reviews of randomised trials on opioids therapy for non-cancer pain (Kalso 2004; Furlan 2006), we found that most of the trials included in our review had a treatment duration of several days or a few weeks only. This is too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition like osteoarthritis. While no evidence of long-term effects is available from randomised trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief (Eriksen 2006).

Potential biases in the review process

We based our review on a broad literature search. Even though we cannot exclude potential publication bias, it seems rather unlikely that we missed relevant trials (Egger 2003). Selection of trials and data extraction were performed independently by two review authors to minimise bias and transcription errors (Egger 2001; Gøtzsche 2007). The most recent systematic review on opioids for osteoarthritis (Avouac 2007), updated in October 2006, considered 18 studies that compared opioids to placebo. We included data from six of these in our meta-analysis and data from four additional trials (Kjaersgaard-Andersen 1990; Quiding 1992; Matsumoto 2005; Kivitz 2006). We excluded six trials with tramadol as the experimental intervention and one trial that was likely to have included only a minority of osteoarthritis patients. In conclusion, we are likely to have included all relevant trials in our systematic review.

Agreements and disagreements with other studies or reviews

We excluded tramadol from our review to avoid overlap with another Cochrane Review that focused on this specific opioid in osteoarthritis (Cepeda 2006). Extracted pain and function outcomes and follow-up time in the previous systematic review about opioids for osteoarthritis (Avouac 2007) were similar to our systematic review. Comparing opioids with placebo controls, Avouac 2007 found a large pooled effects for pain intensity (SMD -0.79, 95% CI -0.98 to -0.59) and a moderate pooled effect for function (SMD -0.31, 95% CI -0.39 to -0.24). These effects are consistent with our results for function but are substantially larger for pain reduction. This discrepancy might be due to the exclusion of some trials in our systematic review. Avouac 2007 reported moderate to large effects of tramadol for pain, between -0.36 to -0.93 standard deviation units, in several large trials and unrealistically large beneficial effects on pain intensity in an oxycodone trial that was excluded from our review (Roth 2000). These trials often did not report function outcomes and could not, therefore, contribute to the pooled analysis, or they reported considerably smaller effects for function than for pain (Avouac 2007). In line with other studies, we found that adverse events occurring in patients treated with opioids often caused withdrawals and dropouts (Kalso 2004; Furlan 2006; Avouac 2007). Tramadol may be similar to or even more effective than the opioids evaluated in our review, in reducing pain and improving function, but safety concerns have to be addressed further (Cepeda 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Opioids decrease pain intensity and improve function but the ben-

efits observed are small to moderate and increases in doses do not appear to result in further pain reduction. The occurrence of adverse events often caused patients to stop taking the preparations, which is likely to limit their usefulness in the long-term treatment of osteoarthritis of the hip or knee. The higher risk of serious adverse events and the potential occurrence of addiction to opioid therapy might further limit their clinical use. Taken together, our results indicate that the small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Even in patients with severe osteoarthritic pain, clinicians are advised to use non-tramadol opioids cautiously and to consider alternatives, such as surgery. In addition, clinicians should inform patients about the substantial risks and only moderate benefits of opioid treatment and therapeutic alternatives.

Implications for research

The effectiveness and safety of opioid and non-opioid analgesics should be directly compared in appropriately powered randomised controlled trials accompanied by network meta-analyses, which integrate direct and indirect evidence in one single analysis while maintaining randomisation (Caldwell 2005). Efficacy and safety data on transdermal opioids are scarce (one trial) suggesting the need for further trials using transdermal preparations. Further trials might be required to better evaluate the effects of the route of administration, the difference between weak and strong opioids, and dose effects. The evidence of the effectiveness and safety of opioid therapy is mainly from a few short-term trials, despite the fact that the underlying condition is chronic and requires safe, long-term treatments (Kalso 2004; Furlan 2006). Further long-term randomised trials or observational studies are needed to increase our understanding of their long-term effectiveness, safety, and the potential for addiction.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Caldwell 2002

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 4 weeks Multicentre trial No power calculation reported
Participants	Patients with prior suboptimal analgesic response to NSAIDs/paracetamol or previous intermittent opioid therapy were eligible 295 patients with knee and/or hip osteoarthritis were reported at baseline Number of females: 184 of 295 (62%) Average age: 62 years
Interventions	*Experimental interventions* a) oral morphine (Avinza), 30mg once daily in the morning b) oral morphine (Avinza), 30mg once daily in the evening c) oral morphine sulphate (Contin), 15mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 4 weeks No analgesics other than study drugs allowed
Outcomes	Extracted pain outcome: global pain after 4 weeks Extracted function outcome: WOMAC disability subscore after 4 weeks Primary outcome: WOMAC OA index
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Unclear	No information provided.

Caldwell 2002 (*Continued*)

Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	No	
Double-dummy technique used?	Yes	
Intention-to-treat analysis performed? Pain	No	No information on exclusions available.
Intention-to-treat analysis performed? Function	No	No information on exclusions available.
No funding by commercial organisation?	No	Sponsor: Elan

Chindalore 2005

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 4 weeks Randomisation stratified according to gender Multicentre trial with 37 centres No power calculation reported
Participants	Patients with moderate to severe hip or knee pain while taking ≥1 oral analgesic medication were eligible 362 patients were randomised 360 patients with hip or knee osteoarthritis were reported at baseline Number of females: 249 of 360 (69%) Average age: 54 years
Interventions	*Experimental interventions* a) oral oxycodone, 10mg 4-times daily b) oral oxycodone, 2.5 mg 4-times daily, plus naltrexone, 0.001 mg 4-times daily (Oxytrex) c) oral oxycodone, 2.5 mg 4-times daily, plus natronex, 0.001 mg twice daily (Oxytrex) *Control intervention* Placebo, twice daily Treatment duration: 3 weeks Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups

Chindalore 2005 (*Continued*)

Outcomes	Extracted pain outcome: global pain after 4 weeks Extracted function outcome: WOMAC disability subscore after 4 weeks Primary outcome: pain intensity during the past 24 hours
Notes	For WOMAC disability, insufficient data were reported to calculate standardised mean differences and it was therefore not included in the meta-analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	1 of 310 patients (0.3%) excluded in experimental groups, 1 of 52 patients (1.9%) excluded in control group.
Intention-to-treat analysis performed? Function	No	1 of 310 patients (0.3%) excluded in experimental groups, 1 of 52 (1.9%) patients excluded in control group.
No funding by commercial organisation?	No	Sponsor: Pain Therapeutics

