Opioids for neuropathic pain (Review)

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[Intervention Review]

Opioids for neuropathic pain

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 3, 2006, which included 23 trials. The use of opioids for neuropathic pain remains controversial. Studies have been small, have yielded equivocal results, and have not established the long-term profile of benefits and risks for people with neuropathic pain.

Objectives

To reassess the efficacy and safety of opioid agonists for the treatment of neuropathic pain.

Search methods

We searched CENTRAL, on *The Cochrane Library* (Issue 10 of 12, 2012), MEDLINE (1966 to Oct week 3, 2012), and EMBASE (1980 to 2012, week 42) for articles in any language, and reference lists of reviews and retrieved articles. Searches were originally run in 2005, then again in 2010 and 2012.

Selection criteria

We included randomized controlled trials (RCTs) in which opioid agonists were given to treat central or peripheral neuropathic pain of any etiology. Pain was assessed using validated instruments, and adverse events were reported. We excluded studies in which drugs other than opioid agonists were combined with opioids or opioids were administered epidurally or intrathecally.

Data collection and analysis

Two review authors independently extracted data and included demographic variables, diagnoses, interventions, efficacy, and adverse effects.

Main results

Thirty-one trials met our inclusion criteria, studying 10 different opioids: 23 studies from the original 2006 review and eight additional studies from this updated review.

Seventeen studies (392 participants with neuropathic pain, average 22 participants per study) provided efficacy data for acute exposure to opioids over less than 24 hours. Sixteen reported pain outcomes, with contradictory results; 8/16 reported less pain with opioids than

placebo, 2/16 reported that some but not all participants benefited, 5/16 reported no difference, and 1/16 reported equivocal results. Six studies with about 170 participants indicated that mean pain scores with opioid were about 15/100 points less than placebo.

Fourteen studies (845 participants, average 60 participants per study) were of intermediate duration lasting 12 weeks or less; most studies lasted less than six weeks. Most studies used imputation methods for participant withdrawal known to be associated with considerable bias; none used a method known not to be associated with bias. The evidence, therefore, derives from studies predominantly with features likely to overestimate treatment effects, i.e. small size, short duration, and potentially inadequate handling of dropouts. All demonstrated opioid efficacy for spontaneous neuropathic pain. Meta-analysis demonstrated at least 33% pain relief in 57% of participants receiving an opioid versus 34% of those receiving placebo. The overall point estimate of risk difference was 0.25 (95% confidence interval (CI) 0.13 to 0.37, P < 0.0001), translating to a number needed to treat for an additional beneficial outcome (NNTB) of 4.0 (95% CI 2.7 to 7.7). When the number of participants achieving at least 50% pain relief was analyzed, the overall point estimate of risk difference between opioids (47%) and placebo (30%) was 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0). In the updated review, opioids did not demonstrate improvement in many aspects of emotional or physical functioning, as measured by various validated questionnaires. Constipation was the most common adverse event (34% opioid versus 9% placebo: number needed to treat for an additional harmful outcome (NNTH) 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0). More participants withdrew from opioid treatment due to adverse events (13%) than from placebo (4%) (NNTH 12.5; 95% CI 8.3 to 25.0). Conversely, more participants receiving placebo withdrew due to lack of efficacy (12%) versus (2%) receiving opioids (NNTH -11.1; 95% CI -20.0 to -8.3).

Authors' conclusions

Since the last version of this review, new studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions. Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.

PLAIN LANGUAGE SUMMARY

Opioids for neuropathic pain

Neuropathic pain is pain caused by nerve damage. It is often difficult to diagnose and treat. The use of opioids (strong pain killers such as morphine) to treat neuropathic pain is controversial owing to concerns about addiction and beliefs that this type of pain does not always respond well to opioids. The review looked at short-term studies lasting less than a day and intermediate-term trials lasting from several days to 12 weeks. The 31 studies found involved 1237 people with neuropathic pain; most studies were small.

Short-term studies produced mixed results, with just over half indicating that opioids might be better than a placebo. While intermediate-term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice. We cannot say whether opioids are better than placebo for neuropathic pain over the long term. Side effects such as constipation, nausea, dizziness, and drowsiness were common, but not life-threatening.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (Issue 3, 2006) on 'Opioids for neuropathic pain'.

Description of the condition

The percentage of people suffering from neuropathic pain is unknown, but is estimated to be as high as 7% to 8% (Bouhassira 2008; Torrance 2006) in developed nations. Estimates of the prevalence of chronic pain (of which neuropathic pain is a subset) suggest that around 20% of both developed and undeveloped nations' populations are affected (Breivik 2004; Breivik 2006). Neuropathic pain may result from a large variety of insults to the peripheral or central somatosensory nervous system, including trauma, inflammation, ischemia, and metabolic and neoplastic disorders. Common examples of peripheral neuropathic pain include diabetic neuropathy and postsurgical neuralgia. Central neuropathic pain includes central post-stroke pain, pain in multiple sclerosis, and pain after spinal cord injury. The main clinical characteristics of neuropathic pain are continuous or intermittent spontaneous pain, typically described as burning, aching, or shooting in quality, and abnormal sensitivity of the painful site to normally innocuous stimuli such as light touch by garments, running water, or even wind (allodynia) (Baron 2010; Maier 2010). Neuropathic pain, like many other forms of chronic pain, often has negative effects on quality of life (Jensen 2007; Meyer-Rosberg 2001). Pharmacotherapy for neuropathic pain has generally involved the use of antidepressants or anticonvulsants, but even with the current generation of these drugs, effective analgesia is achieved in less than half of this population (Dworkin 2010; Finnerup 2010; O'Connor 2009; Sindrup 1999).

Description of the intervention

Opioids are the most effective broad-spectrum analgesics available and are considered the cornerstone of therapy for moderate-to-severe acute pain or pain of similar intensity due to life-threatening illnesses, but their long-term use in non-cancer pain, of which neuropathic pain is a component, is controversial. In the United States, the therapeutic use of opioids in general has risen significantly over the last decade (Manchikanti 2008). Despite this, the safety and efficacy of the different opioids in the treatment of neuropathic pain have yet to be established. Clinical trials assessing the efficacy of opioids for reducing neuropathic pain have been reported for more than 25 years, yet great variability in trial design in terms of the type of neuropathic pain syndrome treated, the type of opioid administered, and the duration of treatment has yielded contradictory results. Studies that have suggested efficacy have used small study populations, raising questions about the validity of the results.

How the intervention might work

Opioids provide analgesia by binding to opioid receptors of the mu and kappa class and blocking the release of neurotransmitters such as substance P. Opioid receptors are expressed both centrally and peripherally during the inflammatory response in injured tissue.

Why it is important to do this review

There is a lack of definitive evidence regarding the efficacy of opioids in reducing neuropathic pain in general, and central neuropathic pain in particular. Equally, there are concerns about tolerability of opioids and the potential for abuse, addiction, hormonal abnormalities, dysfunction of the immune system, and, in some cases, paradoxical hyperalgesia with long-term use (Rhodin 2010; Seghal 2012; Tompkin 2011; Vallejo 2004). Therefore, we conducted a systematic review of published randomized controlled trials (RCTs).

OBJECTIVES

We attempted to answer two questions:

1) What is the efficacy of opioid agonists in relieving neuropathic pain?

2) What is the nature and incidence or severity of adverse effects caused by opioid agonists in people with neuropathic pain?

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) in this review if opioid agonists (but not partial agonists or agonist-antagonists) were given to treat central or peripheral neuropathic pain of any etiology. Studies with pain intensity as the primary or secondary outcome were included. Non-randomized studies and case reports were excluded, as were retrieved trials that presented insufficient data to allow assessment of the outcomes of interest or study quality.

Types of participants

We included men and women of all ages and races or ethnicities. We excluded studies in which participants with both neuropathic and other types of pain (e.g. nociceptive) were enrolled and responses of the two groups were not presented separately.

Types of interventions

We included studies in which one or more opioid agonists or different doses of the same opioid agonist were compared with placebo, each other, or another class of medication used for neuropathic pain (e.g. antidepressants). We included studies in which drugs were administered by any of the following routes: oral, rectal, transdermal, intravenous, intramuscular, or subcutaneous.

We excluded studies in which: drugs other than opioid agonists were combined with opioids (e.g. codeine with acetaminophen); opioids were administered epidurally or intrathecally, as the epidural route is usually reserved for postoperative/labor pain, and while the intrathecal route is used in neuropathic pain (usually via an implantable pump) such therapy is typically classified as neuromodulation rather than analgesia; or if tramadol or tapentadol were used as the active drug, because, although both interact to some degree with opioid receptors, they are not regarded as pure opioid agonists. The efficacy of tramadol in relieving neuropathic pain has been reviewed elsewhere (Duehmke 2006).

Types of outcome measures

We included participant-reported measure(s) of pain intensity or pain relief using validated methods.

Primary outcomes

In our updated review the primary outcomes we sought were the proportion of participants reporting at least 33% pain reduction from baseline or 50% or more pain reduction from baseline. The selection of these outcomes, as opposed to the primary outcomes in our original review (mean pain intensity difference or mean pain relief) was based on the observation that pain relief tends to be bimodal, rendering mean values less useful. A greater than or equal to 33% (or $\geq$ 30%) pain reduction from baseline was based upon analyses demonstrating that such a reduction was required for people with chronic pain to perceive a clinically meaningful change in pain intensity (Farrar 2001). More recent evidence suggests that at least 50% pain relief is clinically significant, because high levels of pain relief are strongly associated with improved fatigue, sleep, depression, work ability and quality of life (Moore 2010a). While such data are rarely reported in older studies, we anticipated that those studies found in our updated search would report them.

Where studies did not report numbers of participants with at least 33% or 50% improvement, but reported numbers of participants reporting certain categories of global impression of change, e.g. "much improved", we translated these categories to equate to either at least 33% pain reduction from baseline or at least 50% pain reduction from baseline (Dworkin 2008).

Secondary outcomes

We extracted data on the following secondary outcomes:

1. Pain intensity or pain intensity difference or pain relief using a visual analog scale (VAS) or numerical rating scale (NRS).
2. Outcomes based on pain questionnaires and quality of life (QoL) measurement instruments, including those recommended as core chronic pain outcome domains (Dworkin 2008) (Multidimensional Pain Inventory and Brief Pain Inventory interference scales, Beck Depression Inventory and Profile of Mood States).
3. Incidence of adverse events during treatment with opioid or control (intermediate-term studies only).
4. Participant dropouts due to adverse events (intermediate-term studies only).
5. Participant dropouts due to lack of efficacy (intermediate-term studies only).

We normalized pain intensity data assessed by means other than a 0 - 100 VAS to such a scale. To do so we either multiplied the original scale employed by an appropriate factor (e.g. by ten if the original scale was a 0 - 10 scale) or by assigning values on a 0 - 100 scale that corresponded to choices on the original assessment scale. For example, if a participant was offered a five-point scale, selection of the third point was scored as 50 on a 0 - 100 scale (0 = no pain, 1 = 25, 2 = 50, 3 = 75, 4 = 100).

Search methods for identification of studies

This search was run for the original review in June 2005 and subsequent searches were run on the 16th of August, 2010. Finally, further searches employing different search strategies were run on the 24th of October 2012. The new search strategies were developed because the older strategies produced an impractical number of references for only two years of literature.

Electronic searches

We searched the following databases:

- CENTRAL, on *The Cochrane Library* (Issue 10 of 12, 2012)
- MEDLINE (1966 to Oct week 3, 2012)
- EMBASE (1980 to to 2012 week 42)

We combined search terms for RCTs with terms for opioids and terms for neuropathic pain. Our original search strategies can be found in Appendix 1; Appendix 2; and Appendix 3. Our updated search strategies (2010 to 2012) can be found in Appendix 4; Appendix 5; and Appendix 6.

There was no language restriction.

Searching other resources

We scanned the reference lists of reviews and retrieved articles. We did not consider abstracts or unpublished reports in this update, but intend to include them in future updates.

Data collection and analysis

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy our inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement by discussion. The studies were not anonymized in any way before assessment.

Data extraction and management

Two review authors extracted and agreed on data, using a standard form, before entry into Review Manager 5 (RevMan). Data extracted included information on study design and duration, methods, interventions, pain outcomes, adverse events, diagnoses, participant inclusion and exclusion criteria, numbers enrolled and completing the study, and functional assessments. We resolved discrepancies in extracted data by discussion prior to their inclusion in the analyses.

Analyses focused on differences in pain intensity, pain relief, and the incidence and severity of adverse events. When necessary and possible we normalized all data to a 0 - 100 mm VAS. We made no attempt to convert surrogate outcomes (e.g. amount of rescue medication used) to a VAS, although we did equate certain global evaluations to either 33% or 50% pain reduction. For studies in which surrogate outcomes were the only results available, we describe them as such. We extracted the number of participants experiencing adverse events from trials in which they were asked about or observed for specific adverse effects such as constipation, also noting withdrawals if described.

Assessment of risk of bias in included studies

In our original review, we graded included studies for methodological quality using the Oxford Quality Scale (Jadad 1996). In our updated review, we instead assessed 'Risk of bias' for both the original included studies and those included from the updated search (see Assessment of risk of bias in included studies). Two review authors independently assessed the risk of bias of all included studies. The review authors made critical assessments for each of the following domains: sequence generation (randomization), allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. The review author judgment for each domain was entered into a 'Risk of bias' table, with answers 'low risk', 'high risk' or 'unclear risk' (indicating either lack of information or uncertainty over the potential for bias).

Measures of treatment effect

In contrast to our original review, we applied a random-effects model to combine data, in part because of the heterogeneity apparent in many of the analyses. We are aware of the possible limitation of using a random-effects model for meta-analysis in case of non-normal distribution of intervention effect data; however, using a fixed-effect model for this purpose may be less appropriate since we cannot assume to know the direction of the effect.

Dichotomous data

Discrete events such as numbers of participants reporting 33% pain relief or better, or 50% pain relief or better, or the number of participants reporting adverse events were used to calculate the risk difference using Review Manager 5 software. When a statistically significant risk difference existed between interventions, we derived the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) (Cook 1995). Additionally, dichotomous outcomes are presented in terms of both raw numbers and percentages of participants in each study arm benefiting from therapy or suffering adverse events.

Continuous data

We undertook meta-analyses when comparable data were available from continuous outcomes. Comparisons between opioids and active control or placebo groups were made separately for pain relief, pain intensity post-intervention, and intensity of a specific adverse event, using weighted mean differences (WMDs).

Unit of analysis issues

We split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis.

Dealing with missing data

We did not contact authors for original data unless data were missing or unclear. If, despite attempts to contact study authors, participant data were missing, analyses were based on participant populations in which outcomes were reported. Discrepancies between the number of participants enrolled and the number of participants in whom outcomes were reported are noted in the Characteristics of included studies table. Where studies reported statistics based on intention-to-treat (ITT) or modified ITT populations, we performed available case analyses. The ITT population consisted of participants who were randomized, took the assigned study medication, and provided at least one post-baseline assessment.

Assessment of heterogeneity

We evaluated heterogeneity between and within trials using both the Chi² test and the I² test. The Chi² test assesses whether observed differences in results are compatible with chance alone. A low P value (or a large Chi² statistic relative to its degrees of freedom) provides evidence of heterogeneity of treatment effects (variation in effect estimates beyond chance). The Chi² test has low power in estimating heterogeneity in the common situation where few trials are analyzed or where included trials have small sample sizes. Although a statistically significant result may indicate a problem with heterogeneity, a non-significant result is not necessarily evidence of lack of heterogeneity. Methods developed for quantifying inconsistency across studies that move the focus away from testing whether heterogeneity is present to assessing its impact on the meta-analysis include the I² statistic. I² = [(Q -df)/ Q] x 100%, where Q is the Chi² statistic and df is its degrees of freedom (Deeks 2011; Higgins 2003). The I² statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity (Deeks 2011). We also assessed heterogeneity by visually studying forest plots.

Assessment of reporting biases

We made no attempt to assess reporting bias.

Data synthesis

We used the random-effects model by DerSimonian and Laird (Deeks 2011) for meta-analysis, using Review Manager 5.

Subgroup analysis and investigation of heterogeneity

Where possible we performed subgroup analysis based on:

- peripheral versus central pain
- spontaneous versus evoked pain

Sensitivity analysis

For our updated review, we decided to perform sensitivity analyses by eliminating:

- cross-over studies
- studies with fewer than 10 participants in an intervention arm or phase

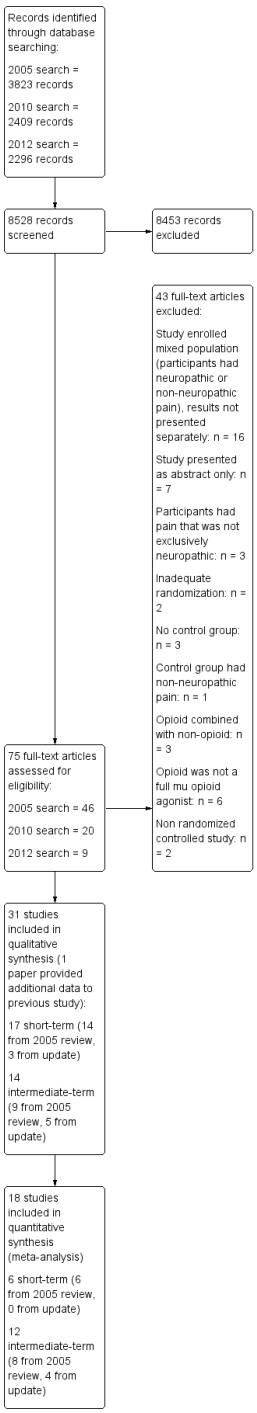
RESULTS

Description of studies

Results of the search

Our 2005 literature search yielded 3823 citations (CENTRAL, 945; MEDLINE, 1531; EMBASE 1347), of which we selected 46 potentially relevant studies for retrieval. The literature search covering 2005 to 16 August 2010 yielded an additional 2409 citations (CENTRAL, 370; MEDLINE, 1025; EMBASE, 1014) of which we selected 19 studies for retrieval. Finally, the 2012 search yielded 2296 citations (CENTRAL, 157; MEDLINE, 1213; EMBASE, 926) of which we selected nine for retrieval (Figure 1).

Figure 1. Study flow diagram.



Included studies

We divided the trials into two categories according to study duration. There is no definition per se of what constitutes a short-term or an intermediate-term trial. Short-term trials, intuitively, were those that employed a single dose or intravenous infusion intervention. We labeled other trials as 'intermediate-term' because we did not consider trial duration to be sufficiently long to make firm conclusions about chronic administration of opioids. In total, our updated review included 17 short-term studies (three from the 2005 - 2012 searches) and 14 intermediate-term studies (five from the 2005 - 2012 search).

Eight of the 28 retrieved articles from the updated search (2010, 2012) met the inclusion criteria and provided data on an additional 510 participants with neuropathic pain who were treated with opioids. Three studies were short-term trials: Juarez-Pichardo 2009 (N = 27); Simpson 2007 (N = 79); and Wallace 2006 (N = 32). The other five studies were intermediate-term trials (Frank 2008; Hanna 2008; Khoromi 2007; Wu 2008; Zin 2010), in which opioids were administered orally over periods of between 35 and 84 days (median = 49 days). Numbers of participants per treatment group ranged from 29 to 169 (median = 50).

Twenty-three of the 46 articles from our 2005 search met the inclusion criteria and provided data on 727 participants with neuropathic pain who were treated with opioids.

The first group consisted of 14 short-term trials (treated as 16 comparisons) (Arner 1988; Attal 2002; Dellemijn 1997; Eide 1994; Eide 1995; Jadad 1992; Jorum 2003; Kupers 1991 central; Kupers 1991 peripheral; Leung 2001; Max 1988; Max 1995; Rabben 1999; Rowbotham 1991; Wu 2002 phantom limb; Wu 2002 stump) in which opioids were administered mostly as brief intravenous infusions and outcomes were measured for less than 24 hours. The number of participants in each of these studies was small (median = 13; range, 7 to 53). We subanalyzed reported outcomes from two of the trials. In one study people with both peripheral and central pain were included and the results reported separately (Kupers 1991 central; Kupers 1991 peripheral). In another study changes in phantom limb pain and stump pain were reported separately (Wu 2002 phantom limb; Wu 2002 stump).

The second group of studies consisted of nine intermediate-term trials (Gilron 2005; Gimbel 2003; Harke 2001; Huse 2001; Morley 2003; Raja 2002; Rowbotham 2003; Watson 1998; Watson 2003) in which opioids were administered orally over longer periods of between eight and 70 days (median = 28 days), generally to larger numbers of participants (median = 57; range, 12 to 159).

Excluded studies

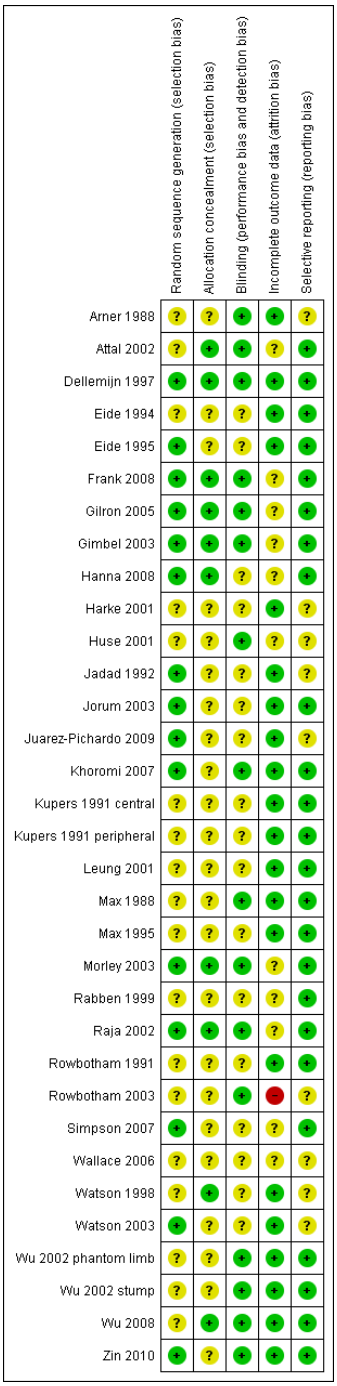
Three controlled trials (Benedetti 1998; Kalman 2002; Maier 2002) failed to meet one or more of the inclusion criteria in our original review. First, an RCT conducted over seven days (Maier 2002) compared morphine with placebo in a mixed group of participants with various neuropathic and nociceptive pain syndromes. The authors reported that "the number of responders was significantly higher in patients with neuropathic than with nociceptive pain". However, efficacy and adverse event data were not presented separately for the different types of pain. Second, a short-term, placebo-controlled trial (Kalman 2002) showed that only four of 14 participants who had multiple sclerosis and central neuropathic pain were categorized as 'responders' to intravenous morphine. The study was non-randomized and single blinded. Third, in an RCT (Benedetti 1998), five different doses of buprenorphine (0.033 to 0.166 mg) were administered randomly to 21 participants with post-thoracotomy neuropathic pain one month after surgery, with reduction of pain by 50% in each person. However, buprenorphine is a partial mu receptor agonist, with different pharmacological properties to members of the full μ opioid agonist class.

Twenty studies were excluded from the updated search (2005 - 2012). Three trials included participants in whom pain could not be attributed entirely to neuropathic origin: in two of them participants with acute herpes zoster were enrolled (Guo 2007; Dworkin 2009); and the third consisted of participants with low back pain (Kalso 2007). The potential cause of pain in these participants can be nociceptive, neuropathic or both, and the effect of opioid treatment on the two types of pain was not reported separately. Similarly, six other trials (Ashburn 2011; Cruciani 2012; Nicholson 2006a; Nicholson 2006b; Webster 2010; Weil 2009) were excluded because enrolled participants had mixed pain syndromes (neuropathic or nociceptive) and results were not presented independently. Two trials included participants with neuropathic pain who were treated with opioids but were not RCTs (Arita 2008; Gatti 2009). Two studies had no control group (Mordarski 2009; Yao 2012). In one study the control group did not have neuropathic pain (Niesters 2011). Finally, six trials were published in an abstract form only (Buynak 2009; Hale 2009; Oh 2012; Podolsky 2009; Varrassi 2011; Webster 2011).

Risk of bias in included studies

Our original review used the Oxford Quality Scale to assess the quality of each included study. In the updated review we replaced this scale with the 'Risk of bias' tool, applying it both to new studies and to those from the original review. A summary of 'Risk of bias' assessments can be found in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Fifteen of the 31 studies described methods for randomization adequately so that they could be assigned a low risk of bias for sequence generation. Ten of the 31 described methods of allocation concealment sufficiently that they could be assigned a low risk of bias. In both cases, the remaining studies did not provide enough information for us to draw any conclusion regarding risk of bias. Also in both cases, the majority of intermediate-term studies had a low risk of bias, whereas a minority of short-term studies described methods adequately. Among the intermediate-term studies, low risk of bias was seen in similar numbers between parallel and cross-over studies.

Blinding

Only five of the 17 short-term studies described methods of blinding sufficiently to be assigned a low risk of bias. Conversely, 10 of the 14 intermediate-term studies were assigned a low risk of bias, with similar numbers between parallel and cross-over studies. All other studies were assigned an unclear risk of bias due to inadequate information.

Incomplete outcome data

Given their nature, the majority of short-term studies (13/17) had a low risk of attrition bias. Among the intermediate-term studies only six of 14 were assigned a low risk of bias, with one study (Rowbotham 2003) assigned a high risk. In this study 12/43 participants in the high-dose levorphanol arm and 3/38 in the low-dose arm withdrew from the study due to adverse events. All other studies were assigned an unclear risk: Frank 2008 reported both available case analysis and per protocol analysis, but a greater number of subjects withdrew due to side effects while assigned an opioid; in Gilron 2005 withdrawals (16/57) were evenly distributed among groups, but reasons for withdrawal not fully described; Gimbel 2003 and Hanna 2008 imputed data using last observation carried forward (LOCF); Huse 2001 made no mention of how missing data were imputed; in Morley 2003 only study completers were analyzed, six participants withdrew from the high-dose phase due to severe nausea - three while taking placebo, three while taking methadone - while number of withdrawals were small, group sizes were also small. Finally, Raja 2002 employed an ITT analysis. For participants who did not complete a treatment period, the last three available pain ratings were used. However, the number of participants who did not complete the opioid phase was not reported.

Selective reporting

The vast majority of both short- and intermediate-term studies reported data on all of the outcomes described in their Methods sections. While study protocols were not available for any of the reported trials, and it is therefore possible that certain outcomes were measured but not reported, the widespread reporting of pain intensity and pain relief values leads us to believe that reporting was complete for most studies.

Other potential sources of bias

Treatment group size was an issue, particularly in short-term studies. Numbers enrolled in each study ranged from 7 to 79 in short-term trials, with five studies enrolling fewer than 10 participants (Arner 1988; Eide 1994; Eide 1995; Jadad 1992; Max 1995) and a further five enrolling fewer than 20 participants (Attal 2002; Jorum 2003; Kupers 1991 central; Leung 2001; Rowbotham 1991). In intermediate-term studies, enrolled arms (parallel studies) or phases (cross-over studies) ranged in size from 12 to 169 participants. Amongst the intermediate-term studies, the mean number of participants enrolled in each arm in parallel studies was 60, whereas the mean total enrolment size in cross-over studies was 52. Studies with small group sizes may overestimate efficacy (Moore 1998; Nuesch 2010).

Evidence from trials in people with arthritis shows that studies lasting less than eight weeks overestimate the effect of treatment (Moore 2010b); the same may be true in studies of neuropathic pain, given that typically both are chronic conditions. Of the 14 intermediate-term studies, nine had treatment phases that lasted less than eight weeks (Frank 2008; Gilron 2005; Gimbel 2003; Harke 2001; Huse 2001; Morley 2003; Watson 1998; Watson 2003; Zin 2010), and only one study was conducted over 12 weeks (Hanna 2008). The five parallel studies had a mean duration of 6.4 weeks, whereas the nine cross-over studies had a mean duration of 5.7 weeks.

Effects of interventions

Short-term studies

Our updated search added two cross-over and one parallel study, which provided additional efficacy data for opioids in 125 participants with neuropathic pain. None of the three studies presented data in a format that we were able to add to our short-term study meta-analyses. In total, 17 RCTs provided efficacy data for acute exposure to opioids in 392 participants with neuropathic pain. In the three new studies, drugs were administered buccally (Simpson 2007) and intravenously (Juarez-Pichardo 2009; Wallace 2006). In total, drugs were administered intravenously in 14 trials, orally in one (Max 1988), intramuscularly in one (Rabben 1999) and

buccally in one (Simpson 2007). The duration of treatment varied from seconds (i.e. a single intramuscular injection) to eight hours, but was less than one hour in 10 trials. The tested drug was morphine in seven trials, alfentanil in four, fentanyl in two, and oxycodone, meperidine, codeine, or the investigational drug CJC-1008 (a chemical modification of the opioid peptide dynorphin A) in one trial each. Placebo was used as a control in 14 trials. The diagnosis was specified in all trials: four trials included people with postherpetic neuralgia (PHN) only (Eide 1994; Max 1988; Rowbotham 1991; Wallace 2006); two involved people with post-traumatic neuralgia (Jorum 2003; Max 1995); in seven, participants with mixed neuropathies were studied (Arner 1988; Dellemijn 1997; Jadad 1992; Juarez-Pichardo 2009; Kupers 1991 central; Kupers 1991 peripheral; Leung 2001; Simpson 2007); two included people with central pain (Attal 2002; Eide 1995); one involved people with secondary (e.g. post-traumatic) trigeminal neuropathy (Rabben 1999); and one enrolled participants with postamputation stump and phantom pain (Wu 2002 phantom limb; Wu 2002 stump). Considerable variation between studies in duration of treatment, and method of pain assessment allowed only limited quantitative synthesis of data.

Outcomes assessed

A change in spontaneous pain intensity was the primary outcome measure in 16 trials. Authors reported mixed results with respect to the analgesic efficacy of opioids for neuropathic pain in general and for specific conditions (i.e. PHN, post-traumatic neuralgia, and central pain). Eight trials showed greater efficacy of the tested opioid versus placebo (Dellemijn 1997; Eide 1995; Jorum 2003; Leung 2001; Rowbotham 1991; Wallace 2006; Wu 2002 phantom limb; Wu 2002 stump) or another active intervention (tramadol, Juarez-Pichardo 2009). In contrast, in five trials, researchers observed equivalent efficacy for opioids and placebo (Arner 1988; Attal 2002; Eide 1994; Max 1988; Max 1995). Two trials demonstrated partial efficacy, meaning that some participants responded to the opioid treatment while others did not (Jadad 1992; Rabben 1999). Another trial showed a reduction in the affective but not in the sensory component of pain (Kupers 1991 central; Kupers 1991 peripheral).

One study, from our updated search, assessed breakthrough pain (Simpson 2007). Fentanyl tablets or placebo were administered buccally to treat nine consecutive episodes of breakthrough pain in each of 79 participants with mixed neuropathies. Drug efficacy was measured for up to 120 minutes for each episode. This study also differed from the other short-term studies in that participants had up to 21 days to complete the nine separate assessments. Because of the unique study design, we were not able to combine data from this study with data from any of the other short-term studies. The study demonstrated statistically significant superiority of fentanyl buccal tablets over placebo for several outcomes, including summed pain intensity over 60 minutes, SPID60 (mean (standard error), 9.63 (0.75) versus 5.73 (0.72), respectively; $P < 0.001$) and proportion of breakthrough episodes with a at least 33% and at least 50% improvement in pain intensity from baseline compared with placebo from 10 minutes (9% versus 3%; $P = 0.008$) through two hours (66% versus 37%; $P < 0.001$).

Meta-analysis

We combined data for meta-analysis from four studies enrolling a total of 90 participants (Attal 2002; Kupers 1991 central; Kupers 1991 peripheral; Rowbotham 1991; Wu 2002 phantom limb; Wu 2002 stump) (Analysis 1.1). The result of the Chi² test for heterogeneity was 0.55 ($P = 0.99$), and the I^2 was 0%, indicating homogeneity between and within studies. The overall mean difference in the last measured pain intensity for active treatment versus placebo was -16 (on a 0 - 100 visual analog scale (VAS)) (95% CI -23 to -9; $P < 0.00001$). We were able to conduct a subanalysis based on origin of neuropathic pain. Data from two trials including a total of 21 participants with central pain and from four trials involving 69 participants with peripheral neuropathic pain were subanalyzed (Analysis 1.1). For peripheral pain, the final pain intensity following opioid administration was 15 points lower than that after placebo (95% CI -23 to -7; $P = 0.0002$), whereas, for central pain, the difference was 18 points (95% CI -30 to -5; $P = 0.006$).

When short-term studies were categorized according to etiology, e.g. post-traumatic neuralgia (Jorum 2003; Max 1995), PHN (Eide 1994; Max 1988; Rowbotham 1991), the results were equivocal. One within-study comparison (Jadad 1992) and two other between-study comparisons (Jorum 2003 versus Max 1995 and Eide 1994 versus Rowbotham 1991) of 'high' versus 'low' opioid doses did not show an association between the opioid dose administered and analgesic efficacy. Two trials reported results in terms of percentage reduction in pain (Leung 2001; Max 1995). Meta-analysis of these two trials demonstrated an additional 26% reduction in pain for opioid versus placebo (95% CI 17 to 35; $P < 0.00001$) (Analysis 1.2), although the total number of participants ($N = 19$) was low.

Sensitivity Analysis

Our two predetermined sensitivity analyses involved removing studies with fewer than 10 participants and removing cross-over studies. Only one study involved in the meta-analysis had fewer than 10 participants in a phase (Max 1995). Removing this study had minimal effect on the point estimate and no effect on statistical significance. All of the short-term studies involved in the meta-analyses employed a cross-over design, therefore sensitivity analysis by study design was not possible.

Intermediate-term studies

The results from the intermediate-term studies are summarized in Appendix 7.

Five trials from our updated search provided data on 385 participants with neuropathic pain treated with opioids (Frank 2008; Hanna 2008; Khoromi 2007; Wu 2008; Zin 2010). The number per treatment group ranged from 29 to 169 (median 50). Three trials had a cross-over design (Frank 2008; Khoromi 2007; Wu 2008) and two had a parallel design (Hanna 2008; Zin 2010).

When both the original and updated searches are combined, 14 trials provided data on 845 people treated with opioids. The number per treatment group ranged from 12 to 169 and the duration of treatment varied from eight days to 12 weeks. Nine trials had a cross-over design and five had a parallel design. Five drugs were tested: morphine in six trials, oxycodone in five trials; methadone in one article comprising two trials; and levorphanol and dihydrocodeine in one trial each. Daily doses ranged from less than 5 mg to 300 mg of oral morphine equivalents, but were generally at the lower end of this range. Placebo was used as a control in all but two studies (Frank 2008; Rowbotham 2003). Five trials, in addition to opioid and placebo, included at least one arm/phase where participants received an active control or combination of interventions: carbamazepine in one trial (Harke 2001), mexiletine (Wu 2008), the tricyclic antidepressants nortriptyline and desipramine (Raja 2002; Khoromi 2007), and gabapentin (Gilron 2005). Khoromi 2007 also included a fourth arm of nortriptyline plus morphine. While many studies allowed participants to continue with any non-opioid drug from their existing regimen, two trials specifically combined an active drug with the opioid and/or the placebo: pregabalin (Zin 2010) and gabapentin (Hanna 2008). Two trials compared different dosages of an opioid: methadone (Morley 2003) and levorphanol (Rowbotham 2003). Eight trials enrolled participants with one specific pain syndrome: diabetic neuropathy (Gimbel 2003; Hanna 2008; Watson 2003), PHN (Raja 2002; Watson 1998), chronic lumbar root pain (Khoromi 2007) and postamputation pain (Huse 2001; Wu 2008). The other studies enrolled people with neuropathic pain of diverse etiologies.

Meta-analysis

Primary outcome - proportion of participants reporting ≥ 33% pain reduction from baseline or ≥ 50% pain reduction from baseline

The more recent studies presented data in a format that allowed us to analyze the number of participants with at least 33% and at least 50% pain relief. For the former, 208 of 367 participants (57%) receiving an opioid achieved at least 33% relief, versus 122 of 360 participants receiving placebo (34%) (Analysis 2.1). The overall point estimate of risk difference was 0.25 (95% CI 0.13 to 0.37, P < 0.0001), translating to an NNTB of 4.0 (95% CI 2.7 to 7.7) There was significant heterogeneity (P = 0.02, I^2 = 63%), which was caused by the much larger risk differences (greater efficacy of opioids) in Gilron 2005 and Watson 1998 in comparison with the other studies. When these studies were removed from the analysis, heterogeneity disappeared, leaving the overall point estimate of risk difference as 0.17 (95% CI: 0.09 to 0.25, P < 0.0001), translating to an NNTB of 5.9 (95% CI 4.0 to 11.1). When number of participants achieving at least 50% pain relief was analyzed, the overall point estimate of risk difference was 0.17 (95% CI 0.02 to 0.33, P = 0.03) (Analysis 2.2), translating to an NNTB of 5.9 (3.0 to 50.0). Both the overall numbers of participants and the percentages achieving at least 50% pain relief were lower, with 72 of 154 (47%) participants receiving opioid versus 46 of 151 (30%) participants receiving placebo achieving at least 50% pain relief. One study (Zin 2010) demonstrated a tendency towards a greater number of participants in the *placebo* group achieving at least 50% pain relief. When this study was removed, the overall point estimate of 0.22 (95% CI: 0.09 to 0.36) in favor of those receiving an opioid, translated to an NNTB of 4.5 (95% CI 2.8 to 11.1) . A smaller number of studies assessed the number of participants with at least 33% or at least 50% pain relief when comparing opioid with an active control (Analysis 3.1; Analysis 3.2). Gilron 2005; Khoromi 2007; and Wu 2008 compared an opioid with gabapentin, a tricyclic antidepressant (nortriptyline), or an antiarrythmic (mexiletine), respectively. Only the last of these demonstrated a statistically significant difference between interventions, with morphine being superior to mexiletine when comparing the number of participants with both at least 33% pain relief (RD = 0.28, 95% CI: 0.08 to 0.48: NNTB = 3.6; 95% CI 2.1 to 12.5) and at least 50% pain relief (RD = 0.20, 95% CI: 0.01 to 0.39: NNTB = 5.0; 95% CI 2.6 to 100.0). Numbers of participants were low in this study, with 50 receiving morphine and 42 mexiletine.

Secondary outcomes

Pain intensity post-intervention

Two studies from our updated search (Khoromi 2007; Wu 2008) added data to our 2005 analysis of pain intensity post-intervention, comparing opioid and placebo (Analysis 2.3). Therefore, nine of the 14 studies provided data suitable for pooling. The meta-analysis now includes 374 opioid-treated and 351 placebo-treated participants and shows the overall mean pain intensity to be 12 points lower in opioid-treated participants than in those treated with placebo (95% CI -15 to -9; P < 0.00001). The addition of the two studies from our updated search (Khoromi 2007; Wu 2008) made a negligible difference to the statistical significance or point estimate. Additionally, the same two studies added data to our analysis comparing mean VAS pain scores for opioids versus active controls (Analysis 3.3). As with comparisons of the number of participants with specified percentages of pain relief, only the com-

parison of morphine versus mexiletine (Wu 2008) demonstrated statistically significant superiority: those receiving morphine had a 13 point lower pain intensity post-intervention (P < 0.0001, 95% CI; -19 to -7). Again, the total number of participants was low.

Evoked pain data that we could meta-analyze were reported in only two studies (Watson 1998; Watson 2003), with low overall numbers of participants. In both these trials oxycodone was significantly superior to placebo in reducing allodynia, categorized as 'skin pain' (Analysis 2.4). When the studies were combined statistically, participants receiving oxycodone had a 24 point lower score (95% CI: -34 to -13, P < 0.0001) on a 0 - 100 VAS.

We found a dose-dependent analgesic effect in two studies (Morley 2003; Rowbotham 2003) that included people with mixed neuropathies. In one (Morley 2003), 'low' and 'high' doses of methadone were each compared separately with placebo; the higher dose produced a greater effect than the lower dose. In the other study (Rowbotham 2003), a direct comparison showed that a higher dose of levorphanol produced a significantly greater analgesic effect than the lower dose. The use of different outcome measures in the two studies precluded the performance of a dose-response meta-analysis.

Quality of life and functioning

Many of the trials measured the effects of opioids on emotional and physical functioning. However, because of the use of multiple measurement tools and differences in the way data were presented, only very limited meta-analysis with low participant numbers was possible. Several studies compared opioid versus placebo for post-intervention results in both the physical and mental health components of the Short Form-36 (Frank 2008; Gilron 2005; Gimbel 2003; Khoromi 2007; Watson 2003; Zin 2010), including three studies from the updated search. The studies reported mixed results; however only two reported data in a format that enabled us to perform meta-analysis (Gilron 2005; Khoromi 2007). From these, only the sub scale 'bodily pain' demonstrated marginal superiority of opioid versus placebo, with those receiving morphine reporting a seven-point improvement (95% CI: 0.1 to 13, Analysis 2.5). For those studies that also reported results for bodily pain, but in a format that we could not add to our meta-analysis, two did not show an improvement of opioid over placebo (Gimbel 2003; Zin 2010), whereas Watson 2003 did report superiority. When comparing opioid versus active control, neither Gilron 2005 nor Khoromi 2007 demonstrated significant differences for any subscales, other than Khoromi 2007 reporting an 11-point improvement in mental health for nortriptyline versus morphine (95% CI: 1 to 21) (Analysis 3.4). Two studies comparing opioid with placebo (Gilron 2005; Gimbel 2003) demonstrated improvements in several aspects of the Brief Pain Inventory, both physical and emotional, with the greatest improvement over placebo occurring in sleep, where those receiving an opioid had a 1.7 point (on an 11-point scale) superiority over placebo (95% CI: -2.4 to -1.1, P < 0.00001, Analysis 2.6). Emotional functioning was measured by several questionnaires, including the Beck Depression Inventory and the Profile of Mood States questionnaire. We were able to meta-analyze data from the Beck Depression Inventory when comparing both opioid and placebo, and opioid with active controls. In both cases, meta-analysis did not demonstrate statistical differences between interventions (Analysis 2.7; Analysis 3.5), although mean scores in all groups were in the minimal to mild depression range (Dworkin 2008). Similarly, no improvement was noted in the Profile of Mood States scores of those with mixed neuropathies treated with two different dosages of levorphanol (Rowbotham 2003) nor in the Rand Mental Health Inventory completed by people with diabetic neuropathy following oxycodone treatment (Gimbel 2003).