Kivitz 2006

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 2 weeks Multicentre trial Power calculation reported
Participants	Patients with suboptimal analgesic response to NSAIDs/paracetamol or previous opioid therapy were eligible 370 patients were randomised 370 patients with knee or hip osteoarthritis were reported at baseline Affected joints: 297 knees and 73 hips Number of females: 224 of 370 (61%)
Interventions	*Experimental interventions* a) oral extended-release oxymorphone, 10mg twice daily b) oral extended-release oxymorphone, 40mg twice daily c) oral extended-release oxymorphone, 50mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 2 weeks No analgesics other than study drugs allowed.
Outcomes	Extracted pain outcome: global pain after 2 weeks. Extracted function outcome: WOMAC disability subscore after 2 weeks Primary outcome: change in pain intensity
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	No	

Kivitz 2006 (*Continued*)

Double-dummy technique used?	Yes	
Intention-to-treat analysis performed? Pain	No	9 of 279 patients (0.7%) excluded in experimental groups, 4 of 91 patients (4.4%) excluded in control group.
Intention-to-treat analysis performed? Function	No	9 of 279 patients (0.7%) excluded in experimental groups, 4 of 91 patients (4.4%) excluded in control group.
No funding by commercial organisation?	No	Sponsor: Endo Pharmaceuticals Inc, Penwest Pharmaceuticals Co.

Kjaersgaard-Andersen 1990

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 4 weeks Multicentre trial with 7 centres Power calculation reported
Participants	Patients with chronic pain requiring analgesic treatment were eligible 158 patients with hip osteoarthritis were reported at baseline Affected joints: 158 hips Number of females: 72 of 158 (46%) Average age: 66 years Average BMI: 26 kg/m^2
Interventions	*Experimental intervention* Oral codeine 60 mg plus paracetamol 1000 mg, 3 times daily *Control intervention* Paracetamol 1000 mg, 3 times daily Treatment duration: 4 weeks No analgesics other than study drugs allowed
Outcomes	Extracted pain outcome: global pain after 4 weeks Extracted function outcome: patient's global assessment after 4 weeks
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided.

Kjaersgaard-Andersen 1990 (*Continued*)

Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Unclear	No information provided.
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	43 of 83 patients (52%) excluded in experimental group, 18 of 75 patients (24%) excluded in control group.
Intention-to-treat analysis performed? Function	No	40 of 83 patients (48%) excluded in experimental group, 15 of 75 patients (20%) excluded in control group.
No funding by commercial organisation?	Unclear	No information provided.

Langford 2006

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 8 weeks Randomisation stratified according to target joint (knee/hip) Multicentre trial Power calculation reported
Participants	Patients without adequate pain control under weak opioid treatment (with and without paracetamol) were eligible 416 patients were randomised 399 patients with knee or hip osteoarthritis were reported at baseline Affected joints: 211 knees and 188 hips Number of females: 265 of 399 (66%)
Interventions	*Experimental intervention* Transdermal fentanyl (Durogesic), median dosage 25μg/hour *Control intervention* Placebo Treatment duration: 6 weeks

Langford 2006 (*Continued*)

	Analgesics other than study drugs allowed and intake assessed, but unclear whether intake was similar between groups
Outcomes	Extracted pain outcome: global pain after 8 weeks Extracted function outcome: WOMAC disability subscore after 8 weeks Primary outcome: pain relief on VAS
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Unclear	No information provided.
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	No information on exclusions available.
Intention-to-treat analysis performed? Function	No	No information on exclusions available.
No funding by commercial organisation?	No	Sponsor: Janssen-Cilag

Markenson 2005

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 13 weeks Multicentre trial with 9 centres Power calculation reported
Participants	Patients with moderate to severe pain while taking NSAIDs/paracetamol, with contraindications to NSAID therapy or with previous oral opioid therapy were eligible 109 patients were randomised 107 patients with osteoarthritis were reported at baseline Affected joints: 33 knees, 19 hips, and 57 other joints Number of females: 78 of 107 (73%) Average age: 63 years
Interventions	*Experimental intervention* Oral oxycodone (OxyContin), 10mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 13 weeks Analgesics other than study drugs allowed and intake assessed, but unclear whether intake was similar
Outcomes	Extracted pain outcome: global pain after 13 weeks Extracted function outcome: WOMAC global scale after 13 weeks
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	Yes	

Markenson 2005 (*Continued*)

Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	No information on exclusions available.
Intention-to-treat analysis performed? Function	No	No information on exclusions available.
No funding by commercial organisation?	No	Sponsor: Purdue Pharma

Matsumoto 2005

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 4 weeks Simple randomisation Multicentre trial Power calculation reported
Participants	Patients with suboptimal analgesic response to NSAIDs, paracetamol, or opioids were eligible 491 patients were randomised 489 patients with OA were reported at baseline Affected joints: 373 knees and 116 hips Number of females: 297 of 489 (61%) Average age: 62 years Average BMI: 34 kg/m^2
Interventions	*Experimental interventions* a) Oral extended-release oxymorphone, 20mg twice daily b) Oral extended-release oxymorphone, 40mg twice daily c) Oral controlled-release oxycodone, 20mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 4 weeks No analgesics other than study drugs allowed
Outcomes	Extracted pain outcome: WOMAC pain subscore after 4 weeks Extracted function outcome: WOMAC disability subscore after 4 weeks Primary outcome: change in arthritis pain intensity
Notes	
Risk of bias	

Matsumoto 2005 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	19 of 367 patients (5.2%) excluded in experimental groups, 5 of 124 (4.0%) patients excluded in control group.
Intention-to-treat analysis performed? Function	No	19 of 367 patients (5.2%) excluded in experimental groups, 5 of 124 (4.0%) patients excluded in control group.
No funding by commercial organisation?	No	Sponsors: TheraQuest Biosciences, Endo Pharmaceuticals, Penwest Pharmaceuticals Co.

Peloso 2000

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 4 weeks Multicentre trial with 4 centres Power calculation reported
Participants	Patients with osteoarthritis symptoms requiring therapy with paracetamol, anti-inflammatory agents or opioids were eligible. 103 patients were randomised 103 patients with osteoarthritis were reported at baseline Affected joints: 94 knees and 49 hips Number of females: 64 of 103 (62%) Average age: 62 years Average BMI: 34 kg/m^2

Peloso 2000 (*Continued*)

	Average disease duration: 10.3 years
Interventions	*Experimental intervention* Oral codeine (Contin), 100mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 4 weeks Analgesics other than study drugs allowed and intake assessed, but unclear whether intake was similar between groups
Outcomes	Extracted pain outcome: global pain after 4 weeks Extracted function outcome: WOMAC disability subscore after 4 weeks Primary outcome: WOMAC pain and overall pain intensity
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Unclear	No information provided.
Blinding of outcome assessors?	Unclear	No information provided.
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	20 of 51 patients (39%) excluded in experimental group, 17 of 52 patients (33%) excluded in control group.
Intention-to-treat analysis performed? Function	No	20 of 51 patients (39%) excluded in experimental group, 17 of 52 patients (33%) excluded in control group.
No funding by commercial organisation?	No	Sponsor: Purdue Frederick