Adverse events and withdrawals due to adverse events or lack of efficacy

As with our 2005 review, we extracted data on the incidence of common opioid-related adverse events from all intermediate-term studies comparing opioids with placebo. In addition, for our updated review, we analyzed adverse events when comparing opioids with active controls and divided participant withdrawals into two categories: those due to adverse events and those due to lack of efficacy, although it could be argued that both denote failure of therapy. Finally, as noted above, we used a random-effects model, as opposed to the fixed-effect model employed in our original review.

All but one of the intermediate-term studies from our updated search contributed data for meta-analysis: Frank 2008 counted each incidence of an adverse event, rather than the number of participants reporting. From our original review, Huse 2001 reported adverse events on a VAS, precluding determination of the numbers of affected participants, and Rowbotham 2003 compared two different doses of the opioid levorphanol; consequently their data could not be combined with other studies. The new studies approximately double the available participants ('N') for each analysis, increasing our confidence in their results. Although overall point estimates remained similar, the increased overall numbers meant that three of the comparisons for opioid versus placebo changed from non-statistically significant to significant (dizziness, drowsiness and vomiting).

The incidence of common adverse events in both opioid and placebo groups remained similar after including the new data: constipation was the most common (34% opioid versus 9% placebo: NNTH 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0) (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5). Data on cognitive im-

pairment as well as on other adverse events were insufficient to allow calculation of the NNTH.

Our new analysis of adverse event rates for opioid versus active interventions generally demonstrated non-statistically significant differences between treatments; however, both constipation (38% opioid versus 9% control: NNTH 3.4; 95% CI 2.6 to 4.8) and drowsiness (23% opioid versus 9% control: NNTH 7.7; 95% CI 5.0 to 16.7) occurred more frequently with opioids (Analysis 5.1; Analysis 5.3).

When opioid therapy is initiated, recipients may abandon treatment because of either adverse events or lack of efficacy. In our updated analysis, more participants withdrew from opioid treatment due to adverse events than from placebo, with 55 (13%) of 435 participants in seven studies withdrawing during opioid therapy versus 18 (4%) of 432 receiving placebo (NNTH 12.5; 95% CI 8.3 to 25.0) (Analysis 4.6). Conversely, more participants receiving placebo withdrew due to lack of efficacy, with eight of 363 (2%) participants receiving opioid withdrawing versus 42 of 360 (12%) receiving placebo (NNTH -11.1; 95% CI -20.0 to -8.3) (Analysis 4.7). Only one study compared withdrawal rates between opioid and an active control, nortriptyline, and did not show a statistically significant difference in rates due to either adverse events or lack of efficacy (Khoromi 2007).

Both the Chi² and I² tests for each adverse event analyzed suggested that heterogeneity existed amongst results. This may have been due to genuine differences in event rates, differences in study populations, or as a result of authors using different measurements or thresholds for reporting adverse events. In most cases, removal of one outlying study from each analysis substantially reduced heterogeneity.

Sensitivity Analysis

As with the short-term studies, our two predetermined sensitivity analyses involved removing studies with fewer than 10 participants and removing cross-over studies. None of the intermediate-term studies had fewer than 10 participants in an individual arm or phase. All of the studies comparing opioid with active control in our meta-analysis employed a cross-over design; therefore sensitivity analysis of such studies was not possible. The majority of studies contributing data to our comparisons of opioid versus placebo also had a cross-over design. Only five studies employed a parallel design (Gimbel 2003; Hanna 2008; Harke 2001; Rowbotham 2003; Zin 2010). Rowbotham 2003 did not contribute data to our analysis. In the few comparisons where there were sufficient numbers of both parallel and cross-over studies, removal of cross-over studies generally had only small effects on the point estimates of efficacy or safety, and in no cases did statistically significant overall estimates become non-significant. Equally, the difference in overall estimates between cross-over and parallel studies was small and did not consistently show more favorable results with cross-over studies.

DISCUSSION

Summary of main results

The results of this review can be divided into two categories according to the duration of included trials.

Short-term studies

Short-term trials demonstrated mixed results with respect to the analgesic efficacy of opioids. Our updated search did not yield any new studies suitable for statistical analysis. Although our meta-analysis showed an overall mean difference in the last measured pain intensity for short-term active treatment versus placebo of -16 points (on a 0 - 100 visual analog scale (VAS)), the result should be interpreted with caution because it is based on only six of 17 studies (and only 90 of 392 participants). Thus, our conclusion regarding this category of studies has not changed from our previous meta-analyses.

Intermediate-term studies

Efficacy

In contrast, intermediate-term trials demonstrated consistent opioid analgesic efficacy in reducing spontaneous neuropathic pain that was almost entirely statistically significant when results were pooled, although studies were small, mostly short, and potentially dealt inadequately with data once participants withdrew from treatment. Our updated review added data to our original analyses, increasing confidence in their findings, but also introduced new outcome analyses, i.e. number of participants with at least 33% and 50% reduction and assessments of functioning, which are considered clinically important in chronic pain (Dworkin 2008). Intermediate-term studies are more clinically relevant than short-term studies because they assess the benefits and risks associated with opioid treatments for weeks to months, i.e. they reflect how opioids are administered for neuropathic pain in clinical practice. This part of the meta-analysis was based on most of the available trials and included the majority of participants. Hence, we conclude that intermediate-term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain as measured by both number of participants with at least 33% and at least 50% pain relief and in mean differences in post-intervention pain intensity. Opioids did not demonstrate improvement in many aspects of emotional or physical functioning, as measured by various validated questionnaires. This raises the concern that improvements in pain relief are not accompanied by similar improvements in activities of daily living or quality of life. It should be noted, however, that our meta-analyses of functioning included few studies, with low overall numbers of participants.

When comparing opioids with active controls, only the comparison of morphine with the rarely used antiarrythmic mexiletine demonstrated superiority of opioid (Wu 2008), with other comparisons not showing statistically significant differences between treatments. This may be due to opioids genuinely having similar efficacy to other interventions, or it may simply be a result of low participant numbers. Indirect comparisons with meta-analyses of other treatments for neuropathic pain offer limited clarification. For example, Moore 2011 compared gabapentin with placebo for several similar efficacy outcomes. While the numbers needed to treat for an additional beneficial outcome (NNTBs) are similar for at least 50% pain relief and 33% pain relief (defined as 'moderate' relief in Moore 2011), placebo rates are much higher in the opioid analyses. Equally, participants in the gabapentin analyses often required the maximum daily dose (3600 mg), whereas in the opioid studies a larger effect was achieved by a low to moderate dose of opioid. Moreover, the dose-dependent analgesic effects shown in two of the opioid studies (Morley 2003; Rowbotham 2003) have not been confirmed by further trials; it is therefore unclear if high doses of opioids produce a greater magnitude of pain reduction in people with neuropathic pain. Thus, we are unable to confirm the commonly held belief that opioids have no ceiling effect in this population. This may be particularly important in light of recent concerns regarding mortality risk associated with high opioid dose regimens (Gomes 2011).

Safety

Our assessment of safety did not find data related to serious adverse events, including mortality, most likely because of the relative rarity of such events, especially with low-to-moderate doses of opioids. Instead, we were able to analyze data related to relatively common, widely identified opioid-induced adverse events. Not surprisingly, and in agreement with our earlier review, many of the most commonly recognized opioid side effects occurred more frequently in those treated with opioid than with placebo. Conversely, there were few statistically significant differences between opioids and active controls, which may be due to controls having similar side-effect profiles, or to the small participant numbers for each comparison. However, constipation and drowsiness did appear to occur more commonly. In placebo-controlled studies, 13% of participants withdrew from opioid therapy due to adverse events, and 2% due to lack of efficacy. While these percentages are not particularly high, most of the study durations were less than eight weeks; therefore numbers may increase over longer periods. Additionally, the available randomized controlled trials (RCTs) do not clearly address the issues of addiction and abuse. The absence of any report of addictive behavior or abuse in any of the intermediate-term trials may have several explanations. It is possible that the prevalence of these behaviors is indeed low (Sullivan 2005). Alternatively, the duration of treatment in these studies may have been too short to allow such behaviors to develop. Furthermore, although not mentioned specifically as an exclusion criterion in all studies, it is reasonable to assume that the recruitment of people with active or potential abuse disorders (Dunbar 1996) into such studies would routinely be avoided. The need to further assess the risk of abuse and addiction continues to be important.

Overall completeness and applicability of evidence

Completeness

The included articles studied participants with a wide range of neuropathies, but predominately postherpetic neuralgia (PHN) and diabetic neuropathy. This reflects the distribution of neuropathic pain in the general population, with the exception that few studies included participants with back pain of neuropathic origin, which is thought to be the most common type of neuropathic pain (Torrance 2006). This may be due to the fact that it is often difficult to diagnose back pain as being purely neuropathic, with it frequently also having features of nociceptive pain. There were insufficient numbers of participants with individual neuropathies to perform a subanalysis of efficacy or safety. While our updated review added a substantial amount of data for each meta-analysis, the overall numbers are still low for most comparisons. In particular, the inconsistency of reporting of outcomes related to functioning precludes our making firm conclusions. Many of the studies reported outcomes only on those participants completing the trial; therefore efficacy may have been over-estimated. In those that performed an intention-to-treat (ITT) or modified ITT analysis, the most commonly used method of imputation was last observation carried forward (LOCF), which again may overestimate efficacy (Moore 2012). None of the studies used baseline observation carried forward (BOCF). The short duration of many intermediate-term studies is also a potential source of bias (Moore 2010a).

Applicability

Several points deserve consideration in terms of applicability of the evidence.

First, the fact that short-term trials, in contrast to the intermediate-term trials, yielded inconsistent efficacy results suggests that short-term opioid administration is unlikely to serve as a useful predictive tool when initiating a trial of opioid therapy in people with neuropathic pain.

Second, the NNTB results further confirm that opioids reduce various forms of neuropathic pain and are relatively safe, and therefore indicate that opioids at low-to-moderate doses are suitable for use over periods of weeks to months in the treatment of neuropathic pain. However, despite the common use of NNTB values to compare relative efficacy of different treatments, especially when head-to-head comparative trials are relatively scarce, their

validity has been questioned for reasons such as differences in trial designs, exclusion of non-placebo-controlled trials, dichotomization of data, and strict and not necessarily clinically relevant cut-off points (i.e. 50% pain relief) (Finnerup 2010).

Third, the use of a single dimension for assessment of efficacy of analgesic treatments is problematic in any form of chronic pain, which is a multi-dimensional phenomenon. This becomes even more problematic in neuropathic pain, where even a single etiological syndrome (e.g. PHN) typically differs considerably from one patient to another in term of its clinical representation. For that reason the use of additional outcome measures rather than a single pain intensity or pain relief method have been recommended (Wittink 2005). Unfortunately, consistent improvement in specific features of neuropathic pain (e.g. evoked pain), in emotional or physical aspects of functioning, or in health-related quality of life could not be demonstrated in the present review.

Fourth, the debate regarding the differential efficacy of opioids for central versus peripheral neuropathic pain (Ballantyne 2003; Canavero 2003; Dellemijn 1999; McQuay 1997; Nicholson 2004) has not been resolved by our study. Results of the included studies varied considerably and the meta-analyses could not include all relevant studies. Despite limited data, the meta-analyses showed similar opioid responsiveness for pain of central and peripheral etiologies.

Fifth, although a dose-dependent analgesic effect was found in two studies, the dose ranges tested are still in the low-intermediate range and do not necessarily reflect clinical practice in some countries (e.g. the USA). This, along with increasing concerns about opioid toxicity, especially at higher dose ranges (greater than the daily equivalent of 200 mg of oral morphine), does not support the use of high doses of opioids for the relief of neuropathic pain.

Lastly, this review also included a quantitative analysis of common opioid-related adverse effects. Although the analysis is based on a relatively large number of participants with neuropathic pain, those enrolled in clinical trials may not be representative of the broader patient population seen in clinical practice. Enrolled participants have met inclusion criteria, and their willingness to enter a clinical trial suggests that they may have a higher adherence profile compared with those who are not enrolled.

Quality of the evidence

The quality of evidence improved somewhat with those articles included in our updated search. Many more of the newer studies reported outcomes considered to be clinically relevant, such as numbers of participants with at least 50% pain relief, and in a format that allowed us to perform meta-analysis (Dworkin 2008). Additionally, the risk of bias for each domain, while low overall, was generally lower in newer studies.

Potential biases in the review process

We believe the search methodology used here to be unbiased, and the selection criteria relevant to the nature of neuropathic pain. However, two aspects of our review methodology have the potential to introduce bias to our analyses. First, we included studies of less than 12 weeks duration. While we included 'short-term' studies purely for 'proof of concept', even amongst our 'intermediate-term' studies only one (Hanna 2008) was conducted over 12 weeks. Studies of less than 12 weeks duration may overestimate treatment efficacy (Moore 2010a). Given the dearth of long-term studies, we adopted a 'best available evidence' approach, and anticipate that future studies will have longer durations, allowing us to better assess the efficacy and safety of opioids administered over clinically relevant time periods.

Second, we analyzed data from cross-over studies in the same manner as that from parallel studies. This approach may give rise to a unit-of-analysis error (Higgins 2011). However, as discussed (Effects of interventions) we performed a sensitivity analysis where cross-over studies were removed from meta-analyses and found negligible differences in estimates of effect for either efficacy or safety.

Agreements and disagreements with other studies or reviews

Most recent guidelines on the pharmacotherapy of neuropathic pain are in agreement with the results of the present review and recommend the use of opioids, typically as second- or third-line treatment options (Attal 2010; Dworkin 2010; Moulin 2007; Pergolizzi 2008).

A systematic review of the evidence for pharmacological treatment of neuropathic pain (Finnerup 2010) also found that opioids have a consistent efficacy in neuropathic pain. Notably, the NNTBs for achieving meaningful pain relief in several neuropathic pain conditions (i.e. painful polyneuropathy, postherpetic neuralgia, peripheral nerve injury and mixed neuropathic pain) varied from 2.1 to 5.1 and were slightly lower than the NNTBs found in the present review. The differences in findings occurred for several reasons. First, we excluded studies with tramadol. Second, we had two additional studies in our NNTB analysis (Khoromi 2007; Zin 2010). Third, Finnerup 2010 combined results for participants with at least 33% and at least 50% pain relief, whereas we analyzed these outcomes separately. Last, and perhaps most importantly, they performed meta-analysis separately for each neuropathic pain syndrome. We combined data as we considered numbers of participants for each syndrome to be insufficient for subanalysis.

AUTHORS' CONCLUSIONS

Implications for practice

Short-term studies provided only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and unclear, potentially inadequate methods for handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. The difference in outcomes between short-term and intermediate-term opioid studies does not support the use of short-term opioid administration as a predictive tool to decide whether to initiate a trial of opioid therapy. Although our review demonstrated clinically significant efficacy of opioids and an increase in the incidence of commonly-reported side effects in the intermediate term for neuropathic pain, the participants in the included studies may not reflect those commonly seen in practice. Therefore, issues such as rare but serious adverse events, abuse of medication, or conversely, non-compliance due to participants' unwillingness to tolerate side effects may not be accurately reflected in our results. Clinicians may be required to assess persons' suitability for a trial of opioid therapy and to monitor progress more rigorously than they would for other pharmacological treatments.

Implications for research

Our updated and revised meta-analysis takes the necessary step of showing efficacy for spontaneous pain during opioid treatment for up to three months. A goal of future studies in this area should be to evaluate the true efficacy of opioids for neuropathic pain by means of trials with wider dose ranges rather than fixed-dose studies. In addition, further RCTs assessing longer-term efficacy, safety (including addiction potential), and improved quality of life should be undertaken before the value of opioids for management of neuropathic pain is finally established.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arner 1988

Methods	Cross-over - at least 4 test infusions with active drug or placebo given
Participants	Participants enrolled: 8 Neuropathic pain diagnosis: Mixed deafferentation
Interventions	Morphine: 15 mg IV over 15 mins Placebo
Outcomes	VAS pain intensity, before and 15 mins after infusion. Means of VAS pain reduction compared between active and placebo phases. In some participants, categorical pain relief was assessed (reasons for only some participants not given). 'Positive' outcome defined as moderate or complete pain relief
Notes	Adverse events, withdrawals not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of methods
Allocation concealment (selection bias)	Unclear risk	No description of methods
Blinding (performance bias and detection bias) All outcomes	Low risk	"Test infusions were prepared with saline or opioids by a nurse who was not a regular member of the ward staff. The infusions were coded and handed over to another nurse"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appear to have completed the study
Selective reporting (reporting bias)	Unclear risk	All outcomes described in Methods section are reported in Results section, but are difficult to interpret. No protocol available

Attal 2002

Methods	Cross-over, single doses, separated by at least 2 weeks
Participants	Participants enrolled: 15 Neuropathic pain diagnosis: central: SC (n = 9), post-stroke pain (n = 6)
Interventions	Morphine IV: 9 to 30 mg (mean 16 ± 6), previously individually titrated to maximum dose tolerated, over 20 mins Placebo
Outcomes	Spontaneous pain intensity at baseline, every 15 mins up to 1 hr, then at 90 and 120 minutes (0 - 100 VAS). Total relief = 100% reduction in pain intensity, major relief = at least 50% reduction, no relief or worse pain = decreased by less than 5% or increased Tactile allodynia Mechanical detection and pain thresholds Thermal detection and pain Global assessment of pain relief (complete through worse pain), blindness
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods not described
Allocation concealment (selection bias)	Low risk	"A study nurse maintained the blind nature of the study and performed the randomization by means of sealed envelopes that contained study medication and order of administration"
Blinding (performance bias and detection bias) All outcomes	Low risk	"IV morphine or saline in the same volume was administered using the dosage determined during the unblinded phase. IV infusion was performed over a 20-minute period by an anesthesiologist unaware of the treatment and who did not participate in the unblinded phase". 7/15 subjects correctly identified the active treatment. The examiner identified active treatment in 10/15 cases
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data from completers only; however only 1 of 16 participants withdrew post-randomization "because he did not wish to continue"

Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section. Data for outcome analyzed are provided

Dellemijn 1997

Methods	Cross-over, single doses (fentanyl vs saline or fentanyl vs diazepam)
Participants	Participants enrolled: 53 Neuropathic pain diagnosis: peripheral (n = 50), central (n = 3)
Interventions	Fentanyl: 5 mcg/kg/min for maximum of 5 hrs Diazepam: 0.2 mcg/kg/min for maximum of 5 hrs Saline
Outcomes	Pain intensity and pain unpleasantness (0 - 100 NRS). Pain intensity difference expressed as percentage of baseline pain intensity. Peak pain intensity difference and average pain intensity difference over 8 hrs. Responders defined as those in whom pain intensity or unpleasantness reduced by 50% at any time point
Notes	90% of fentanyl infusions vs 46% diazepam infusions vs 8% saline infusions stopped early due to adverse events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Performed in the hospital pharmacy in blocks of 4.
Allocation concealment (selection bias)	Low risk	Sealed envelopes from hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Infusions prepared in pharmacy and delivered to study nurse. All infusions identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropouts and for non-intervention-related reasons
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Eide 1994

Methods	Cross-over, single doses, separated by one week
Participants	Participants enrolled: 8 Neuropathic pain diagnosis: PHN
Interventions	Morphine IV: 0.075 mg/kg over 10 mins Ketamine IV: 0.15 mg/kg over 10 mins Placebo
Outcomes	VAS 0 - 100 (no relief through very significant relief) pain relief Assessment of allodynia, wind-up-like pain, tactile sensibility and thermal sensibility
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Eide 1995