Quiding 1992

Methods	Randomised controlled trial 3-arm crossover design Trial duration: 1 week No power calculation reported
Participants	Patients in need of analgesic medication for hip osteoarthritis were eligible 27 patients were randomised 26 patients with OA were reported at baseline Affected joints: 26 hips Number of females: 22 of 26 (85%) Average age: 53 years
Interventions	*Experimental intervention* 30 mg oral codeine plus 200 mg ibuprofen, 6 times in 32 hours *Control intervention* 200 mg ibuprofen, 6 times in 32 hours Treatment duration: 32 hours No analgesics other than study drugs allowed
Outcomes	Extracted pain outcome: global pain after 1 week No function outcome reported No primary outcome reported
Notes	1 trial arm excluded from review

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Described as double-blind?	Yes	
Blinding of patients?	Yes	
Blinding of physicians?	Unclear	No information provided.
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	No	
Double-dummy technique used?	Yes	

Quiding 1992 (*Continued*)

Intention-to-treat analysis performed? Pain	Unclear	No information on exclusions available.
Intention-to-treat analysis performed? Function	Unclear	Not applicable, no function outcome reported.
No funding by commercial organisation?	Unclear	No information provided.

Zautra 2005

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 13 weeks Multicentre trial with 9 centres No power calculation reported
Participants	107 patients were randomised 104 patients with knee osteoarthritis were reported at baseline Number of females: 76 of 104 (73%) Average age: 63 years
Interventions	*Experimental intervention* Oral oxycodone (Oxycontin), 10mg twice daily *Control intervention* Placebo, twice daily Treatment duration: 13 weeks Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups
Outcomes	Extracted pain outcome: global pain after 13 weeks No function outcome reported Primary outcome: coping efficacy and arthritis helplessness
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Yes	
Described as double-blind?	Yes	

Zautra 2005 (*Continued*)

Blinding of patients?	Yes	
Blinding of physicians?	Yes	
Blinding of outcome assessors?	Yes	
Interventions reported as indistinguishable?	Yes	
Double-dummy technique used?	No	
Intention-to-treat analysis performed? Pain	No	1 of 56 patients (1.8%) excluded in experimental group, 2 of 51 patients (3.9%) excluded in control group.
Intention-to-treat analysis performed? Function	Unclear	Not applicable, no function outcome reported.
No funding by commercial organisation?	No	Sponsor: Purdue Pharma

Characteristics of excluded studies *[ordered by study ID]*

Adams 2006	Only active control interventions.
Andrei 1984	Percentage of patients with knee or hip osteoarthritis 17% (5/30).
Boureau 1990	Only active control interventions.
Brooks 1982	Percentage of patients with osteoarthritis 50%, no information about joints involved.
Burch 2004	No randomised controlled trial.
Caldwell 1999	Percentage of patients with knee or hip osteoarthritis likely to be below 50%.
Choquette 2008	No randomised controlled trial.
Doak 1992	Crossover trial providing pooled results only.
Fancourt 1984	Mixed population of rheumatoid arthritis and osteoarthritis, no information about number of patients with osteoarthritis.
Gazi 2005	Only active control interventions.
Hale 2007	Only active control interventions.
Le Loet 2005	Not randomised controlled trial.
McIlwain 2005	Not randomised controlled trial.
Mitchell 1984	Mixed population of rheumatoid arthritis and osteoarthritis, no information about number of patients with osteoarthritis.
Neubauer 1983	Percentage of patients with osteoarthritis 15% (5/33).
Rosenthal 2007	Not randomised controlled trial.
Roth 2000	Percentage of patients with knee or hip osteoarthritis likely to be below 50%.
Salzman 1983	Only active control interventions.
Tassain 2003	Percentage of patients with osteoarthritis 7% (2/28).
Torres 2001	Not randomised controlled trial.
Vignon 1999	Comparison of combination of dextropropoxyphene, acetaminophen, and caffeine with placebo.

(*Continued*)

Vlok 1987	Crossover trial providing pooled results only.
Wallace 1994	Crossover trial providing pooled results only.
Wang 1965	Percentage of patients with osteoarthritis 6% (2/34).

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kroner 1991

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 3 weeks Multicentre trial
Participants	131 patients with hip osteoarthritis were reported at baseline Number of females: 70 of 131 (53%)
Interventions	*Experimental intervention* Codeine 30mg plus paracetamol 500mg *Control intervention* Paracetamol 500mg Treatment duration: 3 weeks
Outcomes	Assessed efficacy outcomes: pain intensity, pain relief, patient's evaluation of the effect of treatment Assessed safety outcomes: number of patients withdrawn due to adverse events, serious adverse events
Notes	Insufficient data provided in published abstract, no full-text article available. Awaiting author response.

DATA AND ANALYSES

Comparison 1. Opioids versus placebo

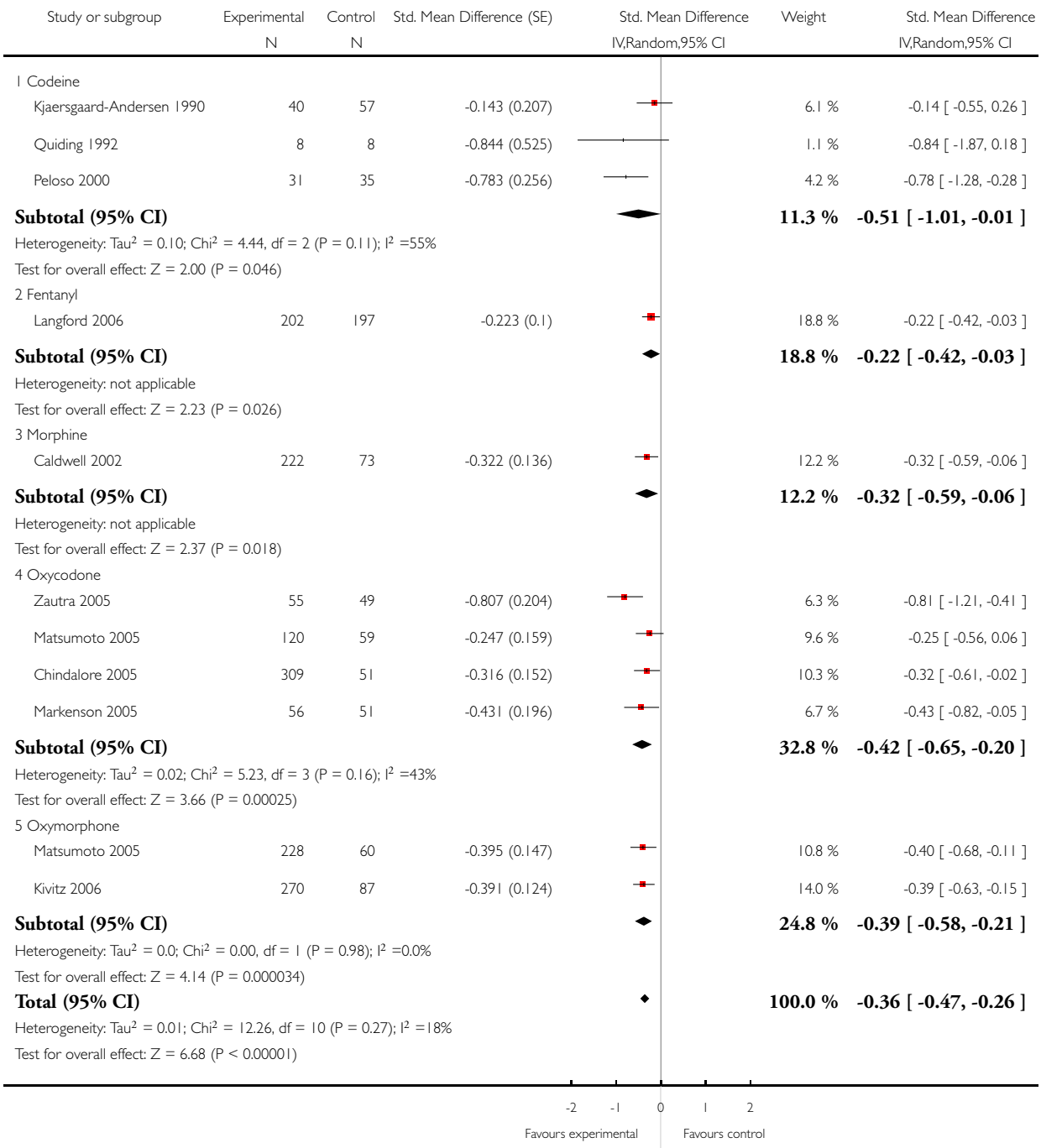
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	10	2268	Std. Mean Difference (Random, 95% CI)	-0.36 [-0.47, -0.26]
1.1 Codeine	3	179	Std. Mean Difference (Random, 95% CI)	-0.51 [-1.01, -0.01]
1.2 Fentanyl	1	399	Std. Mean Difference (Random, 95% CI)	-0.22 [-0.42, -0.03]
1.3 Morphine	1	295	Std. Mean Difference (Random, 95% CI)	-0.32 [-0.59, -0.06]
1.4 Oxycodone	4	750	Std. Mean Difference (Random, 95% CI)	-0.42 [-0.65, -0.20]
1.5 Oxymorphone	2	645	Std. Mean Difference (Random, 95% CI)	-0.39 [-0.58, -0.21]
2 Function	7	1794	Std. Mean Difference (Random, 95% CI)	-0.33 [-0.45, -0.21]
2.1 Codeine	2	169	Std. Mean Difference (Random, 95% CI)	-0.42 [-0.74, -0.10]
2.2 Fentanyl	1	399	Std. Mean Difference (Random, 95% CI)	-0.28 [-0.48, -0.09]
2.3 Morphine	1	295	Std. Mean Difference (Random, 95% CI)	-0.29 [-0.56, -0.03]
2.4 Oxycodone	2	286	Std. Mean Difference (Random, 95% CI)	-0.44 [-1.12, 0.24]
2.5 Oxymorphone	2	645	Std. Mean Difference (Random, 95% CI)	-0.32 [-0.50, -0.13]
3 Number of patients experiencing any adverse event	4	1080	Risk Ratio (IV, Random, 95% CI)	1.55 [1.41, 1.70]
3.1 Codeine	1	66	Risk Ratio (IV, Random, 95% CI)	1.28 [0.94, 1.75]
3.2 Fentanyl	1	416	Risk Ratio (IV, Random, 95% CI)	1.55 [1.33, 1.81]
3.3 Oxycodone	2	294	Risk Ratio (IV, Random, 95% CI)	1.62 [1.36, 1.92]
3.4 Oxymorphone	1	304	Risk Ratio (IV, Random, 95% CI)	1.59 [1.28, 1.97]
4 Number of patients who withdrew because of adverse events	10	2403	Risk Ratio (IV, Random, 95% CI)	4.05 [3.06, 5.38]
4.1 Codeine	3	277	Risk Ratio (IV, Random, 95% CI)	3.67 [2.16, 6.24]
4.2 Fentanyl	1	399	Risk Ratio (IV, Random, 95% CI)	2.63 [1.64, 4.23]
4.3 Morphine	1	295	Risk Ratio (IV, Random, 95% CI)	3.49 [1.45, 8.39]
4.4 Oxycodone	4	758	Risk Ratio (IV, Random, 95% CI)	7.75 [3.76, 15.97]
4.5 Oxymorphone	2	674	Risk Ratio (IV, Random, 95% CI)	5.32 [2.93, 9.68]
5 Number of patients experiencing any serious adverse event	3	681	Risk Ratio (IV, Random, 95% CI)	3.35 [0.83, 13.56]
5.1 Codeine	1	158	Risk Ratio (IV, Random, 95% CI)	Not estimable
5.2 Fentanyl	1	416	Risk Ratio (IV, Random, 95% CI)	2.78 [0.57, 13.60]
5.3 Oxycodone	1	107	Risk Ratio (IV, Random, 95% CI)	6.39 [0.34, 120.71]
6 Withdrawal symptoms	1	499	Std. Mean Difference (IV, Fixed, 95% CI)	0.60 [0.42, 0.79]

Analysis 1.1. Comparison 1 Opioids versus placebo, Outcome 1 Pain.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 1 Pain