Methods	Cross-over, single doses, separated by 2 hrs
Participants	Participants enrolled: 9 Neuropathic pain diagnosis: central spinal cord injury
Interventions	Alfentanil IV: 7 mcg/kg over 5 mins + 0.6 mcg/kg/min for 17 to 21 mins Ketamine IV: 60 mcg/kg over 5 mins + 6 mcg/kg/min for 17 to 21 mins Placebo
Outcomes	Median % reduction in VAS (0 = no pain, 100 = unbearable pain) continuous pain intensity Allodynia Wind-up-like pain Thermal pain threshold

Eide 1995 (*Continued*)

Notes	Pain intensity reduction data extracted from figure	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Latin square
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Frank 2008

Methods	Cross-over, each arm 6 weeks, with 2-week washout between	
Participants	Participants enrolled: 96 Neuropathic pain diagnosis: mixed	
Interventions	Dihydrocodeine: oral 30 - 240 mg/day Nabilone: oral 0.25 - 2 mg/day	
Outcomes	Pain intensity: Mean VAS 0 - 100 computed over the last 2 weeks of each treatment period SF-36 Hospital Anxiety and Depression Score	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Treatment was allocated by random permuted blocks of 10".
Allocation concealment (selection bias)	Low risk	Coded envelopes retained in pharmacy

Frank 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The pharmacy supplied identical white capsules containing 250 mcg nabilone or 30 mg dihydrocodeine"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Both available case analysis and per protocol analysis presented. Similar outcomes in each population. Greater number of participants withdrew due to side effects in dihydrocodeine phases
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Gilron 2005

Methods	Cross-over, each arm 5 weeks (including titration and washout)
Participants	Neuropathic pain diagnosis: Diabetic neuropathy (n = 35), PHN (n = 22)
Interventions	Morphine oral long-acting: up to 120 mg/day Gabapentin: up to 3200 mg/day Morphine/Gabapentin combination: up to 60 mg/2400 mg combined/day Placebo (lorazepam): up to 1.6 mg/day All drugs titrated upwards over 3 weeks, maintained at maximum tolerated dose for one week, then tapered and 3-day washout on 5th week
Outcomes	VAS 0 - 10 (0 = no pain, 10 = worst imaginable) pain intensity at maximum tolerated dose averaged over 7 days McGill Pain Questionnaire Brief Pain Inventory Beck Depression Inventory SF-36 Mini-Mental State Examination Global pain relief (worse through complete relief) Incidence and severity (mild, moderate, severe) of adverse events
Notes	Baseline pain intensity: 5.72 ± 0.23 (SE)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Balanced Latin-square cross-over design assigned by hospital pharmacist
Allocation concealment (selection bias)	Low risk	Allocation concealed by a hospital pharmacist

Gilron 2005 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants received identical-appearing capsules in a double-dummy design. Active placebo (lorazepam) used. Participants asked to guess treatment allocation - slightly higher correct responses when receiving placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals (16/57) evenly distributed amongst groups, but reasons for withdrawal not fully described
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Gimbel 2003

Methods	Parallel, 6 weeks
Participants	Study arms enrolled: Opioid group: 82; Control group: 77 Neuropathic pain diagnosis: Diabetic neuropathy
Interventions	Oxycodone oral long-acting: 10 to 60 mg twice daily (mean: 37 ± 21) Placebo
Outcomes	Average, current and worst daily NRS (0 - 10) pain intensity Satisfaction with pain medication Sleep Quality Brief Pain Inventory Rand Mental Health Inventory Sickness Impact Profile SF-36 Incidence and severity of adverse events
Notes	Average pain intensity of ≥ 5 required for enrolment. Jensen 2006 reported on the same study and participants, but also presented scores for each item on the Neuropathic Pain Scale, from which we were able to extract data for Analysis 2.1.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer generated randomization schedule with permuted blocks of size 4 was used to assign subjects to study treatment"
Allocation concealment (selection bias)	Low risk	Randomized information sealed at sponsor site

Gimbel 2003 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo described as being identical to opioid
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although a relatively large number of dropouts (44/159), they were equally distributed between the groups (19 vs. 25) and reasons specified. Analysis performed on ITT population using LOCF
Selective reporting (reporting bias)	Low risk	Data provided for primary outcome and most secondary outcomes described in Methods section. Some secondary outcomes only listed as being NS between groups

Hanna 2008

Methods	Parallel, 12 weeks
Participants	Study arms enrolled: Oxycodone group: 169; Placebo group: 169 Neuropathic pain diagnosis: Diabetic neuropathy
Interventions	Oxycodone oral long-acting: 10 - 80 mg/day Placebo
Outcomes	Primary: Pain intensity difference (Box-scale 11 pain scores) Secondary: escape medication use; sleep disturbance/sleep quality; participants' global assessment of pain Exploratory: SF-BPI; Short-Form McGill Pain Questionnaire; EuroQoL, EQ-5D; and subject resource utilization
Notes	Oxycodone or placebo was added to participants' standing gabapentin therapy. Gabapentin dose ranged from 100 - 4800 mg/day

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using a validated interactive voice response system that automated the assignment of treatment groups to randomization numbers in accordance with a randomization schedule. Treatment allocation was in balanced blocks of 4 and was stratified by country"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"matched placebo oxycodone tablets", but not stated whether they appeared identical

Hanna 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data imputed using LOCF
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Harke 2001

Methods	Parallel, 2-phase, 8 days each phase
Participants	Study arms enrolled: Morphine group: 21; Placebo group I: 17; Carbamazepine group: 22; Placebo group II: 21 Neuropathic pain diagnosis: Mixed peripheral
Interventions	Morphine oral long-acting: 30 mg 3 times daily Placebo Carbamazepine: 200 mg oral 3 times daily
Outcomes	Pain intensity NRS (0 - 10) Time to reactivation of spinal cord stimulator
Notes	Participants had peripheral neuropathic pain reduced by spinal cord stimulation. They were switched into a painful state after device deactivation. In Phase 1, participants were randomly allocated to receive either carbamazepine (600 mg/day) or placebo during an spinal cord stimulator-free period of 8 days. In Phase 2, oral morphine or placebo were administered under similar conditions

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal withdrawals
Selective reporting (reporting bias)	Unclear risk	Not clear from Methods section what outcomes were considered

Huse 2001

Methods	Cross-over, 4 weeks
Participants	Participants enrolled: 12 Neuropathic pain diagnosis: Phantom limb
Interventions	Morphine oral long-acting: 70 - 300 mg/day Placebo
Outcomes	Pain intensity VAS (0 - 1): mean and numbers with 50% reduction Electrical pain threshold (mA) Pain-Related Self-Treatment Scale Brief Stress Scale West Haven-Yale Multidimensional Pain Inventory 'd2-test' (test for attention performance)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Morphine and placebo described as identical and were prepared by the pharmacy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants were required to complete hourly pain diaries for 4 weeks - no mention of imputation of missing values
Selective reporting (reporting bias)	Unclear risk	Large number of outcomes assessed, but not all reported

Jadad 1992

Methods	Cross-over, 8 hrs, separated by 24 hrs.
Participants	Participants enrolled: 7 Neuropathic pain diagnosis: central (n = 1), peripheral (n = 6)
Interventions	Morphine (low vs high dose): PCA up to 30 mg/hr for up to 8 hrs, or up to 90 mg/hr for up to 8 hrs
Outcomes	% maximal total pain relief

Jadad 1992 (*Continued*)

Notes	Study compared responses in participants with nociceptive and neuropathic pain. Participant information reflects only those with neuropathic pain	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	Unclear risk	"codes kept in a sealed envelope until the patients had completed both sessions", but no mention of who generated the codes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The syringes were filled by a nurse and connected by a nurse not involved with the assessments", but no description of whether comparator syringes appeared identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant withdrew after first session. Reasons for dropout described and unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	Some outcomes reported only as P values, but none used in analyses

Jorum 2003

Methods	Cross-over, single doses, separated by at least 2 hrs	
Participants	Participants enrolled: 12 Neuropathic pain diagnosis: PTN (n = 11), PHN (n = 1)	
Interventions	Alfentanil: 7 μg/kg over 5 mins + 0.6 μg/kg/min over 20 mins Ketamine: 60 μg/kg over 5 mins + 6 μg/kg/min over 20 mins Placebo	
Outcomes	Pain elicited at threshold level for cold pain (0 - 10 VAS) Radiation of pain from site of stimulation (Y or N) Mechanical allodynia and ongoing pain (0 - 10 VAS) All measurements taken before (baseline) and during drug infusion	
Notes	Data extracted from figure	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Jorum 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Using a Latin square design, the participants were randomized to one of 12 possible sequences by the use of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Intervention preparation performed "by someone not present during the examination", but no mention of whether syringes appeared identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all participants completed the study and contributed data for all outcomes
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Juarez-Pichardo 2009

Methods	Parallel, single doses
Participants	Participants enrolled: oxycodone/lidocaine group 14; tramadol/lidocaine group 13 Neuropathic pain diagnosis: mixed
Interventions	Oxcodone: 10 mg plus lidocaine 3 mg/kg Tramadol: 100 mg plus lidocaine 3 mg/kg Both administered over 2 hrs as single intravenous infusions
Outcomes	VAS (0 - 10): spontaneous pain, tactile and thermal (cold) allodynia, hyperalgesia Nausea and vomiting (VAS) Satisfaction Sedation Vital signs
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described

Juarez-Pichardo 2009 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Authors state that investigators were unaware of intervention administered (no mention of participant blinding), but methods to ensure blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	All outcomes described in Methods section are reported in Results section, but method of presenting outcomes not described in Methods section

Khoromi 2007

Methods	Cross-over, 9 weeks each phase
Participants	Participants enrolled: 55 (28 participants received all 4 treatments) Neuropathic pain diagnosis: Chronic lumbar root pain
Interventions	Morphine: 10 - 60 mg/day (mean: 62 ± 29) Nortriptyline: 25 - 100 mg/day (mean: 84 ± 24) Morphine + nortriptyline (not included in our analysis) Placebo
Outcomes	NRS: average and worst leg pain Global pain relief SF-36 Beck Depression Inventory Oswestry Disability Index
Notes	Negative results may be due to small groups, newspaper recruitment, or type of neuropathic pain (lumbar radiculopathy)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were assigned by random numbers within blocks of four to one of four treatment sequences "
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical blue and pink pills for all groups of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 28 of 55 randomized participants completed all 4 arms of the study. Efficacy analysis included participants who completed at least 2 treatment arms. Drop-

		outs adequately described
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Kupers 1991 central

Methods	Cross-over, 50 mins, separated by at least 24 hrs
Participants	Participants enrolled: 6 Neuropathic pain diagnosis: central
Interventions	Morphine: 0.3 mg/kg in 5 divided bolus doses every 10 mins Placebo
Outcomes	Change (pre- to post-injection) in affective and sensory dimensions of pain sensation (McGill Pain Questionnaire, 0 - 100 NRS)
Notes	Data extracted in part from figure Results refer to the "affective" component of pain Adverse events not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"All drugs were administered intravenously by a third person. Both the patient and the clinician who made the assessments were not told which of the two drugs was being given", but no mention of whether interventions appeared identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Kupers 1991 peripheral

Methods	Cross-over, 50 mins, separated by at least 24 hrs
Participants	Participants enrolled: 8 Neuropathic pain diagnosis: peripheral
Interventions	Morphine: 0.3 mg/kg in 5 divided bolus doses every 10 mins Placebo
Outcomes	See Kupers 1991 central
Notes	See Kupers 1991 central Kupers 1991 central and Kupers 1991 peripheral are same study - we divided results by participants with peripheral pain or with central pain

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"All drugs were administered intravenously by a third person. Both the patient and the clinician who made the assessments were not told which of the two drugs was being given", but no mention of whether interventions appeared identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Leung 2001

Methods	Cross-over, single doses, separated by 1 week
Participants	Participants enrolled: 12 Neuropathic pain diagnosis: RSD (n = 6), PHN (n = 4), SC (n = 1), causalgia (n = 1)
Interventions	Alfentanil: 20 min infusion aimed at achieving plasma levels of 25, 50 and 75 ng/ml Ketamine: 20 min infusion aimed at achieving plasma levels of 50, 100 and 150 ng/ml Placebo (diphenhydramine)

Leung 2001 (*Continued*)

Outcomes	% VAS (0 - 100) reduction in spontaneous and evoked pain Effect on neurosensory threshold and allodynic area
Notes	Data extracted from figures

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Diphenhydramine used as a placebo due to side effect profile similar to other interventions, but no mention of whether interventions appeared identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Max 1988

Methods	Cross-over, single doses, separated by at least 48 hrs
Participants	Participants enrolled: 46 Neuropathic pain diagnosis: PHN
Interventions	Codeine: 120 mg single oral dose Clonidine: 0.2 mg single oral dose Ibuprofen: 800 mg single oral dose Placebo
Outcomes	Pain intensity and relief at baseline, and each hr through 6 hrs Categorical scales of pain (severe = 3, none = 0) and relief (complete = 4, none = 0); VAS for pain and relief (100 mm) McGill Pain Questionnaire and verbal descriptor scales (13-word lists of descriptors for pain intensity, pain unpleasantness, and "overall" pain) SPID and TOTPAR derived from above scales
Notes	

Risk of bias

Max 1988 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Capsules had identical appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/46 did not provide data, but only 1 case was due to opioid side effect
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Max 1995

Methods	Cross-over, single infusions, separated by 1 day
Participants	Participants enrolled: 8 Neuropathic pain diagnosis: PTN
Interventions	Alfentanil: 1.5 µg/kg/min for 60 mins; rate doubled as required at 60 and 90 mins for a total of 2 hrs Ketamine: 0.75 mg/kg/hr for 20 mins; rate doubled as required at 60 and 90 mins for a total of 2 hrs Placebo
Outcomes	Background pain (0 - 100 VAS) Mechanical allodynia (0 - 100 VAS) % pain relief from both of above
Notes	SD calculated from data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Solutions prepared by third party, but no mention of appearing identical

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Morley 2003

Methods	Randomized, double-blind, placebo-controlled cross-over. Two phases, each 20 days
Participants	Participants enrolled: Low-dose phase: 19 High-dose phase: 17 Neuropathic pain diagnosis: Mixed lasting > 3 months
Interventions	Phase I: Methadone oral: 5 mg twice daily alternating with placebo on odd days and rest on even days Phase II: Methadone oral: 10 mg twice daily alternating with placebo on odd days and rest on even days
Outcomes	All outcomes assessed each evening in patient diaries. Maxium and average pain intensity, pain relief (VAS). Adverse effects with severity (mild, moderate, severe). Any additional "prn" medications required
Notes	For each phase, results of 5 days with active intervention were compared with results of 5 days with placebo. Analyses of safety and efficacy in this review are based on Phase I (low-dose phase). Participants had neuropathic pain that had not been satisfactorily relieved by other interventions or by current or previous drug regimens. Participants were permitted to continue with concurrent medications, some of which were opioids

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eight replications of a Latin square design
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication containers appeared identical, and medications "were not distinguishable by taste or appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only participants completing study were analyzed, 6 participants withdrew from high-dose phase due to severe nausea - 3

		while taking placebo, 3 while taking methadone
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Rabben 1999

Methods	Cross-over, single doses, separated by 1 week
Participants	Participants enrolled: 30 Neuropathic pain diagnosis: Trigeminal neuropathic pain
Interventions	Meperidine: 1.0 mg/kg IM Ketamine: 0.4 mg/kg IM + midazolam: 0.05 mg/kg IM
Outcomes	Pain intensity (VAS 0 - 100) pre- and post-intervention % of initial pain at best time point (= maximal response) Three different subgroups of response were defined: no analgesic effect, short-term analgesic effect, and long-term analgesic effect
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized in blocks of four according to sex, age, and duration of pain"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants receiving pethidine withdrew due to nausea
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Raja 2002

Methods	Randomized, double-blind, active- and placebo-controlled, cross-over. Each treatment period lasted approximately 8 weeks and had a titration, maintenance, and taper phase. The treatment periods were separated by a 1-week drug-free, washout period
Participants	Participants enrolled: Opioid arm: 76 Control arm: 76 Placebo arm: 76 Neuropathic pain diagnosis: PHN (pain persisting ≥ 3 months after resolution of cutaneous lesions)
Interventions	Morphine oral: 15 to 240 mg/day or methadone oral 5 to 80 mg/day (means 91 ± 49.3 and 15 ± 2.0) Nortriptyline or desipramine: 10 to 160 mg/day (means 89 ± 27.1 and 63 ± 3.6) Placebo
Outcomes	Primary outcomes: pain intensity, pain relief, cognitive function (symbol substitution task) Secondary outcomes: physical functioning, sleep, mood, side effects, treatment preference Pain intensity (0 - 10 NRS) and pain relief (0 - 100 NRS) values were collected by twice-weekly telephone interviews during the trial. All other outcome measures were obtained during clinic visits at the end of the drug-free baseline period and at the end of the maintenance phase for each drug
Notes	Study compared opioid (morphine or methadone) vs tricyclic antidepressant (nortriptyline or desipramine) vs placebo. Participants received methadone only if they did not tolerate morphine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization sequence was computer generated by the biostatistician"
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	"The pharmacist formulated the study drugs in identical gel capsules to maintain the blinding. All investigators were blinded to the drug treatments during the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis employed. For participants who did not complete a treatment period, the last 3 available pain ratings were used. Number of participants who did not complete methadone phase not reported

Raja 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Rowbotham 1991

Methods	Cross-over, single infusions, separated by at least 48 hrs
Participants	Participants enrolled: 19 Neuropathic pain diagnosis: PHN
Interventions	Morphine: 0.3 mg/kg (max 25 mg) over 1 hr Lidocaine: 5 mg/kg (max 450 mg) over 1 hr Placebo
Outcomes	Pain intensity pre- and post-infusion, and pain relief (0 - 100 VAS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant did not complete all 3 sessions, withdrawing from lidocaine session due to side effects, but supplying data for first 30 minutes
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Rowbotham 2003

Methods	Parallel, 8 weeks
Participants	Study arms enrolled: Levorphanol high-dose group: 43 Levorphanol low-dose group: 38 Neuropathic pain diagnosis: Mixed

Rowbotham 2003 (*Continued*)

Interventions	Levorphanol: 0.75 mg (1 - 7 capsules) 3 times daily (mean 8.9 mg/day) Levorphanol: 0.15 mg (1 - 7 capsules) 3 times daily (mean 2.7 mg/day)
Outcomes	Pain intensity (0 - 100 VAS): change in weekly average from baseline to 8th week of treatment Pain relief (categorical, 0 - 5) Profile of Mood States Questionnaire Symbol-Digit Modalities Test Multidimensional Pain Inventory Opiate-Agonist Effects Scale and Opiate Withdrawal Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	" Low-strength capsules and high-strength capsules were identical in appearance and were packaged in patient-specific bottles"
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals due to adverse events: 12 in the high-strength group vs. 3 in the low-strength group
Selective reporting (reporting bias)	Unclear risk	Data not provided for some secondary outcomes

Simpson 2007

Methods	Randomized, double-blind, placebo-controlled cross-over. Single doses for each of 9 consecutive breakthrough pain episodes separated by at least 2 hours. Maximum study duration of 21 days
Participants	N = 79 (77 completed); had a $\geq$ 3 month history of chronic persistent neuropathic pain; mean age 48 years; mean pain intensity = 5.1/10
Interventions	Fentanyl buccal tablets 100 - 800 mcg, based on effective dose established during open-label phase Placebo Participants received 6 doses of active intervention and 3 of placebo, according to 1 of 3 prespecified treatment sequences. Placebo tablets were not supplied in consecutive episodes

Simpson 2007 (*Continued*)

Outcomes	Primary efficacy measure: SPID from 5 - 60 mins after administration of study drug Secondary efficacy measures: PIDs at 5, 10, 15, 30, 45, 60, 90, and 120 mins after administration of study drug; Proportion of breakthrough pain episodes with > 33% and > 50% improvement in PI from baseline; PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes (0 = none to 4 = complete); Proportion of breakthrough pain episodes in which participants reported achieving meaningful PR; Time to meaningful PR; Proportion of BTP episodes in which pre-study supplemental opioids were required. AEs reported by the participants or recorded by the investigators; serious AEs; withdrawals due to AEs; and the results of physical examinations, examinations of the oral mucosa, clinical laboratory tests, and vital signs
Notes	Dose-titration phase before study enrolled 103 participants. 23 participants withdrew during this phase, 12 because of adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"matching" placebo. "Both patients and investigators were blinded". No further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	77 (97%) participants completed the study. When supplemental opioid was used for inadequate pain reduction, LOCF was used for efficacy measures. Participants used supplemental opioid for 59 (14%) of the 432 episodes treated with FBT and for 77 (36%) of the 213 episodes in which placebo was administered
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section