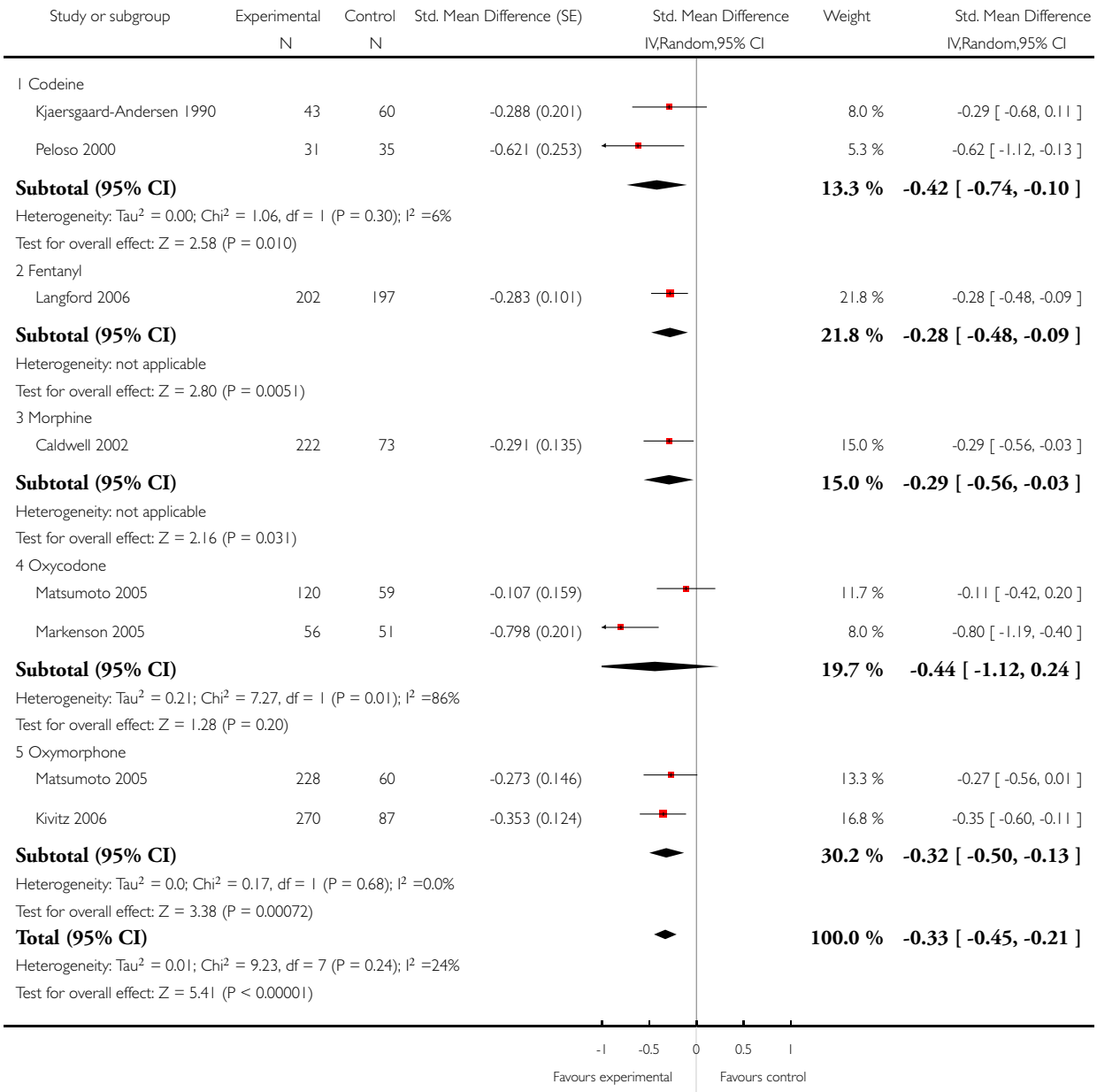


Analysis 1.2. Comparison 1 Opioids versus placebo, Outcome 2 Function.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 2 Function

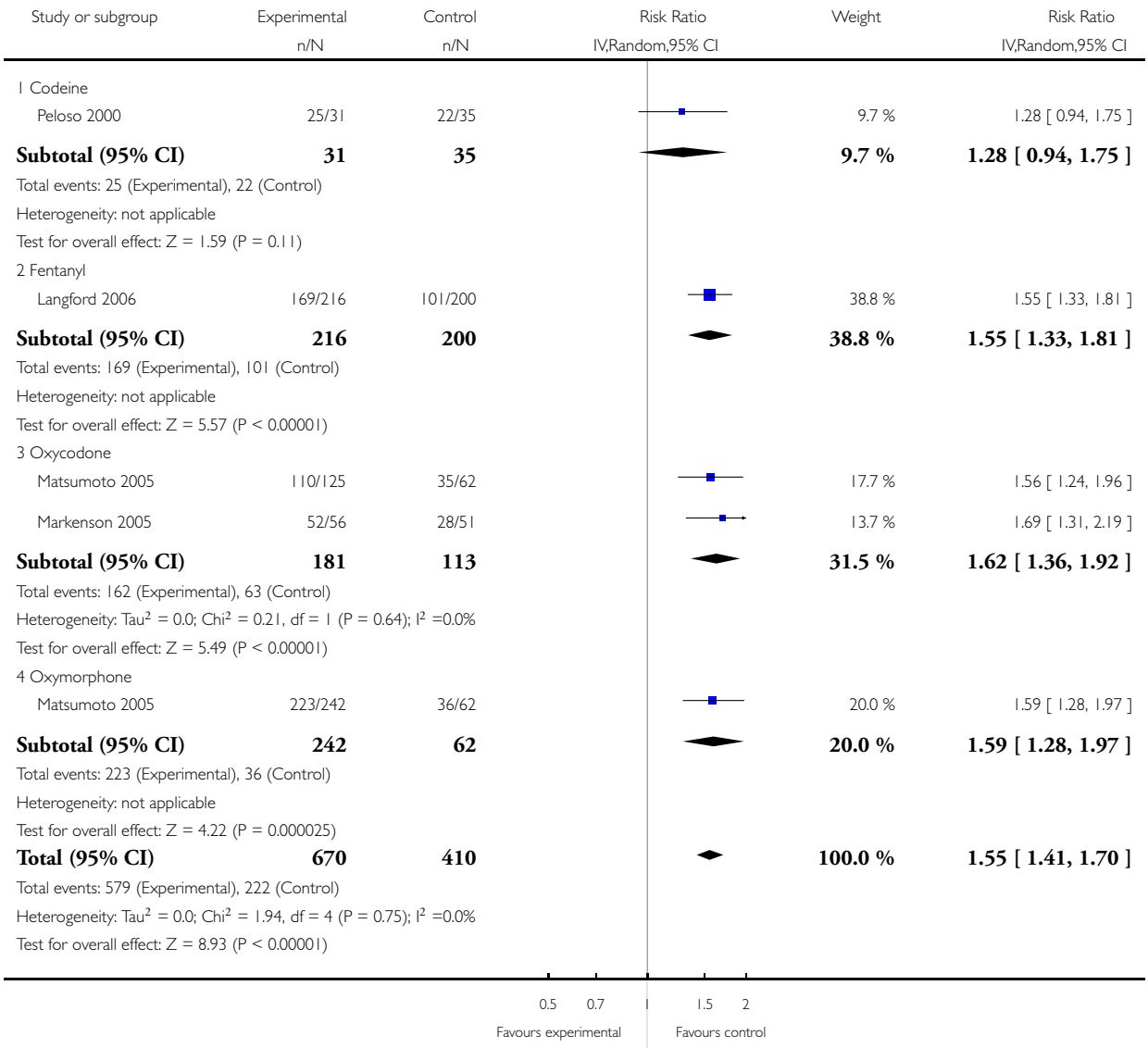


Analysis 1.3. Comparison 1 Opioids versus placebo, Outcome 3 Number of patients experiencing any adverse event.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 3 Number of patients experiencing any adverse event