Wallace 2006

Methods	Randomized, double-blind, placebo-controlled cross-over.
Participants	N = 32 (26 completed); PHN for at least 3 months with baseline VAS ≥ 45/100
Interventions	CJC-1008 (experimental dynorphin analog): 3 mg/kg single dose Placebo
Outcomes	Pain intensity difference VAS, overall and for each of 3 pain types (constant, spontaneous or allodynia); Categorical pain intensity; Categorical pain relief; Physical examination, vital signs. Evaluations every 15 mins for first hr; 2, 3, 4, 6 and 8 hrs; and during return visits to study site at 2, 7 and 28 days post-dose
Notes	Participants crossed over to alternative intervention once pain returned to baseline level

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26/32 participants completed study. Efficacy outcomes only in those completing the study for all but primary outcome. Reasons for dropouts not described. LOCF used for missing data
Selective reporting (reporting bias)	Unclear risk	Not all data are presented in results section; all data presented are in graphical form only

Watson 1998

Methods	Cross-over, 4 weeks
Participants	Participants enrolled: 50 Neuropathic pain diagnosis: PHN
Interventions	Oxycodone oral long-acting: 10 - 30 mg twice daily (mean: 45 ± 17) Placebo

Watson 1998 (*Continued*)

Outcomes	Daily pain intensity (0 - 100 VAS) and pain relief (categorical 0 - 5) Allodynia weekly intensity (0 - 100 VAS) and relief (categorical 0 - 5) Disability (categorical 0 - 3) Effectiveness rating (categorical 0 - 3) Profile of Mood States Questionnaire Beck Depression Inventory
Notes	Adverse events in placebo group not listed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Low risk	Opaque, patient-specific envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of dropouts, reasons, similar in both groups
Selective reporting (reporting bias)	Unclear risk	Data not provided for some secondary outcomes

Watson 2003

Methods	Cross-over, 4 weeks
Participants	Participants enrolled: Opioid phase: 45 Active placebo phase: 45 Neuropathic pain diagnosis: Diabetic neuropathy
Interventions	Oxycodone oral long-acting: 10 - 40 mg twice daily (mean: 40.0 ± 18.5) Benztropine: 0.25 to 1.0 mg twice daily (mean: 1.2 ± 0.6)
Outcomes	Daily pain, steady pain, brief pain, and skin (allodynia) pain intensity (0 - 100 VAS and categorical 0 - 4) Pain relief (categorical 0 - 5, lower score = more relief): NNTB for moderate pain relief derived Pain Disability Index Pain and Sleep Questionnaire SF-36
Notes	

Watson 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for both evaluable and ITT populations presented - similar results
Selective reporting (reporting bias)	Unclear risk	Data not presented for some secondary outcomes

Wu 2002 phantom limb

Methods	Cross-over, single infusions, separated by 24 hrs
Participants	Participants enrolled: 20 Neuropathic pain diagnosis: Phantom limb pain
Interventions	Morphine: 0.05 mg/kg bolus + 0.2 mg/kg over 40 mins Lidocaine: 1.0 mg/kg bolus + 4.0 mg/kg over 40 mins Active placebo (diphenhydramine) 10 mg bolus + 40 mg over 40 mins
Outcomes	Phantom and stump pain intensity (0 - 100 VAS) pre- and post-infusion % pain relief % overall satisfaction
Notes	Data on initial and end VAS extracted from figures. SD data received from direct communication with one of the authors 25% of participants had only mild pain on days of infusion

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"subjects were randomized in balanced blocks of 12"
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Wu 2002 phantom limb (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Interventions were prepared by a pharmacist and were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout because of absence of pain before initiation of infusion
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

Wu 2002 stump

Methods	See Wu 2002 phantom limb
Participants	Participants enrolled: 22 Neuropathic pain diagnosis: Stump pain
Interventions	See Wu 2002 phantom limb
Outcomes	See Wu 2002 phantom limb
Notes	See Wu 2002 phantom limb. Wu 2002 phantom limb refers to those participants with phantom limb pain; Wu 2002 stump to those with stump pain. Total number of participants = 31; 11 participants had stump pain alone, 9 had phantom pain alone, and 11 had both stump and phantom pains

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Wu 2002 phantom limb
Allocation concealment (selection bias)	Unclear risk	See Wu 2002 phantom limb
Blinding (performance bias and detection bias) All outcomes	Low risk	See Wu 2002 phantom limb
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Wu 2002 phantom limb
Selective reporting (reporting bias)	Low risk	See Wu 2002 phantom limb

Wu 2008

Methods	Cross-over, 8 weeks each phase
Participants	Participants enrolled: 60 Neuropathic pain diagnosis: Post-amputation stump pain (n = 8), phantom pain (n = 8) or both (n = 44)
Interventions	Morphine: oral sustained release 15 - 180 mg/day (mean 112 ± 62.7) Mexiletine: 300 - 1200mg/day (mean: 933 ± 257) Placebo
Outcomes	Change in pain intensity (0 - 10 NRS) from baseline to end of therapy Pain relief (0 - 100%) Multidimensional Pain Inventory
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**"**The subjects were randomized in balanced blocks of 12"
Allocation concealment (selection bias)	Low risk	"The sequence of drug and placebo .. for each subject was provided in sealed envelops to the investigational pharmacy and the monitoring committee"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Mexiletine and placebo were similarly packaged in sealed capsules that were identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts described, equally distributed. Both case analysis of all randomized participants and per protocol analysis performed.
Selective reporting (reporting bias)	Low risk	Data provided for primary outcome and for most secondary outcomes. Some secondary outcomes only listed as being NS between groups

Zin 2010

Methods	Parallel, 5 weeks
Participants	Study arms enrolled: Oxycodone (plus pregabalin) group: 29 Placebo (plus pregabalin) group: 33 Neuropathic pain diagnosis: Postherpetic neuralgia, painful diabetic neuropathy

Zin 2010 (*Continued*)

Interventions	Oxycodone: liquid 5 mg twice daily Placebo: identical liquid twice daily Pregabilin (in both groups): 75 - 600 mg/day
Outcomes	2-cm drop in pain-intensity score and a pain-intensity score of < 4 cm measured by VAS from baseline, following pregabalin dosage escalation > 50% pain reduction from baseline Sleep interference score Neuropathic pain scale SF-36 questionnaire Profile of Mood States Trail-making test Patient global impression of change Clinician global impression of change
Notes	Participants were randomized to receive either oxycodone or placebo for 1 week, and were then started on open-label pregabalin (75, 150, 300 and 600 mg/day) according to a forced titration dosing regimen, while continuing the same dosage of oxycodone or placebo for 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**"**patients were assigned to 1 of 2 treatment group using a computer generated randomization number in block size of 10 "
Allocation concealment (selection bias)	Unclear risk	"All the study medications were supplied to patient by the clinical-trial pharmacist at the GPH"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All of the characteristics (appearance,taste,and method of administration) of the oxycodone and placebo mixture were identical to ensure that study blinding was maintained "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and AEs adequately presented. ITT analysis with attention to missing observation (LOCF)
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods section are reported in Results section.

AE = adverse event; CI = 95% confidence interval; ITT = intention-to-treat; IV = intravenous; LOCF = last observation carried forward; NNTB = number needed to treat for an additional beneficial outcome; NNTH = number needed to treat for an additional harmful outcome; NR = not reported; NRS = numerical rating scale; NS = non significant (P > 0.05); PCA = patient controlled analgesia; PHN = postherpetic neuralgia; PTN = post-traumatic neuralgia; RSD = reflex sympathetic dystrophy; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36 Questionnaire; VAS = visual analog scale;

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

Study	Reason for exclusion
Arita 2008	Not an RCT
Arkinstall 1995	Non-neuropathic pain
Ashburn 2011	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Benedetti 1998	Opioid studied - buprenorphine - is not a full mu receptor agonist
Bohme 2002	Opioid studied - buprenorphine - is not a full mu receptor agonist
Buynak 2009	Presented in abstract form only
Cathelin 1980a	Opioid studied - buprenorphine - is not a full mu receptor agonist
Cathelin 1980b	Presented in abstract form only
Cruciani 2012	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Dworkin 2009	Participants had mixed nociceptive and neuropathic pain (acute herpes zoster) - effects of opioid on each not presented separately
Gatti 2009	Not an RCT
Guo 2007	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Gustorff 2005	Only 5 participants had neuropathic pain (information provided by contacting author); data not presented separately
Hale 2009	Presented in abstract form only
Heiskanen 2002	Morphine plus placebo versus morphine plus dextromethorphan
Kalman 2002	Non-randomized and single-blinded study
Kalso 2007	Participants had mixed nociceptive and neuropathic pain (low back pain) - effects of opioid on each not presented separately
Katz 2000	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently

(*Continued*)

Likar 2003	Opioid studied - buprenorphine - is not a full mu receptor agonist
Maier 2002	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
McLeane 2003	Non-neuropathic pain
McQuay 1992	No control group
Mok 1981	Non-neuropathic pain
Mordarski 2009	No control group
Nicholson 2006a	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Nicholson 2006b	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Niesters 2011	Control group did not have neuropathic pain
Oh 2012	Abstract only
Palangio 2000	Non-neuropathic pain
Parker 1982	Combination of opioid plus other drug
Peat 1999	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Podolsky 2009	Presented in abstract form only
Price 1982	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Sheather-Reid 1998	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Sittl 2003	Non-randomized
Sorge 2004	Opioid combined with cholecystokinin versus opioid
Vargha 1983	Opioid studied - buprenorphine - is not a full mu receptor agonist. Non-neuropathic pain
Varrassi 2011	Abstract only

(*Continued*)

Webster 2010	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Webster 2011	Abstract only
Weil 2009	Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Worz 2003	Opioid studied - buprenorphine - is not a full mu receptor agonist
Yao 2012	No control group

RCT = randomized controlled trial

DATA AND ANALYSES

Comparison 1. Short-term Efficacy Studies: opioid vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity post-opioid/placebo	6	180	Mean Difference (IV, Random, 95% CI)	-15.81 [-22.54, -9.07]
1.1 Peripheral Pain	4	138	Mean Difference (IV, Random, 95% CI)	-15.01 [-22.97, -7.06]
1.2 Central Pain	2	42	Mean Difference (IV, Random, 95% CI)	-17.81 [-30.48, -5.15]
2 % Pain reduction post-opioid/placebo	2	38	Mean Difference (IV, Random, 95% CI)	25.78 [16.91, 34.65]

Comparison 2. Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least 33% pain relief	6	727	Risk Difference (M-H, Random, 95% CI)	0.25 [0.13, 0.37]
2 Number of participants with at least 50% pain relief	5	305	Risk Difference (M-H, Random, 95% CI)	0.17 [0.02, 0.33]
3 Pain intensity post-opioid/placebo	9	725	Mean Difference (IV, Random, 95% CI)	-12.01 [-15.40, -8.62]
4 Evoked pain intensity post-opioid/placebo	2	148	Mean Difference (IV, Random, 95% CI)	-23.73 [-34.50, -12.96]
5 SF-36 Health Survey	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Physical functioning	2	142	Mean Difference (IV, Random, 95% CI)	3.16 [-5.46, 11.77]
5.2 Role-physical	2	142	Mean Difference (IV, Random, 95% CI)	9.62 [-7.73, 26.97]
5.3 Bodily pain	2	142	Mean Difference (IV, Random, 95% CI)	6.78 [0.08, 13.48]
5.4 General health	2	142	Mean Difference (IV, Random, 95% CI)	-0.62 [-8.08, 6.85]
5.5 Vitality	2	142	Mean Difference (IV, Random, 95% CI)	1.62 [-5.82, 9.07]
5.6 Social functioning	2	142	Mean Difference (IV, Random, 95% CI)	3.40 [-5.09, 11.88]
5.7 Role-emotional	2	142	Mean Difference (IV, Random, 95% CI)	7.97 [-5.06, 21.00]
5.8 Mental health	2	142	Mean Difference (IV, Random, 95% CI)	3.09 [-3.05, 9.23]
6 Brief Pain Inventory: Pain Interference items	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 General activity	2	245	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.67, -0.14]
6.2 Mood	2	245	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.31, 0.07]
6.3 Walking	2	245	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.28, 0.20]
6.4 Normal work	2	245	Mean Difference (IV, Random, 95% CI)	-0.82 [-1.59, -0.05]
6.5 Social relations	2	245	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.25, -0.16]
6.6 Sleep	2	245	Mean Difference (IV, Random, 95% CI)	-1.74 [-2.42, -1.06]
6.7 Enjoyment of life	2	245	Mean Difference (IV, Random, 95% CI)	-1.18 [-1.91, -0.44]

7 Beck Depression Inventory	3	273	Mean Difference (IV, Random, 95% CI)	0.21 [-2.29, 2.71]

Comparison 3. Intermediate-term Efficacy Studies: opioid vs active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least 33% pain relief	3	243	Risk Difference (M-H, Random, 95% CI)	0.17 [0.04, 0.31]
1.1 opioid vs gabapentin	1	88	Risk Difference (M-H, Random, 95% CI)	0.18 [-0.01, 0.37]
1.2 opioid vs tricyclic antidepressant	1	63	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.22, 0.26]
1.3 opioid vs antiarrythmic	1	92	Risk Difference (M-H, Random, 95% CI)	0.28 [0.08, 0.48]
2 Number of participants with at least 50% pain relief	2	155	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.20, 0.33]
2.1 opioid vs tricyclic antidepressant	1	63	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.30, 0.15]
2.2 opioid vs antiarrythmic	1	92	Risk Difference (M-H, Random, 95% CI)	0.20 [0.01, 0.39]
3 Pain intensity post-opioid/active control	4	388	Mean Difference (IV, Random, 95% CI)	-7.19 [-13.13, -1.25]
3.1 opioid vs gabapentin	1	88	Mean Difference (IV, Random, 95% CI)	-5.0 [-14.40, 4.40]
3.2 opioid vs tricyclic antidepressant	2	208	Mean Difference (IV, Random, 95% CI)	-3.30 [-13.48, 6.89]
3.3 opioid vs antiarrythmic	1	92	Mean Difference (IV, Random, 95% CI)	-13.0 [-19.12, -6.88]
4 SF-36 Health Survey	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Physical functioning	2	144	Mean Difference (IV, Random, 95% CI)	-5.09 [-13.81, 3.63]
4.2 Role-physical	2	144	Mean Difference (IV, Random, 95% CI)	-5.38 [-19.05, 8.29]
4.3 Bodily pain	2	144	Mean Difference (IV, Random, 95% CI)	-3.11 [-9.91, 3.70]
4.4 General health	2	144	Mean Difference (IV, Random, 95% CI)	-4.44 [-11.75, 2.86]
4.5 Vitality	2	144	Mean Difference (IV, Random, 95% CI)	-6.60 [-13.63, 0.44]
4.6 Social functioning	2	144	Mean Difference (IV, Random, 95% CI)	-6.04 [-14.44, 2.35]
4.7 Role-emotional	2	144	Mean Difference (IV, Random, 95% CI)	-6.39 [-19.37, 6.60]
4.8 Mental health	2	144	Mean Difference (IV, Random, 95% CI)	-6.24 [-14.06, 1.57]
5 Beck Depression Inventory	3	276	Mean Difference (IV, Random, 95% CI)	1.40 [-0.38, 3.17]
5.1 opioid vs gabapentin	1	88	Mean Difference (IV, Random, 95% CI)	0.30 [-2.46, 3.06]
5.2 opioid vs tricyclic antidepressant	2	188	Mean Difference (IV, Random, 95% CI)	2.17 [-0.14, 4.49]

Comparison 4. Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants reporting constipation	10	1114	Risk Difference (M-H, Random, 95% CI)	0.25 [0.18, 0.33]
2 Participants reporting dizziness	10	1114	Risk Difference (M-H, Fixed, 95% CI)	0.14 [0.10, 0.18]
3 Participants reporting drowsiness/somnolence	8	738	Risk Difference (M-H, Random, 95% CI)	0.14 [0.03, 0.25]
4 Participants reporting nausea	10	1114	Risk Difference (M-H, Random, 95% CI)	0.16 [0.08, 0.25]
5 Participants reporting vomiting	7	813	Risk Difference (M-H, Random, 95% CI)	0.08 [0.01, 0.15]
6 Particpants withdrawing due to adverse events	7	867	Risk Difference (M-H, Random, 95% CI)	0.08 [0.04, 0.12]
7 Participants withdrawing due to lack of efficacy	5	723	Risk Difference (M-H, Random, 95% CI)	-0.09 [-0.12, -0.05]

Comparison 5. Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants reporting constipation	4	397	Risk Difference (M-H, Random, 95% CI)	0.29 [0.21, 0.38]
2 Participants reporting dizziness	4	397	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.03]
3 Participants reporting drowsiness/somnolence	4	397	Risk Difference (M-H, Random, 95% CI)	0.13 [0.06, 0.20]
4 Participants reporting nausea	4	393	Risk Difference (M-H, Random, 95% CI)	0.13 [-0.01, 0.26]
5 Participants reporting vomiting	1	97	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.04, 0.04]
6 Participants withdrawing due to adverse events	1	75	Risk Difference (M-H, Random, 95% CI)	0.06 [-0.06, 0.19]
7 Participants withdrawing due to lack of efficacy	1	75	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.05, 0.05]

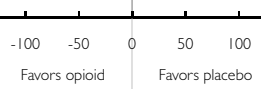
Analysis 1.1. Comparison 1 Short-term Efficacy Studies: opioid vs placebo, Outcome 1 Pain intensity post-opioid/placebo.

Review: Opioids for neuropathic pain

Comparison: 1 Short-term Efficacy Studies: opioid vs placebo

Outcome: 1 Pain intensity post-opioid/placebo

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Peripheral Pain							
Kupers 1991 peripheral	8	28 (14)	8	40 (28)		9.6 %	-12.00 [-33.69, 9.69]
Rowbotham 1991	19	33 (33)	19	44 (29)		11.6 %	-11.00 [-30.75, 8.75]
Wu 2002 phantom limb	20	30 (22)	20	46 (22)		24.4 %	-16.00 [-29.64, -2.36]
Wu 2002 stump	22	33 (18)	22	50 (26)		26.0 %	-17.00 [-30.21, -3.79]
Subtotal (95% CI)	**69**		**69**			**71.7 %**	**-15.01 [-22.97, -7.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.70 (P = 0.00022)							
2 Central Pain							
Attal 2002	15	33 (23)	15	52 (19)		19.9 %	-19.00 [-34.10, -3.90]
Kupers 1991 central	6	43 (13)	6	58 (26)		8.4 %	-15.00 [-38.26, 8.26]
Subtotal (95% CI)	**21**		**21**			**28.3 %**	**-17.81 [-30.48, -5.15]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.76 (P = 0.0058)							
Total (95% CI)	**90**		**90**			**100.0 %**	**-15.81 [-22.54, -9.07]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 5 (P = 0.99); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.60 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.71), $I^2 = 0.0\%$							



Analysis 1.2. Comparison 1 Short-term Efficacy Studies: opioid vs placebo, Outcome 2 % Pain reduction post-opioid/placebo.