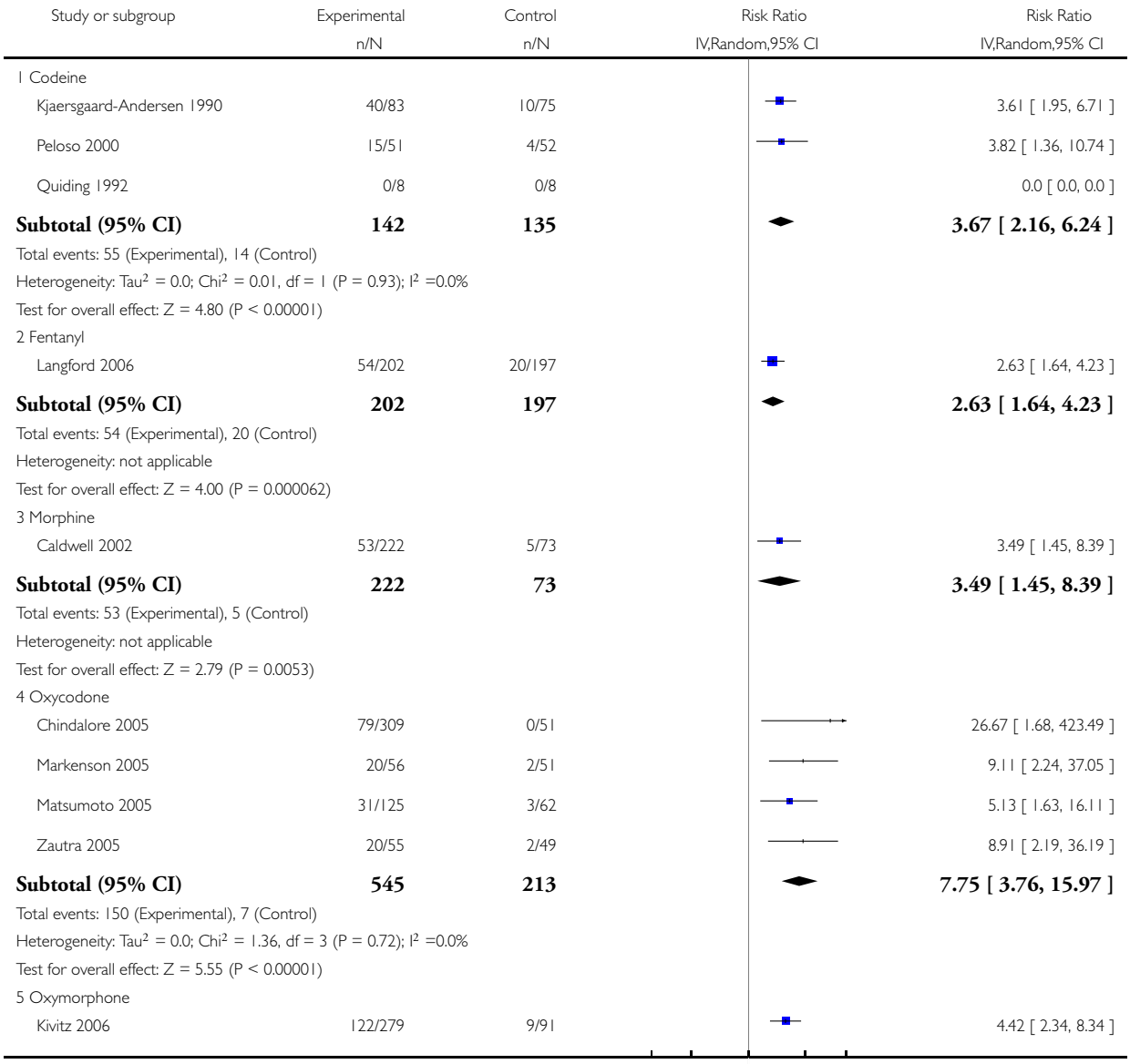


Analysis 1.4. Comparison 1 Opioids versus placebo, Outcome 4 Number of patients who withdrew because of adverse events.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 4 Number of patients who withdrew because of adverse events



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Matsumoto 2005	103/242	3/62		8.80 [2.89, 26.79]
Subtotal (95% CI)	**521**	**153**		**5.32 [2.93, 9.68]**
Total events: 225 (Experimental), 12 (Control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 1.11, df = 1 (P = 0.29); I^2 =10%				
Test for overall effect: Z = 5.48 (P < 0.00001)				
Total (95% CI)	**1632**	**771**		**4.05 [3.06, 5.38]**
Total events: 537 (Experimental), 58 (Control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.77, df = 9 (P = 0.37); I^2 =8%				
Test for overall effect: Z = 9.71 (P < 0.00001)				

0.02 0.1 1 10 50

Favours experimental Favours control

Analysis 1.5. Comparison 1 Opioids versus placebo, Outcome 5 Number of patients experiencing any serious adverse event.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 5 Number of patients experiencing any serious adverse event

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 Codeine				
Kjaersgaard-Andersen 1990	0/83	0/75		0.0 [0.0, 0.0]
Subtotal (95% CI)	**83**	**75**		**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Fentanyl				
Langford 2006	6/216	2/200		2.78 [0.57, 13.60]
Subtotal (95% CI)	**216**	**200**		**2.78 [0.57, 13.60]**
Total events: 6 (Experimental), 2 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.26 (P = 0.21)				
3 Oxycodone				
Markenson 2005	3/56	0/51		6.39 [0.34, 120.71]
Subtotal (95% CI)	**56**	**51**		**6.39 [0.34, 120.71]**

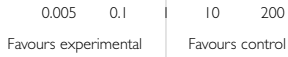
0.005 0.1 1 10 200

Favours experimental Favours control

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Total events: 3 (Experimental), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.24 (P = 0.22)				
Total (95% CI)	**355**	**326**		**3.35 [0.83, 13.56]**
Total events: 9 (Experimental), 2 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%				
Test for overall effect: Z = 1.70 (P = 0.090)				



Analysis 1.6. Comparison 1 Opioids versus placebo, Outcome 6 Withdrawal symptoms.

Review: Oral or transdermal opioids for osteoarthritis of the knee or hip

Comparison: 1 Opioids versus placebo

Outcome: 6 Withdrawal symptoms

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Langford 2006	202	0.66 (0.57)	297	0.39 (0.34)		100.0 %	0.60 [0.42, 0.79]
Total (95% CI)	**202**		**297**			**100.0 %**	**0.60 [0.42, 0.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.46 (P < 0.00001)							

APPENDICES

Appendix 1. MEDLINE, EMBASE and CINAHL search strategy

OVID MEDLINE	OVID EMBASE	CINAHL through EBSCOhost
Search terms for design 1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trial.sh. 4. random allocation.sh. 5. double blind method.sh. 6. single blind method.sh. 7. clinical trial.pt. 8. exp clinical trial/ 9. (clin$ adj25 trial$).ti,ab. 10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 11. placebos.sh. 12. placebo$.ti,ab. 13. random$.ti,ab. 14. research design.sh. 15. comparative study.sh. 16. exp evaluation studies/ 17. follow up studies.sh. 18. prospective studies.sh. 19. (control$ or prospectiv$ or volunteer$).ti,ab.	**Search terms for design** 1. randomized controlled trial.sh. 2. randomization.sh. 3. double blind procedure.sh. 4. single blind procedure.sh. 5. exp clinical trials/ 6. (clin$ adj25 trial$).ti,ab. 7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 8. placebo.sh. 9. placebo$.ti,ab. 10. random$.ti,ab. 11. methodology.sh. 12. comparative study.sh. 13. exp evaluation studies/ 14. follow up.sh. 15. prospective study.sh. 16. (control$ or prospectiv$ or volunteer$).ti,ab.	**Search terms for design** 1. (MH "Clinical Trials+") 2. (MH "Random Assignment") 3. (MH "Double-Blind Studies") or (MH "Single-Blind Studies") 4. TX (clin$ n25 trial$) 5. TX (sing$ n25 blind$) 6. TX (sing$ n25 mask$) 7. TX (doubl$ n25 blind$) 8. TX (doubl$ n25 mask$) 9. TX (trebl$ n25 blind$) 10. TX (trebl$ n25 mask$) 11. TX (tripl$ n25 blind$) 12. TX (tripl$ n25 mask$) 13. (MH "Placebos") 14. TX placebo$ 15. TX random$ 16. (MH "Study Design+") 17. (MH "Comparative Studies") 18. (MH "Evaluation Research") 19. (MH "Prospective Studies+") 20. TX (control$ or prospectiv$ or volunteer$) 21. S1 or S2 or (…….) or S20
Search terms for Osteoarthritis 20. exp osteoarthritis/ 21. osteoarthriti$.ti,ab,sh. 22. osteoarthro$.ti,ab,sh. 23. gonarthriti$.ti,ab,sh. 24. gonarthro$.ti,ab,sh. 25. coxarthriti$.ti,ab,sh. 26. coxarthro$.ti,ab,sh. 27. arthros$.ti,ab. 28. arthrot$.ti,ab. 29. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab. 30. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	**Search terms for Osteoarthritis** 17. exp osteoarthritis/ 18. osteoarthriti$.ti,ab,sh. 19. osteoarthro$.ti,ab,sh. 20. gonarthriti$.ti,ab,sh. 21. gonarthro$.ti,ab,sh. 22. coxarthriti$.ti,ab,sh. 23. coxarthro$.ti,ab,sh. 24. arthros$.ti,ab. 25. arthrot$.ti,ab. 26. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab. 27. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	**Search terms for Osteoarthritis** 22. osteoarthriti$ 23. (MH "Osteoarthritis") 24. TX osteoarthro$ 25. TX gonarthriti$ 26. TX gonarthro$ 27. TX coxarthriti$ 28. TX coxarthro$ 29. TX arthros$ 30. TX arthrot$ 31. TX knee$ n3 pain$ 32. TX hip$ n3 pain$ 33. TX joint$ n3 pain$ 34. TX knee$ n3 ach$ 35. TX hip$ n3 ach$ 36. TX joint$ n3 ach$

(*Continued*)

		37. TX knee$ n3 discomfort$ 38. TX hip$ n3 discomfort$ 39. TX joint$ n3 discomfort$ 40. TX knee$ n3 stiff$ 41. TX hip$ n3 stiff$ 42. TX joint$ n3 stiff$ 43. S22 or S23 or S24….or S42
Search terms for Opioids 31. exp Analgesics, Opioid/ 32. exp Narcotics/ 33. acetyldihydrocodeine.tw. 34. alfentanil.tw. 35. allylprodine.tw. 36. alphamethylfentanyl.tw. 37. alphaprodine.tw. 38. benzylmorphine.tw. 39. betaprodine.tw. 40. bezitriamide.tw. 41. buprenorphine.tw. 42. butorphanol.tw. 43. bremazocine.tw. 44. carfentan$.tw. 45. codeine.tw. 46. contin.tw. 47. dextromoramide.tw. 48. dextropropoxyphene.tw. 49. dezocine.tw. 50. diacetylmorphine.tw. 51. diamorphine.tw. 52. dihydrocodeine.tw. 53. dihydromorphine.tw. 54. dihydromorphone.tw. 55. diphenoxylate.tw. 56. dipipanone.tw. 57. enadoline.tw. 58. ethylketazocine.tw. 59. ethylmorphine.tw. 60. etonitazene.tw. 61. etorphine.tw. 62. fentanyl.tw. 63. heroin.tw. 64. hydrocodone.tw. 65. hydromorphin$.tw. 66. hydromorphone.tw.	**Search terms for Opioids** 28. exp Analgesics, Opioid/ 29. exp Narcotic Analgesic Agent/ 30. acetyldihydrocodeine.tw. 31. alfentanil.tw. 32. allylprodine.tw. 33. alphamethylfentanyl.tw. 34. alphaprodine.tw. 35. benzylmorphine.tw. 36. betaprodine.tw. 37. bezitriamide.tw. 38. buprenorphine.tw. 39. butorphanol.tw. 40. bremazocine.tw. 41. carfentan$.tw. 42. codeine.tw. 43. contin.tw. 44. dextromoramide.tw. 45. dextropropoxyphene.tw. 46. dezocine.tw. 47. diacetylmorphine.tw. 48. diamorphine.tw. 49. dihydrocodeine.tw. 50. dihydromorphine.tw. 51. dihydromorphone.tw. 52. diphenoxylate.tw. 53. dipipanone.tw. 54. enadoline.tw. 55. ethylketazocine.tw. 56. ethylmorphine.tw. 57. etonitazene.tw. 58. etorphine.tw. 59. fentanyl.tw. 60. heroin.tw. 61. hydrocodone.tw. 62. hydromorphin$.tw. 63. hydromorphone.tw.	**Search terms for Opioids** 44. MH " Analgesics, Opioid" 45. MH "Narcotics" 46. TX acetyldihydrocodeine 47. TX alfentanil 48. TX allylprodine 49. TX alphamethylfentanyl 50. TX alphaprodine 51. TX benzylmorphine 52. TX betaprodine 53. TX bezitriamide 54. TX buprenorphine 55. TX butorphanol 56. TX bremazocine 57. TX carfentan$ 58. TX codeine 58. TX contin 60. TX dextromoramide 61. TX dextropropoxyphene 62. TX dezocine 63. TX diacetylmorphine 64. TX diamorphine 65. TX dihydrocodeine 66. TX dihydromorphine 67. TX dihydromorphone 68. TX diphenoxylate 69. TX dipipanone 70. TX enadoline 71. TX ethylketazocine 72. TX ethylmorphine 73. TX etonitazene 74. TX etorphine 75. TX fentanyl 76. TX heroin 77. TX hydrocodone 78. TX hydromorphin$ 79. TX hydromorphone

(*Continued*)

67. ketazocine.tw.
68. ketobemidone.tw.
69. lefetamine.tw.
70. levomethadon.tw.
71. levomethadyl.tw.
72. levomethorphan$.tw.
73. levorphanol.tw.
74. loperamide.tw.
75. meperidine.tw.
76. meptazinol.tw.
77. methadone.tw.
78. methadyl.tw.
79. methylmorphine.tw.
80. morphin$.tw.
81. nalbuphine.tw.
82. narcotic$.tw.
83. nicocodeine.tw.
84. nicomorphine.tw.
85. normorphine.tw.
86. noscapin$.tw.
87. ohmefentanyl.tw.
88. opiate$.tw.
89. opioid$.tw.
90. opium.tw.
91. oripavine.tw.
92. oxycodone.tw.
93. oxycontin.tw.
94. oxymorphone.tw.
95. papaveretum.tw.
96. papaverin.tw.
97. pentazocine.tw.
98. percocet.tw.
99. peronine.tw.
100. pethidine.tw.
101. phenazocine.tw.
102. phencyclidine.tw.
103. pholcodine.tw.
104. piritramid$.tw.
105. prodine.tw.
106. promedol.tw.
107. propoxyphene.tw.
108. remifentanil.tw.
109. sufentanil.tw.
110. tapentadol.tw.
111. thebaine.tw.
112. tilidine.tw.

64. ketazocine.tw.
65. ketobemidone.tw.
66. lefetamine.tw.
67. levomethadon.tw.
68. levomethadyl.tw.
69. levomethorphan$.tw.
70. levorphanol.tw.
71. loperamide.tw.
72. meperidine.tw.
73. meptazinol.tw.
74. methadone.tw.
75. methadyl.tw.
76. methylmorphine.tw.
77. morphin$.tw.
78. nalbuphine.tw.
79. narcotic$.tw.
80. nicocodeine.tw.
81. nicomorphine.tw.
82. normorphine.tw.
83. noscapin$.tw.
84. ohmefentanyl.tw.
85. opiate$.tw.
86. opioid$.tw.
87. opium.tw.
88. oripavine.tw.
89. oxycodone.tw.
90. oxycontin.tw.
91. oxymorphone.tw.
92. papaveretum.tw.
93. papaverin.tw.
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95. percocet.tw.
96. peronine.tw.
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98. phenazocine.tw.
99. phencyclidine.tw.
100. pholcodine.tw.
101. piritramid$.tw.
102. prodine.tw.
103. promedol.tw.
104. propoxyphene.tw.
105. remifentanil.tw.
106. sufentanil.tw.
107. tapentadol.tw.
108. thebaine.tw.
109. tilidine.tw.

80. TX ketazocine
81. TX ketobemidone
82. TX lefetamine
83. TX levomethadon
84. TX levomethadyl
85. TX levomethorphan$
86. TX levorphanol
87. TX loperamide
88. TX meperidine
89. TX meptazinol
90. TX methadone
91. TX methadyl
92. TX methylmorphine
93. TX morphin$
94. TX nalbuphine
95. TX narcotic$
96. TX nicocodeine
97. TX nicomorphine
98. TX normorphine
99. TX noscapin$
100. TX ohmefentanyl
101. TX opiate$
102. TX opioid$
103. TX opium
104. TX oripavine
105. TX oxycodone
106. TX oxycontin
107. TX oxymorphone
108. TX papaveretum
109. TX papaverin
110. TX pentazocine
111. TX percocet
112. TX peronine
113. TX pethidine
114. TX phenazocine
115. TX phencyclidine
116. TX pholcodine
117. TX piritramid$
118. TX prodine
119. TX promedol
120. TX propoxyphene
121. TX remifentanil
122. TX sufentanil
123. TX tapentadol
124. TX thebaine
125. TX tilidine
126. S44 or S45 or S125

(*Continued*)

Combining terms	Combining terms	Combining terms
113. or/31-112	110. or/28-109	127. S21 and S43 and S126
114. or/1-19	111. or/1-16	
115. or/20-30	112. or/17-27	
116. and/113-115	113. and/110-112	
117. animal/	114. animal/	
118. animal/ and human/	115. animal/ and human/	
119. 117 not 118	116. 114 not 115	
120. 116 not 119	117. 113 not 116	
121. remove duplicates from 120	118. remove duplicates from 117	

Appendix 2. CENTRAL search strategy

CENTRAL
Search terms for Osteoarthritis #1. MeSH descriptor Osteoarthritis explode all trees #2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Clinical Trials *Search terms for Opioids* #3. MeSH descriptor Analgesics, Opioid explode all trees #4. MeSH descriptor Narcotics explode all trees #5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR contin OR dextromoramide OR dextropropoxyphene OR dezocine OR diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine) in Clinical Trials *Combining terms* #6. (#1 OR #2) #7. (#3 OR #4 OR #5) #8. (#6 AND #7) in Clinical Trials

WHAT'S NEW

Last assessed as up-to-date: 12 May 2008.

13 May 2008	Amended	Change in authorship
1 May 2008	Amended	CMSG ID C141-R

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

Protocol completion: Nüesch, Rutjes, Husni, Jüni

Acquisition of data: Nüesch, Rutjes

Analysis and interpretation of data: Nüesch, Rutjes, Husni, Welch, Jüni

Manuscript preparation: Nüesch, Rutjes, Husni, Welch, Jüni

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Mrs Nüesch and Dr Rutjes contributed equally to this review.

DECLARATIONS OF INTEREST

None

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The cut off to distinguish between short-term and long-term trials was changed from 26 weeks to one month.