Review: Opioids for neuropathic pain

Comparison: 1 Short-term Efficacy Studies: opioid vs placebo

Outcome: 2 % Pain reduction post-opioid/placebo

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Leung 2001	12	62 (11)	12	36 (12)		92.7 %	26.00 [16.79, 35.21]
Max 1995	7	45 (35)	7	22 (27)		7.3 %	23.00 [-9.75, 55.75]
Total (95% CI)	**19**		**19**			**100.0 %**	**25.78 [16.91, 34.65]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 5.70 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 1 Number of participants with at least 33% pain relief.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 1 Number of participants with at least 33% pain relief

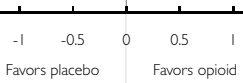
Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	35/44	13/42		16.3 %	0.49 [0.30, 0.67]
Gimbel 2003	37/82	20/77		19.1 %	0.19 [0.05, 0.34]
Hanna 2008	68/121	52/127		20.9 %	0.15 [0.03, 0.28]
Khoromi 2007	13/32	11/33		13.1 %	0.07 [-0.16, 0.31]
Watson 1998	22/38	7/38		15.2 %	0.39 [0.20, 0.59]
Wu 2008	33/50	19/43		15.3 %	0.22 [0.02, 0.42]
Total (95% CI)	**367**	**360**		**100.0 %**	**0.25 [0.13, 0.37]**

Total events: 208 (Opioid), 122 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.65$, df = 5 (P = 0.02); I^2 =63%

Test for overall effect: Z = 4.18 (P = 0.000030)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 2 Number of participants with at least 50% pain relief.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 2 Number of participants with at least 50% pain relief

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Huse 2001	5/12	1/12		14.1 %	0.33 [0.01, 0.65]
Khoromi 2007	8/32	5/33		23.3 %	0.10 [-0.10, 0.29]
Watson 2003	21/34	8/34		21.3 %	0.38 [0.17, 0.60]
Wu 2008	23/50	13/43		23.2 %	0.16 [-0.04, 0.35]
Zin 2010	15/26	19/29		18.1 %	-0.08 [-0.34, 0.18]
Total (95% CI)	**154**	**151**		**100.0 %**	**0.17 [0.02, 0.33]**

Total events: 72 (Opioid), 46 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.82$, df = 4 (P = 0.07); $I^2 = 55\%$

Test for overall effect: Z = 2.23 (P = 0.026)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 3 Pain intensity post-opioid/placebo.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 3 Pain intensity post-opioid/placebo

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Gilron 2005	44	37 (23)	43	45 (22)		11.3 %	-8.00 [-17.46, 1.46]
Gimbel 2003	82	41 (27)	77	53 (26)		14.3 %	-12.00 [-20.24, -3.76]
Huse 2001	12	33 (16)	12	40 (12)		8.2 %	-7.00 [-18.32, 4.32]
Khoromi 2007	28	34 (28)	28	37 (27)		5.2 %	-3.00 [-17.41, 11.41]
Morley 2003	18	60 (20)	18	64 (19)		6.6 %	-4.00 [-16.74, 8.74]
Raja 2002	66	44 (24)	56	60 (20)		15.6 %	-16.00 [-23.81, -8.19]
Watson 1998	38	35 (25)	38	54 (25)		8.3 %	-19.00 [-30.24, -7.76]
Watson 2003	36	26 (25)	36	47 (27)		7.3 %	-21.00 [-33.02, -8.98]
Wu 2008	50	38 (12)	43	50 (17)		23.3 %	-12.00 [-18.07, -5.93]
Total (95% CI)	**374**		**351**			**100.0 %**	**-12.01 [-15.40, -8.62]**

Heterogeneity: $Tau^2 = 3.26$; $Chi^2 = 9.10$, df = 8 (P = 0.33); $I^2 = 12\%$

Test for overall effect: Z = 6.94 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 4 Evoked pain intensity post-opioid/placebo.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

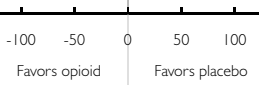
Outcome: 4 Evoked pain intensity post-opioid/placebo

Study or subgroup	Opioid		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Watson 1998	38	32 (27)	38	50 (30)		47.9 %	-18.00 [-30.83, -5.17]
Watson 2003	36	14 (20)	36	43 (31)		52.1 %	-29.00 [-41.05, -16.95]
Total (95% CI)	**74**		**74**			**100.0 %**	**-23.73 [-34.50, -12.96]**

Heterogeneity: $Tau^2 = 20.16$; $Chi^2 = 1.50$, df = 1 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 4.32 (P = 0.000016)

Test for subgroup differences: Not applicable

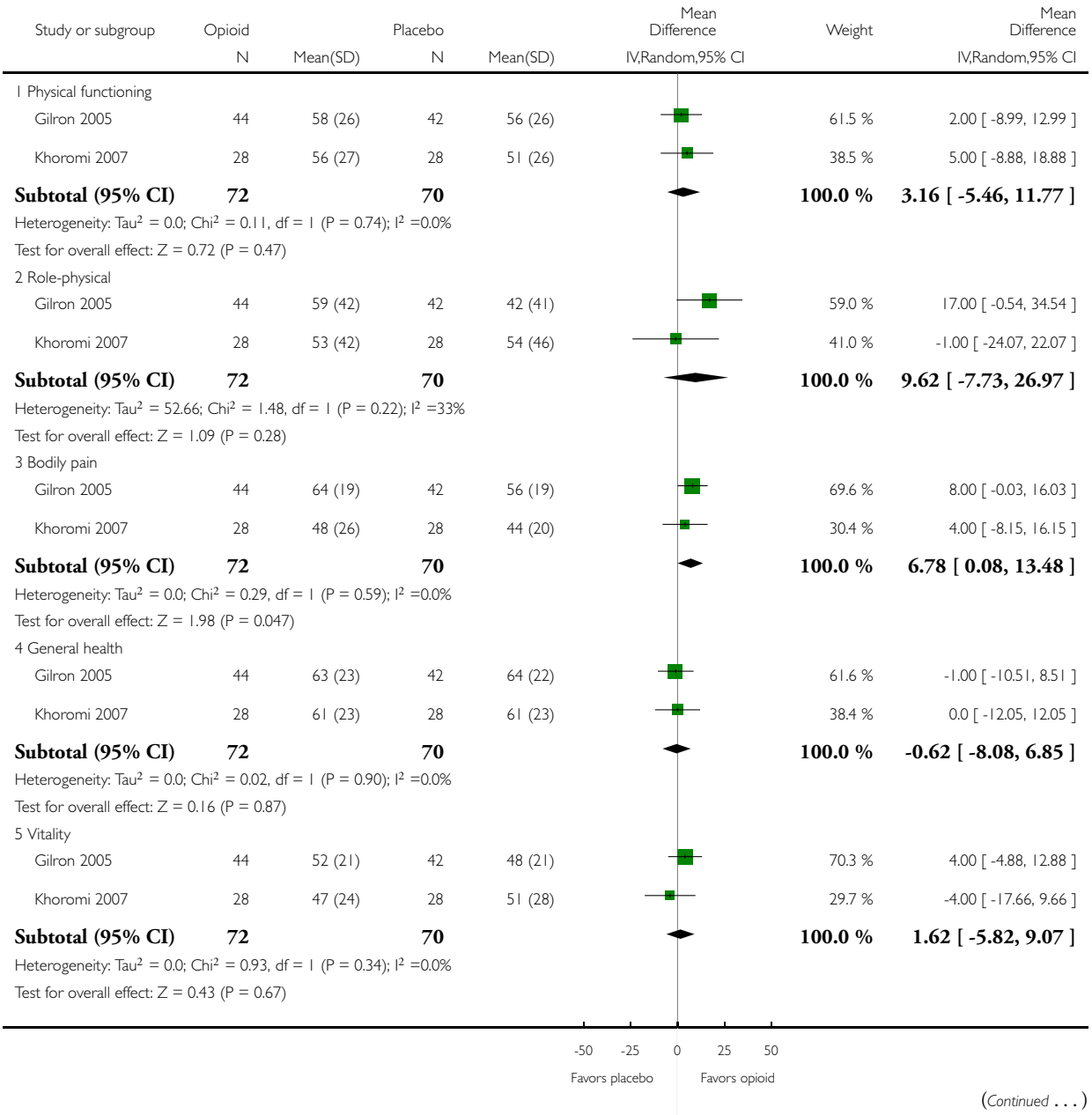


Analysis 2.5. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 5 SF-36 Health Survey.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 5 SF-36 Health Survey



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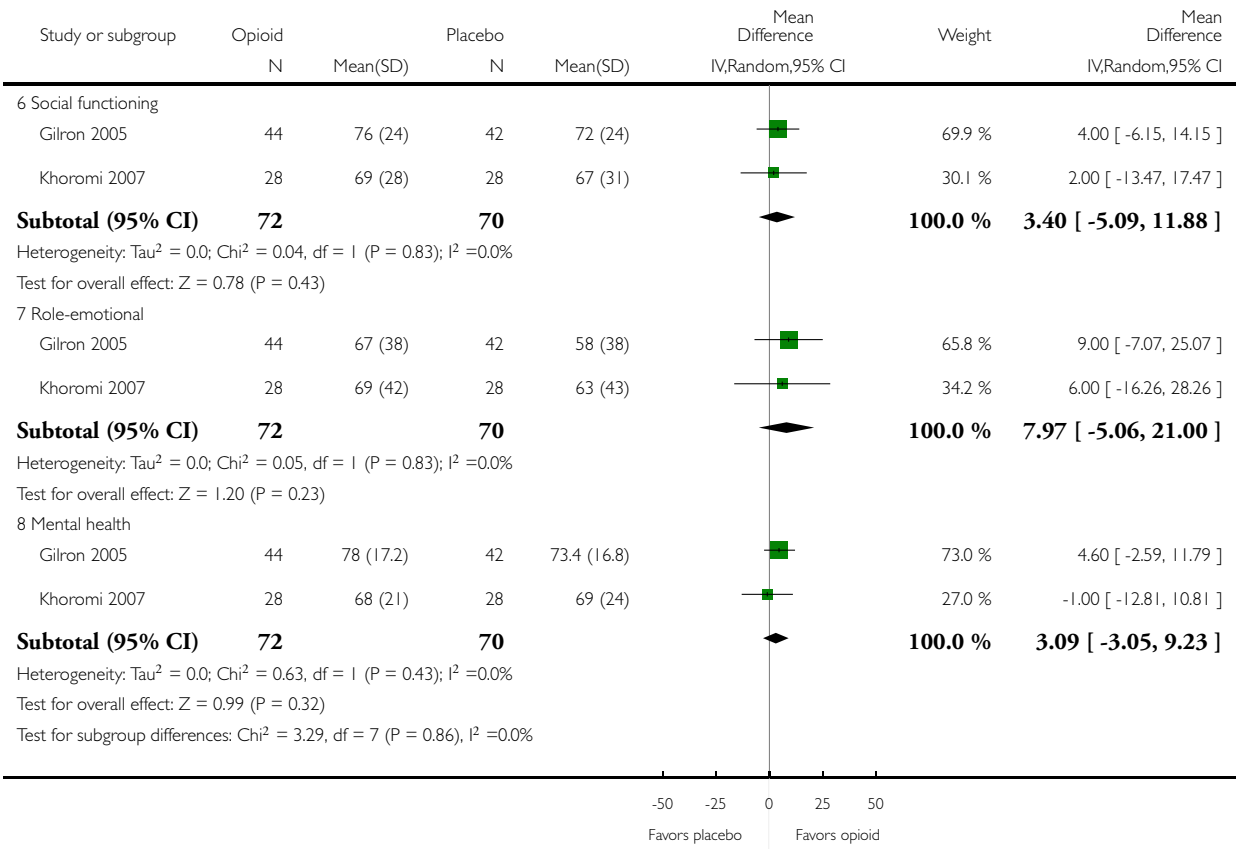


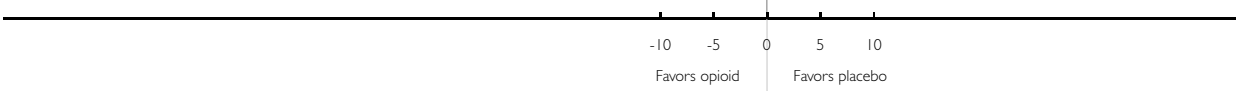
Analysis 2.6. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 6 Brief Pain Inventory: Pain Interference items.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 6 Brief Pain Inventory: Pain Interference items

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 General activity							
Gilron 2005	44	3.1 (2.6)	42	4.5 (2.6)		38.2 %	-1.40 [-2.50, -0.30]
Gimbel 2003	82	3.5 (2.6)	77	4.1 (2.5)		61.8 %	-0.60 [-1.39, 0.19]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-0.91 [-1.67, -0.14]**
Heterogeneity: Tau² = 0.08; Chi² = 1.34, df = 1 (P = 0.25); I² =25%							
Test for overall effect: Z = 2.33 (P = 0.020)							
2 Mood							
Gilron 2005	44	2.5 (2.6)	42	3.3 (2.6)		39.4 %	-0.80 [-1.90, 0.30]
Gimbel 2003	82	3.2 (2.9)	77	3.7 (2.8)		60.6 %	-0.50 [-1.39, 0.39]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-0.62 [-1.31, 0.07]**
Heterogeneity: Tau² = 0.0; Chi² = 0.17, df = 1 (P = 0.68); I² =0.0%							
Test for overall effect: Z = 1.76 (P = 0.079)							
3 Walking							
Gilron 2005	44	3.2 (3.2)	42	4.3 (3.2)		30.0 %	-1.10 [-2.45, 0.25]
Gimbel 2003	82	4.2 (2.9)	77	4.5 (2.8)		70.0 %	-0.30 [-1.19, 0.59]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-0.54 [-1.28, 0.20]**
Heterogeneity: Tau² = 0.0; Chi² = 0.94, df = 1 (P = 0.33); I² =0.0%							
Test for overall effect: Z = 1.43 (P = 0.15)							
4 Normal work							
Gilron 2005	44	2.3 (2.6)	42	3.6 (2.6)		40.3 %	-1.30 [-2.40, -0.20]
Gimbel 2003	82	3.9 (2.8)	77	4.4 (2.7)		59.7 %	-0.50 [-1.35, 0.35]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-0.82 [-1.59, -0.05]**
Heterogeneity: Tau² = 0.07; Chi² = 1.27, df = 1 (P = 0.26); I² =21%							
Test for overall effect: Z = 2.10 (P = 0.036)							
5 Social relations							
Gilron 2005	44	1.6 (1.9)	42	2.2 (1.9)		46.3 %	-0.60 [-1.40, 0.20]
Gimbel 2003	82	2.4 (2.4)	77	3.2 (2.4)		53.7 %	-0.80 [-1.55, -0.05]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-0.71 [-1.25, -0.16]**
Heterogeneity: Tau² = 0.0; Chi² = 0.13, df = 1 (P = 0.72); I² =0.0%							
Test for overall effect: Z = 2.54 (P = 0.011)							



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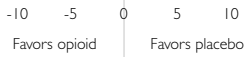
Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
6 Sleep							
Gilron 2005	44	1.6 (2.6)	42	3.4 (2.6)		38.5 %	-1.80 [-2.90, -0.70]
Gimbel 2003	82	3.6 (2.9)	77	5.3 (2.7)		61.5 %	-1.70 [-2.57, -0.83]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-1.74 [-2.42, -1.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.99 (P < 0.00001)							
7 Enjoyment of life							
Gilron 2005	44	2.5 (3.2)	42	4.1 (3.2)		29.3 %	-1.60 [-2.95, -0.25]
Gimbel 2003	82	3.6 (2.8)	77	4.6 (2.8)		70.7 %	-1.00 [-1.87, -0.13]
Subtotal (95% CI)	**126**		**119**			**100.0 %**	**-1.18 [-1.91, -0.44]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.53$, df = 1 (P = 0.46); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.15 (P = 0.0017)							
Test for subgroup differences: $Chi^2 = 8.38$, df = 6 (P = 0.21), $I^2 = 28\%$							



Analysis 2.7. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 7 Beck Depression Inventory.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 7 Beck Depression Inventory

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Gilron 2005	44	6.7 (6.6)	42	8.5 (6.5)		39.0 %	-1.80 [-4.57, 0.97]
Khoromi 2007	32	9.6 (8.5)	33	9 (8.5)		24.6 %	0.60 [-3.53, 4.73]
Raja 2002	66	12.1 (8.9)	56	10 (7.8)		36.4 %	2.10 [-0.86, 5.06]
Total (95% CI)	**142**		**131**			**100.0 %**	**0.21 [-2.29, 2.71]**

Heterogeneity: $Tau^2 = 2.18$; $Chi^2 = 3.61$, df = 2 (P = 0.16); $I^2 = 45\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable

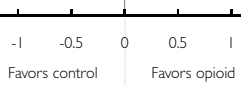
Analysis 3.1. Comparison 3 Intermediate-term Efficacy Studies: opioid vs active control, Outcome 1 Number of participants with at least 33% pain relief.

Review: Opioids for neuropathic pain

Comparison: 3 Intermediate-term Efficacy Studies: opioid vs active control

Outcome: 1 Number of participants with at least 33% pain relief

Study or subgroup	Opioid n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 opioid vs gabapentin					
Gilron 2005	35/44	27/44		38.4 %	0.18 [-0.01, 0.37]
Subtotal (95% CI)	**44**	**44**		**38.4 %**	**0.18 [-0.01, 0.37]**
Total events: 35 (Opioid), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.91 (P = 0.056)					
2 opioid vs tricyclic antidepressant					
Khoromi 2007	13/32	12/31		26.0 %	0.02 [-0.22, 0.26]
Subtotal (95% CI)	**32**	**31**		**26.0 %**	**0.02 [-0.22, 0.26]**
Total events: 13 (Opioid), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.88)					
3 opioid vs antiarrythmic					
Wu 2008	33/50	16/42		35.6 %	0.28 [0.08, 0.48]
Subtotal (95% CI)	**50**	**42**		**35.6 %**	**0.28 [0.08, 0.48]**
Total events: 33 (Opioid), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.78 (P = 0.0055)					
Total (95% CI)	**126**	**117**		**100.0 %**	**0.17 [0.04, 0.31]**
Total events: 81 (Opioid), 55 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.67, df = 2 (P = 0.26); I^2 =25%					
Test for overall effect: Z = 2.48 (P = 0.013)					
Test for subgroup differences: Chi^2 = 2.67, df = 2 (P = 0.26), I^2 =25%					



Analysis 3.2. Comparison 3 Intermediate-term Efficacy Studies: opioid vs active control, Outcome 2 Number of participants with at least 50% pain relief.

Review: Opioids for neuropathic pain

Comparison: 3 Intermediate-term Efficacy Studies: opioid vs active control

Outcome: 2 Number of participants with at least 50% pain relief

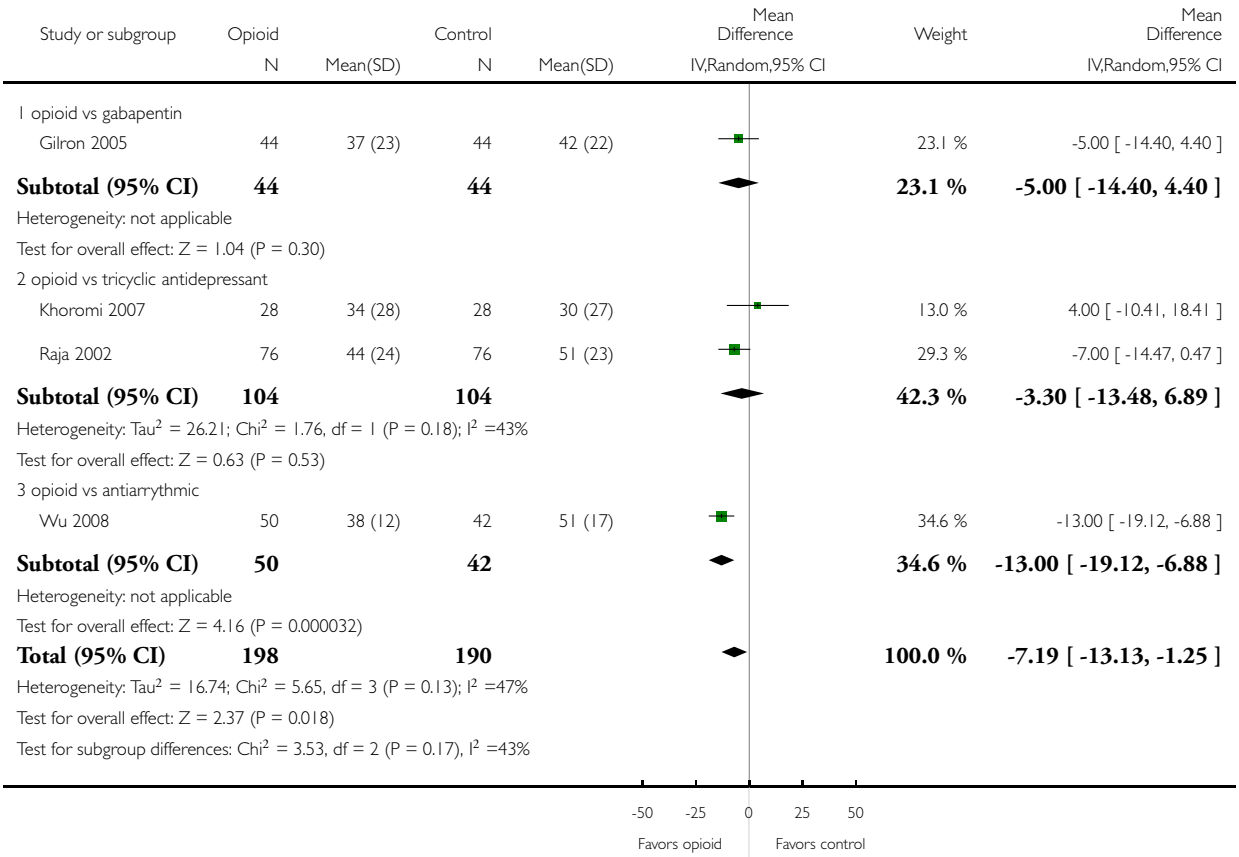
Study or subgroup	Opioid n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 opioid vs tricyclic antidepressant					
Khoromi 2007	8/32	10/31		47.7 %	-0.07 [-0.30, 0.15]
Subtotal (95% CI)	**32**	**31**		**47.7 %**	**-0.07 [-0.30, 0.15]**
Total events: 8 (Opioid), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
2 opioid vs antiarrythmic					
Wu 2008	23/50	11/42		52.3 %	0.20 [0.01, 0.39]
Subtotal (95% CI)	**50**	**42**		**52.3 %**	**0.20 [0.01, 0.39]**
Total events: 23 (Opioid), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.043)					
Total (95% CI)	**82**	**73**		**100.0 %**	**0.07 [-0.20, 0.33]**
Total events: 31 (Opioid), 21 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 3.26, df = 1 (P = 0.07); I^2 =69%					
Test for overall effect: Z = 0.51 (P = 0.61)					
Test for subgroup differences: Chi^2 = 3.26, df = 1 (P = 0.07), I^2 =69%					

Analysis 3.3. Comparison 3 Intermediate-term Efficacy Studies: opioid vs active control, Outcome 3 Pain intensity post-opioid/active control.

Review: Opioids for neuropathic pain

Comparison: 3 Intermediate-term Efficacy Studies: opioid vs active control

Outcome: 3 Pain intensity post-opioid/active control



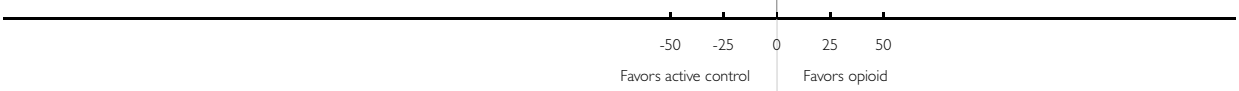
Analysis 3.4. Comparison 3 Intermediate-term Efficacy Studies: opioid vs active control, Outcome 4 SF-36 Health Survey.

Review: Opioids for neuropathic pain

Comparison: 3 Intermediate-term Efficacy Studies: opioid vs active control

Outcome: 4 SF-36 Health Survey

Study or subgroup	Opioid N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Physical functioning							
Gilron 2005	44	57.8 (26.5)	44	61.1 (26.5)		62.0 %	-3.30 [-14.37, 7.77]
Khoromi 2007	28	56 (27)	28	64 (27)		38.0 %	-8.00 [-22.14, 6.14]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-5.09 [-13.81, 3.63]**
Heterogeneity: Tau² = 0.0; Chi² = 0.26, df = 1 (P = 0.61); I² =0.0%							
Test for overall effect: Z = 1.14 (P = 0.25)							
2 Role-physical							
Gilron 2005	44	58.7 (41.8)	44	63.1 (41.1)		62.3 %	-4.40 [-21.72, 12.92]
Khoromi 2007	28	53 (42)	28	60 (43)		37.7 %	-7.00 [-29.26, 15.26]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-5.38 [-19.05, 8.29]**
Heterogeneity: Tau² = 0.0; Chi² = 0.03, df = 1 (P = 0.86); I² =0.0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
3 Bodily pain							
Gilron 2005	44	64.4 (19.2)	44	65.6 (19.2)		72.0 %	-1.20 [-9.22, 6.82]
Khoromi 2007	28	48 (26)	28	56 (23)		28.0 %	-8.00 [-20.86, 4.86]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-3.11 [-9.91, 3.70]**
Heterogeneity: Tau² = 0.0; Chi² = 0.77, df = 1 (P = 0.38); I² =0.0%							
Test for overall effect: Z = 0.89 (P = 0.37)							
4 General health							
Gilron 2005	44	63.1 (22.6)	44	66.5 (22.6)		59.9 %	-3.40 [-12.84, 6.04]
Khoromi 2007	28	61 (23)	28	67 (21)		40.1 %	-6.00 [-17.54, 5.54]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-4.44 [-11.75, 2.86]**
Heterogeneity: Tau² = 0.0; Chi² = 0.12, df = 1 (P = 0.73); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.23)							
5 Vitality							
Gilron 2005	44	51.5 (21.2)	44	56.1 (21.2)		63.0 %	-4.60 [-13.46, 4.26]
Khoromi 2007	28	47 (24)	28	57 (20)		37.0 %	-10.00 [-21.57, 1.57]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-6.60 [-13.63, 0.44]**
Heterogeneity: Tau² = 0.0; Chi² = 0.53, df = 1 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 1.84 (P = 0.066)							



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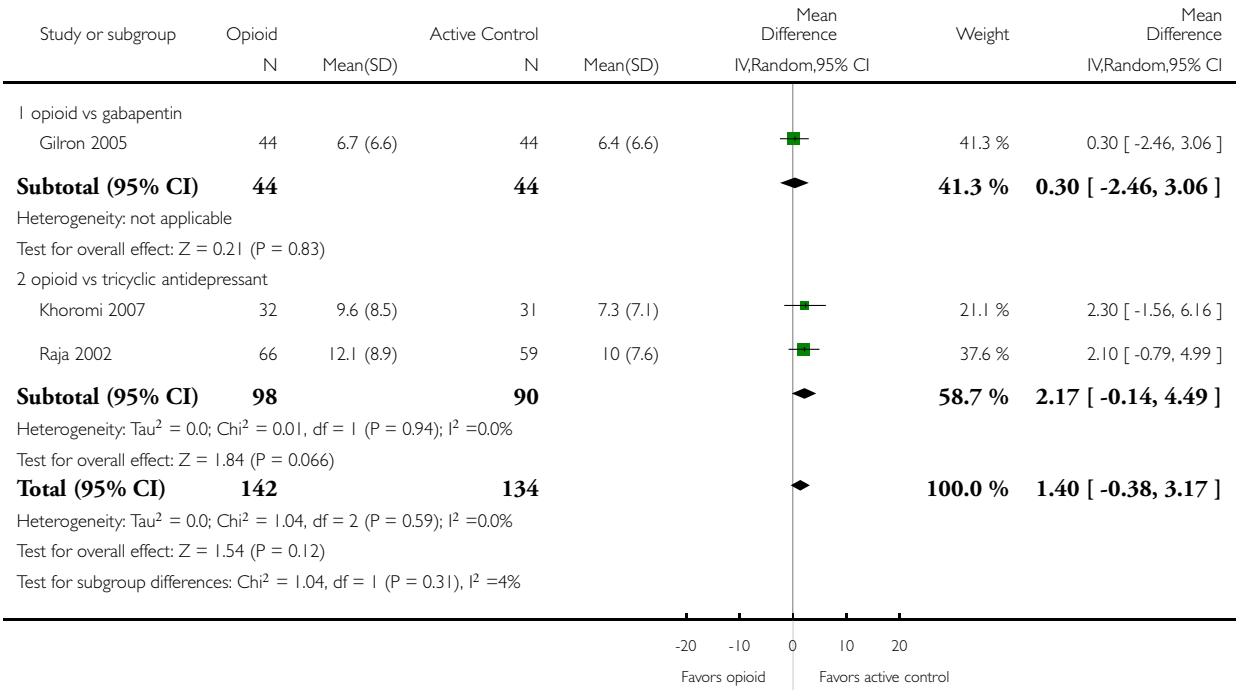
Study or subgroup	Opioid N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
6 Social functioning							
Gilron 2005	44	75.9 (24.5)	44	80.5 (24.5)		67.2 %	-4.60 [-14.84, 5.64]
Khoromi 2007	28	69 (28)	28	78 (28)		32.8 %	-9.00 [-23.67, 5.67]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-6.04 [-14.44, 2.35]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 1.41 (P = 0.16)							
7 Role-emotional							
Gilron 2005	44	66.9 (38.5)	44	75.1 (38.5)		65.2 %	-8.20 [-24.29, 7.89]
Khoromi 2007	28	69 (42)	28	72 (42)		34.8 %	-3.00 [-25.00, 19.00]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-6.39 [-19.37, 6.60]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 0.96 (P = 0.33)							
8 Mental health							
Gilron 2005	44	78 (17.2)	44	80.9 (17.2)		58.7 %	-2.90 [-10.09, 4.29]
Khoromi 2007	28	68 (21)	28	79 (16)		41.3 %	-11.00 [-20.78, -1.22]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-6.24 [-14.06, 1.57]**
Heterogeneity: Tau^2 = 13.63; Chi^2 = 1.71, df = 1 (P = 0.19); I^2 =42%							
Test for overall effect: Z = 1.57 (P = 0.12)							
Test for subgroup differences: Chi^2 = 0.70, df = 7 (P = 1.00), I^2 =0.0%							

Analysis 3.5. Comparison 3 Intermediate-term Efficacy Studies: opioid vs active control, Outcome 5 Beck Depression Inventory.

Review: Opioids for neuropathic pain

Comparison: 3 Intermediate-term Efficacy Studies: opioid vs active control

Outcome: 5 Beck Depression Inventory



Analysis 4.1. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 1 Participants reporting constipation.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 1 Participants reporting constipation

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	19/49	2/44		10.1 %	0.34 [0.19, 0.49]
Gimbel 2003	35/82	11/77		11.0 %	0.28 [0.15, 0.42]
Hanna 2008	45/169	10/169		14.3 %	0.21 [0.13, 0.28]
Harke 2001	2/21	0/17		9.9 %	0.10 [-0.06, 0.25]
Khoromi 2007	18/28	2/28		7.7 %	0.57 [0.37, 0.77]
Morley 2003	2/19	1/19		9.0 %	0.05 [-0.12, 0.22]
Raja 2002	23/76	8/76		11.5 %	0.20 [0.07, 0.32]
Watson 2003	13/45	4/45		9.8 %	0.20 [0.04, 0.36]
Wu 2008	17/50	2/43		10.3 %	0.29 [0.15, 0.44]
Zin 2010	18/27	8/30		6.3 %	0.40 [0.16, 0.64]
Total (95% CI)	**566**	**548**		**100.0 %**	**0.25 [0.18, 0.33]**

Total events: 192 (Opioid), 48 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.01$, df = 9 (P = 0.003); $I^2 = 64\%$

Test for overall effect: Z = 6.49 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 2 Participants reporting dizziness.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 2 Participants reporting dizziness

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Gilron 2005	0/49	0/44		8.3 %	0.0 [-0.04, 0.04]
Gimbel 2003	26/82	8/77		14.3 %	0.21 [0.09, 0.33]
Hanna 2008	37/169	9/169		30.4 %	0.17 [0.09, 0.24]
Harke 2001	4/21	0/17		3.4 %	0.19 [0.01, 0.38]
Khoromi 2007	4/28	1/28		5.0 %	0.11 [-0.04, 0.25]
Morley 2003	6/19	0/19		3.4 %	0.32 [0.10, 0.53]
Raja 2002	14/76	5/76		13.7 %	0.12 [0.01, 0.22]
Watson 2003	7/45	3/45		8.1 %	0.09 [-0.04, 0.22]
Wu 2008	2/50	2/43		8.3 %	-0.01 [-0.09, 0.08]
Zin 2010	22/27	17/30		5.1 %	0.25 [0.02, 0.48]
Total (95% CI)	**566**	**548**		**100.0 %**	**0.14 [0.10, 0.18]**

Total events: 122 (Opioid), 45 (Placebo)

Heterogeneity: $Chi^2 = 62.01$, df = 9 ($P<0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 7.20$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 3 Participants reporting drowsiness/somnolence.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 3 Participants reporting drowsiness/somnolence

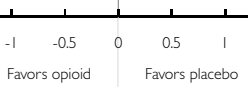
Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	8/49	6/44		13.2 %	0.03 [-0.12, 0.17]
Gimbel 2003	33/82	1/77		14.6 %	0.39 [0.28, 0.50]
Khoromi 2007	7/28	1/28		12.0 %	0.21 [0.04, 0.39]
Morley 2003	2/19	2/19		11.2 %	0.0 [-0.20, 0.20]
Raja 2002	23/76	11/76		13.8 %	0.16 [0.03, 0.29]
Watson 2003	9/45	11/45		12.1 %	-0.04 [-0.22, 0.13]
Wu 2008	9/50	3/43		13.8 %	0.11 [-0.02, 0.24]
Zin 2010	19/27	14/30		9.3 %	0.24 [-0.01, 0.49]
Total (95% CI)	**376**	**362**		**100.0 %**	**0.14 [0.03, 0.25]**

Total events: 110 (Opioid), 49 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 29.54$, df = 7 (P = 0.00012); $I^2 = 76\%$

Test for overall effect: Z = 2.44 (P = 0.015)

Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 4 Participants reporting nausea.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 4 Participants reporting nausea

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	2/49	0/44		13.5 %	0.04 [-0.03, 0.11]
Gimbel 2003	30/82	6/77		11.2 %	0.29 [0.17, 0.41]
Hanna 2008	43/169	18/169		13.0 %	0.15 [0.07, 0.23]
Harke 2001	7/21	1/17		6.8 %	0.27 [0.04, 0.51]
Khoromi 2007	2/28	0/28		11.6 %	0.07 [-0.04, 0.18]
Morley 2003	7/19	4/19		5.3 %	0.16 [-0.13, 0.44]
Raja 2002	30/76	5/76		11.1 %	0.33 [0.21, 0.45]
Watson 2003	16/45	8/45		8.6 %	0.18 [0.00, 0.36]
Wu 2008	4/50	1/43		12.7 %	0.06 [-0.03, 0.14]
Zin 2010	13/27	8/30		6.3 %	0.21 [-0.03, 0.46]
Total (95% CI)	**566**	**548**		**100.0 %**	**0.16 [0.08, 0.25]**

Total events: 154 (Opioid), 51 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 38.33$, df = 9 (P = 0.00002); $I^2 = 77\%$

Test for overall effect: Z = 3.98 (P = 0.000070)

Test for subgroup differences: Not applicable

Analysis 4.5. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 5 Participants reporting vomiting.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 5 Participants reporting vomiting

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	0/49	0/44		21.8 %	0.0 [-0.04, 0.04]
Gimbel 2003	17/82	2/77		16.4 %	0.18 [0.09, 0.28]
Hanna 2008	16/169	7/169		20.7 %	0.05 [0.00, 0.11]
Harke 2001	5/21	1/17		7.3 %	0.18 [-0.03, 0.39]
Morley 2003	4/19	1/19		7.5 %	0.16 [-0.05, 0.37]
Watson 2003	5/45	2/45		14.9 %	0.07 [-0.04, 0.18]
Zin 2010	3/27	2/30		11.4 %	0.04 [-0.10, 0.19]
Total (95% CI)	**412**	**401**		**100.0 %**	**0.08 [0.01, 0.15]**

Total events: 50 (Opioid), 15 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 22.84$, df = 6 (P = 0.00085); $I^2 = 74\%$

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 4.6. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 6 Particpants withdrawing due to adverse events.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 6 Particpants withdrawing due to adverse events

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gimbel 2003	7/82	4/77		21.2 %	0.03 [-0.04, 0.11]
Hanna 2008	27/169	9/169		30.9 %	0.11 [0.04, 0.17]
Khoromi 2007	5/41	1/39		10.4 %	0.10 [-0.02, 0.21]
Morley 2003	1/19	0/19		7.2 %	0.05 [-0.08, 0.19]
Watson 1998	5/50	3/50		11.5 %	0.04 [-0.07, 0.15]
Watson 2003	7/45	1/45		9.9 %	0.13 [0.02, 0.25]
Zin 2010	3/29	0/33		8.8 %	0.10 [-0.02, 0.23]
Total (95% CI)	**435**	**432**		**100.0 %**	**0.08 [0.04, 0.12]**

Total events: 55 (Opioid), 18 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.82$, df = 6 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 4.39 (P = 0.000011)

Test for subgroup differences: Not applicable

Analysis 4.7. Comparison 4 Adverse Events from Intermediate-term Studies: opioid vs placebo, Outcome 7 Participants withdrawing due to lack of efficacy.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: opioid vs placebo

Outcome: 7 Participants withdrawing due to lack of efficacy

Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gimbel 2003	1/82	11/77		18.9 %	-0.13 [-0.21, -0.05]
Hanna 2008	6/169	20/169		39.9 %	-0.08 [-0.14, -0.03]
Khoromi 2007	0/41	3/39		14.4 %	-0.08 [-0.17, 0.02]
Watson 2003	1/42	7/42		8.5 %	-0.14 [-0.26, -0.02]
Zin 2010	0/29	1/33		18.3 %	-0.03 [-0.11, 0.05]
Total (95% CI)	**363**	**360**		**100.0 %**	**-0.09 [-0.12, -0.05]**

Total events: 8 (Opioid), 42 (Placebo)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.00$, df = 4 (P = 0.41); $I^2 = 0\%$

Test for overall effect: Z = 4.78 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 1 Participants reporting constipation.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 1 Participants reporting constipation

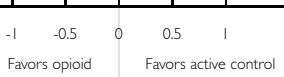
Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	19/49	1/48		27.8 %	0.37 [0.22, 0.51]
Khoromi 2007	18/28	7/28		11.9 %	0.39 [0.15, 0.63]
Raja 2002	23/76	8/76		33.6 %	0.20 [0.07, 0.32]
Wu 2008	17/50	2/42		26.7 %	0.29 [0.15, 0.44]
Total (95% CI)	**203**	**194**		**100.0 %**	**0.29 [0.21, 0.38]**

Total events: 77 (Opioid), 18 (Active control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.97$, df = 3 (P = 0.26); $I^2 = 24\%$

Test for overall effect: Z = 6.53 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 2 Participants reporting dizziness.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 2 Participants reporting dizziness

Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	0/49	1/48		56.7 %	-0.02 [-0.08, 0.03]
Khoromi 2007	4/28	2/28		6.8 %	0.07 [-0.09, 0.23]
Raja 2002	14/76	13/76		11.9 %	0.01 [-0.11, 0.13]
Wu 2008	2/50	2/42		24.7 %	-0.01 [-0.09, 0.08]
Total (95% CI)	**203**	**194**		**100.0 %**	**-0.01 [-0.05, 0.03]**

Total events: 20 (Opioid), 18 (Active control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.79$, df = 3 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 3 Participants reporting drowsiness/somnolence.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 3 Participants reporting drowsiness/somnolence

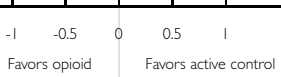
Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	8/49	4/48		29.0 %	0.08 [-0.05, 0.21]
Khoromi 2007	7/28	2/28		14.0 %	0.18 [-0.01, 0.37]
Raja 2002	23/76	8/76		31.6 %	0.20 [0.07, 0.32]
Wu 2008	9/50	4/42		25.4 %	0.08 [-0.05, 0.22]
Total (95% CI)	**203**	**194**		**100.0 %**	**0.13 [0.06, 0.20]**

Total events: 47 (Opioid), 18 (Active control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.42$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 3.71 (P = 0.00021)

Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 4 Participants reporting nausea.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 4 Participants reporting nausea

Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	2/49	0/44		26.8 %	0.04 [-0.03, 0.11]
Khoromi 2007	2/28	0/28		24.1 %	0.07 [-0.04, 0.18]
Raja 2002	30/76	5/76		23.3 %	0.33 [0.21, 0.45]
Wu 2008	4/50	0/42		25.9 %	0.08 [0.00, 0.16]
Total (95% CI)	**203**	**190**		**100.0 %**	**0.13 [-0.01, 0.26]**

Total events: 38 (Opioid), 5 (Active control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 26.57$, df = 3 (P<0.00001); $I^2 = 89\%$

Test for overall effect: Z = 1.77 (P = 0.077)

Test for subgroup differences: Not applicable

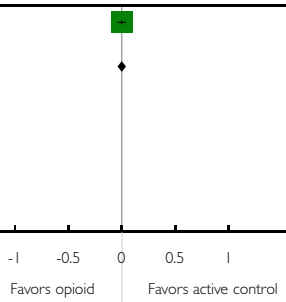
Analysis 5.5. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 5 Participants reporting vomiting.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 5 Participants reporting vomiting

Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	0/49	0/48		100.0 %	0.0 [-0.04, 0.04]
Total (95% CI)	**49**	**48**		**100.0 %**	**0.0 [-0.04, 0.04]**
Total events: 0 (Opioid), 0 (Active control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					



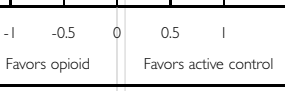
Analysis 5.6. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 6 Participants withdrawing due to adverse events.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 6 Participants withdrawing due to adverse events

Study or subgroup	Opioid n/N	Active control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Khoromi 2007	5/41	2/34		100.0 %	0.06 [-0.06, 0.19]
Total (95% CI)	**41**	**34**		**100.0 %**	**0.06 [-0.06, 0.19]**
Total events: 5 (Opioid), 2 (Active control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Not applicable					

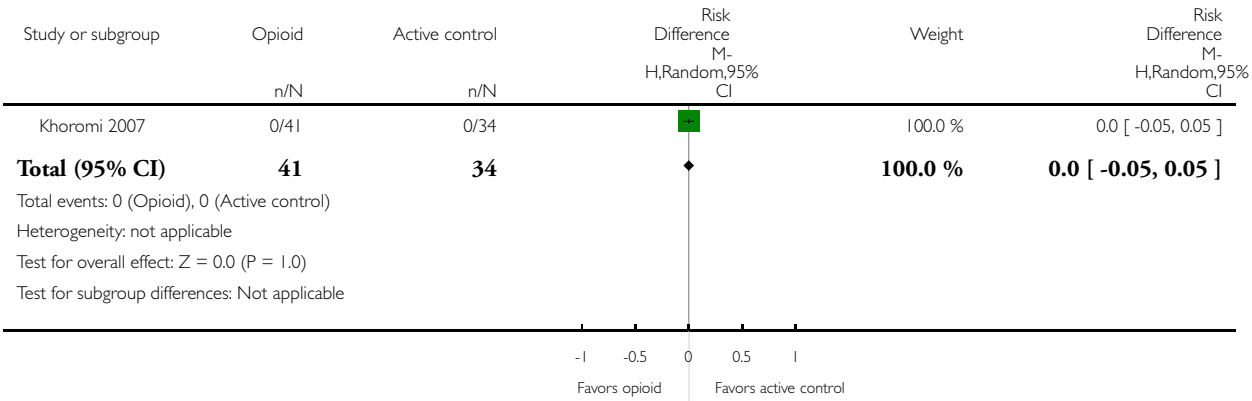


Analysis 5.7. Comparison 5 Adverse Events from Intermediate-term Studies: opioid vs active control, Outcome 7 Participants withdrawing due to lack of efficacy.

Review: Opioids for neuropathic pain

Comparison: 5 Adverse Events from Intermediate-term Studies: opioid vs active control

Outcome: 7 Participants withdrawing due to lack of efficacy



APPENDICES

Appendix 1. CENTRAL search strategy (pre-2012)

#1	MeSH descriptor Pain, this term only
#2	MeSH descriptor Neuralgia, this term only
#3	MeSH descriptor Pain, Intractable, this term only
#4	MeSH descriptor Complex Regional Pain Syndromes explode all trees

(*Continued*)

#5	MeSH descriptor Diabetic Neuropathies, this term only
#6	MeSH descriptor Trigeminal Neuralgia, this term only
#7	MeSH descriptor Somatosensory Disorders explode all trees
#8	(neuropathic near/2 pain*):ti
#9	(neuralgia):ti
#10	(complex regional pain syndrome):ti
#11	(reflex sympathetic dystrophy):ti
#12	(causalgia):ti
#13	(post-herpetic neuralgia):ti
#14	(phantom limb pain):ti
#15	(allodynia):ti
#16	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17	MeSH descriptor Narcotics, this term only
#18	MeSH descriptor Analgesics, Opioid, this term only
#19	(morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone):ti,ab,kw
#20	(#17 OR #18 OR #19)
#21	(#16 AND #20)
#22	(#21)Cochrane Reviews
#23	(#21)Other reviews
#24	(#21)CENTRAL

Appendix 2. MEDLINE search strategy (pre-2012)

1. pain.sh.
2. neuralgia.sh.
3. pain, intractable.sh.
4. exp Complex Regional Pain Syndromes/
5. diabetic neuropathies.sh.
6. trigeminal neuralgia.sh.
7. exp somatosensory disorders/
8. (neuropathic adj2 pain).tw.
9. neuralgia.tw.
10. complex regional pain syndrome.tw.
11. reflex sympathetic dystrophy.tw.
12. causalgia.tw.
13. post-herpetic neuralgia.tw.
14. phantom limb pain.tw.
15. allodynia.tw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Narcotics/
18. *"Analgesics, Opioid"/
19. (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).mp.
20. 17 or 18 or 19
21. randomized controlled trial.pt.
22. meta-analysis.pt.
23. controlled-clinical-trial.pt.
24. clinical-trial.pt.
25. random:.ti,ab,sh.
26. (meta-anal: or metaanaly: or meta analy:).ti,ab,sh.
27. ((doubl: or singl:) and blind:).ti,ab,sh.
28. exp clinical trials/
29. crossover.ti,ab,sh.
30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. Animals/
32. 16 and 20 and 30
33. 32 not 31

[mp=title, original title, abstract, name of substance, mesh subject heading].

Appendix 3. EMBASE search strategy (pre-2012)

1 PAIN/
2 NEURALGIA/
3 Neuropathic Pain/
4 exp Complex Regional Pain Syndrome/
5 (diabetic adj neuropath$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
6 Trigeminus Neuralgia/
7 Somatosensory Disorder/
8 (neuropathic adj pain$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

9 "complex regional pain syndrome$".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
10 neuralgi$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
11 "reflex sympathetic dystroph$".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
12 causalgi$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
13 Postherpetic Neuralgia/
14 ("post herpetic neuralgi$" or "post-herpetic neuralgi$").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
15 Phantom Pain/
16 (phantom adj pain$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
17 Intractable Pain/
18 (intractable adj pain$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
19 Allodynia/
20 allodynia.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
21 or/1-20
22 Narcotic Agent/
23 (narcotic adj agent$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
24 (analgesic$ adj3 opioid$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
25 (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).mp.
26 22 or 23 or 24 or 25
27 21 and 26
28 random*.ti,ab.
29 factorial*.ti,ab.
30 (crossover* or cross over* or cross-over*).ti,ab.
31 placebo*.ti,ab.
32 (doubl* adj blind*).ti,ab.
33 (singl* adj blind*).ti,ab.
34 assign*.ti,ab.
35 allocat*.ti,ab.
36 volunteer*.ti,ab.
37 CROSSOVER PROCEDURE.sh.
38 DOUBLE-BLIND PROCEDURE.sh.
39 RANDOMIZED CONTROLLED TRIAL.sh.
40 SINGLE BLIND PROCEDURE.sh.
41 or/28-40
42 ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
43 HUMAN/
44 42 and 43
45 42 not 44
46 41 not 45
47 27 and 46

Appendix 4. CENTRAL search strategy 2012

#1 MeSH descriptor: [Pain] this term only
#2 MeSH descriptor: [Neuralgia] this term only
#3 MeSH descriptor: [Pain, Intractable] this term only
#4 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#5 MeSH descriptor: [Diabetic Neuropathies] explode all trees
#6 MeSH descriptor: [Trigeminal Neuralgia] explode all trees
#7 MeSH descriptor: [Somatosensory Disorders] explode all trees
#8 (neuropathic near/2 pain*):ti,ab,kw (Word variations have been searched)
#9 (neuralgia):ti,ab,kw (Word variations have been searched)
#10 (complex regional pain syndrome):ti,ab,kw (Word variations have been searched)
#11 (reflex sympathetic dystrophy):ti,ab,kw (Word variations have been searched)
#12 (causalgia):ti,ab,kw (Word variations have been searched)
#13 (post-herpetic neuralgia):ti,ab,kw (Word variations have been searched)
#14 (phantom limb pain):ti,ab,kw (Word variations have been searched)
#15 (allodynia):ti,ab,kw (Word variations have been searched)
#16 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
#17 MeSH descriptor: [Narcotics] this term only
#18 MeSH descriptor: [Analgesics, Opioid] this term only
#19 (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone):ti,ab,kw (Word variations have been searched)
#20 (#17 or #18 or #19)
#21 #16 and #20 from 2010 to 2012

Appendix 5. MEDLINE search strategy 2012

1 Pain/ (103631)
2 neuralgia/ (6938)
3 pain, intractable/ (5344)
4 exp Complex Regional Pain Syndromes/ (4141)
5 diabetic neuropathies/ (11390)
6 trigeminal neuralgia/ (5361)
7 exp somatosensory disorders/ (14530)
8 (neuropathic adj2 pain).tw. (8560)
9 neuralgia.tw. (7586)
10 complex regional pain syndrome.tw. (1303)
11 reflex sympathetic dystrophy.tw. (1481)
12 causalgia.tw. (426)
13 post-herpetic neuralgia.tw. (486)
14 phantom limb pain.tw. (539)
15 allodynia.tw. (4255)
16 or/1-15 (148967)
17 Narcotics/ (14099)
18 *"Analgesics, Opioid"/ (17512)
19 (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).tw. (72647)
20 or/17-19 (87255)
21 randomized controlled trial.pt. (339247)

22 controlled clinical trial.pt. (85403)
23 randomized.ab. (242011)
24 placebo.ab. (135530)
25 drug therapy.fs. (1577150)
26 randomly.ab. (173651)
27 trial.ab. (250716)
28 groups.ab. (1135692)
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (2936803)
30 exp animals/ not humans.sh. (3795620)
31 29 not 30 (2494786)
32 16 and 20 and 31 (8133)
33 (201008* or 201009* or 201010* or 201011* or 201012* or 2011* or 2012*).ed. (1814643)
34 32 and 33 (1213)

Appendix 6. EMBASE search strategy 2012

1 Pain/ (174379)
2 neuralgia/ (6265)
3 pain, intractable/ (3738)
4 exp Complex Regional Pain Syndromes/ (7151)
5 diabetic neuropathies/ (16484)
6 trigeminal neuralgia/ (8199)
7 exp somatosensory disorders/ (55288)
8 (neuropathic adj2 pain).tw. (13683)
9 neuralgia.tw. (10683)
10 complex regional pain syndrome.tw. (1981)
11 reflex sympathetic dystrophy.tw. (1952)
12 causalgia.tw. (538)
13 post-herpetic neuralgia.tw. (825)
14 phantom limb pain.tw. (807)
15 allodynia.tw. (6059)
16 or/1-15 (268307)
17 Narcotics/ (10729)
18 *"Analgesics, Opioid"/ (6948)
19 (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).tw. (98508)
20 or/17-19 (111821)
21 16 and 20 (17023)
22 random$.tw. (773434)
23 factorial$.tw. (20181)
24 crossover$.tw. (45540)
25 cross over$.tw. (20720)
26 cross-over$.tw. (20720)
27 placebo$.tw. (186291)
28 (doubl$ adj blind$).tw. (138167)
29 (singl$ adj blind$).tw. (12952)
30 assign$.tw. (215292)
31 allocat$.tw. (72818)
32 volunteer$.tw. (167332)
33 Crossover Procedure/ (35309)

34 double-blind procedure.tw. (223)
35 Randomized Controlled Trial/ (333591)
36 Single Blind Procedure/ (16539)
37 or/22-36 (1272131)
38 (animal/ or nonhuman/) not human/ (4520391)
39 37 not 38 (1121112)
40 21 and 39 (3305)
41 (201008* or 201009* or 211010* or 211011* or 201012* or 2011* or 2012*).dd. (2723769)
42 40 and 41 (926)

Appendix 7. Intermediate-term studies: outcome of treatment

Study	Diagnosis	Interventions	Outcome		
			Pain Intensity	Pain Relief	Functioning/other
Frank 2008	Mixed neuropathic	1. Dihydrocodeine 2. Nabilone	Daily VAS 1. BL 58.6 ± 24.1, endpoint not reported 2. BL 59.9 ± 24.4, endpoint not reported		SF36 - significant differences in some subscales HADS -NSD
Gilron 2005	Diabetic neuropathy	1. LA morphine 2. Gabapentin 3. Morphine/ gabapentin combination 4. Placebo (lorazepam)	Pain intensity (0 - 10 scale ± SE) at maximum tolerated dose: 3.70 ± 0.34 vs. 4.15 ± 0.33 gabapentin arm vs. 3.06 ± 0.33 combination arm vs. 4.49 ± 0.34 placebo arm (combination lower than morphine arm, P = 0.04, gabapentin arm, p < 0.001, or placebo, P < 0.001. All other comparisons NS) % change in pain intensity greater in combination arm vs. placebo: 20.4%, P = 0.03		

(*Continued*)

			All other comparisons NS		
Gimbel 2003	Diabetic neuropathy	1. LA oxycodone 2. Placebo	VAS: 4.1 ± 0.3 vs 5.3 ± 0.3 NRS (0 - 10) BL - end of treatment 1. 7.9 ± 1.7 - 4.7 ± 2.9 2. 7.8 ± 1.6 - 5.8 ± 2.6	≥ 33% reduction in intensity item in NPS: oxycodone 37/82, placebo 20/77	Satisfaction with medication, sleep quality & 9/14 BPI parameters oxycodone > placebo; Median time to pain < 4: 6 vs. 17 days; % days with mild pain: 47 ± 39 vs 29 ± 37; no difference in RMHI, SIP, SF-36
Hanna 2008	Diabetic neuropathy	1. LA oxycodone + gabapentin 2. Placebo+ gabapentin	Box scale-11 pain scores ; PID (BL to end of treatment) 1. 2.1 ± 2.61 2. 1.5 ± 2.38	Categorical pain relief scale - % good + very good 56% vs. 41%	Sleep Disturbances, SF BPI, MPQ, EuroQol 5D Questionnaire - SSD in favor of oxycodone group. NND Sleep Quality -NSD .NND
Harke 2001	Mixed peripheral	1. LA morphine 2 Placebo 3. Carbamazepine 4. Placebo	No sig differences between morphine & placebo carbamazepine superior to placebo in NPS and in time without spinal cord stimulator		
Huse 2001	Phantom limb	1. LA morphine 2. Placebo	VAS (0 - 10): 3.3 ± 1.6 vs 4.0 ± 1.2 50% ΔVAS: 42% vs 8% PES sensory: 0.7 ± 0.8 vs 1.7 ± 0.8 PES affective: 0.8 ± 0.6 vs 1.6 ± 0.7		No correlation between ΔVAS and PRSS, Brief Stress Scale or WHYMPI; 'd2-test': 101 ± 19 vs. 106 ± 18
Khoromi 2007	Chronic lumbar root pain	1. Morphine 2. nortriptyline 3. Morphine + nortriptyline 4. Placebo	NRS-average leg pain (0 - 10): BL to end of treatment 1. 4.9 ± 2.4 to 3.4 ±2.8	CGPRS (0 - 5) Mod or more pain relief N (%) 1. 13/32 (4%) 2. 12/31 (40%)	SF36 NSD BDI: BL to end of treatment 1. 8 ± 6.7 to 9.6 ± 8.5

(*Continued*)

			2. 4.9 ± 2.4 to 3 ± 2.7 3. 4.9 ± 2.4 to 3.4 ± 2.5 4. 4.9 ± 2.4 to 3.7 ± 2.7 NRS-worst leg pain (0-10): BL to end of treatment 1. 5.7 ± 2.4 to 4.5 ± 3.1 2. 5.7 ± 2.4 to 3.8 ± 3 3. 5.7 ± 2.4 to 3.8 ± 2.4 4. 5.7 ± 2.4 to 4.6 ± 2.8	3. 18/28 (67%) 4. 11/33 (37%)	2. 8 ± 6.7 to 7.3 ± 7.1 3. 8 ± 6.7 to 6 ± 5 4. 8 ± 6.7 to 9 ± 8.5 ODI - NSD BDI: BL to end of treatment 1. 30 ± 15 to 25.7 ± 16.5 2. 30 ± 15 to 27.5 ± 16.7 3. 30 ± 15 to 27.4 ± 15.4 4. 30 ± 15 to 30.5 ± 15.9
Morley 2003	Mixed	1. Methadone low-dose 2. Placebo 3. Methadone high-dose 4. Placebo	Low-dose vs placebo: VAS max : 69 ± 17 vs 74 ± 13 ns VAS ave: 60 ± 20 vs 64 ± 19 ns High dose vs placebo: VAS max : 64 ± 23 vs 64 ± 27 VAS ave : 58 ± 25 vs 64 ± 22	Low-dose vs placebo: VAS : 23 ± 19 vs 15 ± 16 ns High dose vs placebo: VAS: 32 ± 27 vs 23 ± 21	
Raja 2002	Postherpetic neuralgia	1. Morphine or methadone 2. Nortriptyline or desipramine 3. Placebo	VAS: 1. 4.4 ± 2.4 2. 5.1 ± 2.3 3. 6.0 ± 2.0 Both active treatments superior to placebo	%: 1. 38.2 ± 32.2 2. 31.9 ± 30.4 3. 11.2 ± 19.8 Both active treatments superior to placebo	Wechsler Adult Intelligence Scale-Revised slightly worsened with TCA; Sleep improved from baseline with active treatments; All other outcomes unchanged
Rowbotham 2003	Mixed neuropathic	1. Levorphanol high dose 2. Levorphanol low	VAS 1. 42.1 ± 26.5 (-	Categorical pain relief scale - NSD	PMS-unchanged; SDMT

(*Continued*)

		dose	36%) 2. 53.4 ± 24.7 (-21%)		& MPI improved in both groups
Watson 1998	Postherpetic neuralgia	1. LA oxycodone 2. Placebo	Daily VAS: 35 ± 25 vs 54 ± 25 Daily CPS: 1.7 ± 0.7 vs 2.3 ± 0.7	Daily categorical pain relief scale: 2.9 ± 1.1 vs. 1.9 ± 1.0	Categorical Disability Scale: 0.3 ± 0.8 vs. 0.7 ± 1.0 Effectiveness scale: 1.8 ± 1.1 vs. 0.7 ± 1.0 POMS & BDI no difference
Watson 2003	Diabetic neuropathy	1. LA oxycodone 2. Placebo	Daily VAS: 26.3 ± 24.7 vs 46.7 ± 26.9 Daily CPS: 1.3 ± 0.9 vs 1.9 ± 0.9	Categorical pain relief scale: 1.8 ± 1.4 vs. 2.79 ± 1.2	Overall Pain and Sleep Questionnaire, PDI, SF36 oxycodone superior vs. placebo; NNTB for moderate relief = 2.6
Wu 2008	Post-amputation Pain	1.SR Morphine 2.Mexiletine 3.Placebo	Change in overall pain intensity BL - end of treatment; NRS (0 - 10), (95% confidence interval) 1. -2.8 (-3.4 to -2.3) 2. -1.5 (-2.2 to -0.9) 3. -1.4 (-2.2 to -0.6)	1. 1. 53% 2. 2. 53% 3. 3. 19% > 33% PR, N (%) 1.33/50 (66%) 2. 16/42 (38%) 3.19/43 (44%) > 50% PR, N (%) 1. 23/50 (46%) 2. 11/42 (26%) 3. 13/43 (30%)	WHYMPI - no differences between groups
Zin 2010	Postherpetic Neuralgia Painful Diabetic Neuropathy	1. Pregabalin + oxycodone 2. Pregabalin + placebo	VAS (0 - 10) BL- end of treatment 1. 6.85 ± 0.3 - 3.59 ± 2.35 2. 6.73 ± 0.29 - 4.03 ± 2.33	> 50% PR from BL to end of treatment 1. 15/26 (58%) 2. 19/29 (66%) NSD	Sleep Interference Score - NSD; NPS - most subscales NSD; SF36 - most subscales NSD; POMS - NSD; COG-NITIVE PERFORMANCE-TMTB - NSD; PGIC - NSD; CGIC- NSD

Data are presented as mean ± standard deviation unless specified

ΔVAS = change in VAS from baseline; 'd2-test' = test for attention performance; BDI = Beck Depression Inventory; BL= baseline; BPI = Brief Pain Inventory; CGIC = Clinician global impression of change; CGPRS = Categorical Global Pain Relief Scale; CPS = Categorical Pain Scale; HADS = Hospital Anxiety and Depression Score LA = long-acting; MPI = Multidimensional Pain Inventory; NND = no numerical data; NPS = Neuropathic Pain scale; ODI = Oswestry Disability Index; PDI = Pain Disability Index; PES = Pain Experience Scale; PGIC = Patient global impression of change; POMS = Profile of Mood States; PR = pain reduction; PRSS = Pain-Related Self-Treatment Scale; RMHI = Rand Mental Health Inventory; SA = short acting; SDMT = Symbol-Digit Modalities Test; SF = Short Form; SF36 = Short Form 36; SIP = Sickness Impact Profile; TCA = tricyclic antidepressants; VAS = visual analog scale; WHYMPI = West Haven-Yale Multidimensional Pain Inventory

WHAT'S NEW

Last assessed as up-to-date: 21 August 2013.

Date	Event	Description
4 September 2013	Amended	Slight amendment to wording of search strategy sections.

HISTORY

Review first published: Issue 3, 2006

Date	Event	Description
21 August 2013	New citation required but conclusions have not changed	New studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions
24 October 2012	New search has been performed	Updated search, added data to existing meta-analyses, created new meta-analyses, revised text accordingly
6 November 2008	Amended	Further RevMan 5 changes made.
22 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AM: screened retrieved papers against inclusion criteria, appraised risk of bias and extracted data from papers and wrote parts of the Background in the updated review.

EE: conceived the review and provided clinical perspective. Designed and coordinated review, participated in retrieval of papers, screened retrieved papers against inclusion criteria, appraised quality of papers, extracted data from papers, wrote parts of the updated review (Abstract, Applicability of evidence, Agreements and disagreements with other studies or reviews).

EM: developed the search strategy, organized retrieval of and screened retrieved papers against inclusion criteria in original review, appraised risk of bias of papers, extracted data from papers, meta-analyzed data, compiled Characteristics of included studies; Characteristics of excluded studies tables. Wrote Methods and Results Section and parts of Discussion (Summary of main results, Overall completeness of evidence, Quality of the evidence; Potential biases in the review process).

DECLARATIONS OF INTEREST

EE has received research support from government and industry sources at various times, and consulted for and received lecture fees from various pharmaceutical companies related to analgesics and other healthcare interventions.

SOURCES OF SUPPORT

Internal sources

- Richard Saltonstall Charitable Foundation, USA.
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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects; *therapeutic use]; Nervous System Diseases [complications; *drug therapy]; Pain [*drug therapy; etiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans