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Opioids for neuropathic pain

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ABSTRACT

Background

The use of opioids for neuropathic pain remains controversial. Studies have been small, have yielded equivocal results, and have not established the long-term risk-benefit ratio of this treatment.

Objectives

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

Search strategy

We searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2005), MEDLINE (1966 to June 2005), and EMBASE (1980 to 2005 Week 27) for articles in any language, and reference lists of reviews and retrieved articles.

Selection criteria

Trials were included 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. Studies in which drugs other than opioid agonists were combined with opioids or opioids were administered epidurally or intrathecally were excluded.

Data collection and analysis

Data were extracted by two independent investigators and included demographic variables, diagnoses, interventions, efficacy, and adverse effects.

Main results

Twenty-three trials met the inclusion criteria and were classified as short-term (less than 24 hours; n = 14) or intermediate-term (median = 28 days; range = eight to 70 days; n = 9). The short-term trials had contradictory results. In contrast all nine intermediate-term trials demonstrated opioid efficacy for spontaneous neuropathic pain. Meta-analysis of seven intermediate-term studies showed mean post-treatment visual analog scale scores of pain intensity after opioids to be 13 points lower on a scale from zero to 100 than after placebo (95% confidence interval -16 to -9; P < 0.00001). The most common adverse events were nausea (33% opioid versus 9% control: number needed to treat to harm (NNH) 4.2) and constipation (33% opioid versus 10% control: NNH 4.2), followed by drowsiness (29% opioid versus 12% control: NNH 6.2), dizziness (21% opioid versus 6% control: NNH 7.1), and vomiting (15% opioid versus
Where reported, 23 (11%) of 212 participants withdrew because of adverse events during opioid therapy versus nine (4%) of 202 receiving placebo.

**Authors’ conclusions**

Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain, whereas intermediate-term studies demonstrate significant efficacy of opioids over placebo, which is likely to be clinically important. Reported adverse events of opioids are common but not life threatening. Further randomized controlled trials are needed to establish long-term efficacy, safety (including addiction potential), and effects on quality of life.

**PLAIN LANGUAGE SUMMARY**

Opioids for neuropathic pain

Opioids, pain killers such as morphine, are effective for the treatment of long-term pain due to nerve damage. Neuropathic pain, pain caused by nerve damage, 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 authors looked at both short- and intermediate-term trials. They found mixed results regarding the effectiveness of short-term use of opioids. Intermediate-term trials demonstrated that opioids are effective for the subtypes of neuropathic pain tested and for the relatively short duration of published studies. Side effects such as nausea, dizziness, and drowsiness were common, but not life threatening.

**BACKGROUND**

The number of people suffering from neuropathic pain in the United States is unknown, but is estimated to lie between two and six million (Berger 2003; Foley 2003). 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). 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 poststroke 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) (Yarnitsky 1998). Neuropathic pain, like many other forms of chronic pain, often has negative effects on quality of life. 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 (Sindrup 1999).

Clinical trials to assess the efficacy of opioids for reducing neuropathic pain have been reported for more than 15 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. The lack of definitive evidence regarding the efficacy of opioids in reducing neuropathic pain in general, and central neuropathic pain in particular, as well as concerns about adverse effect profiles and the potential for abuse, addiction, hormonal abnormalities, dysfunction of the immune system, and, in some cases, paradoxical hyperalgesia (Ballantyne 2003; Canavero 2003; Dellemijn 1999; McQuay 1997), discourage the use of opioids in the treatment of neuropathic pain (Carver 2001).

**OBJECTIVES**

Given growing interest and concerns regarding the prescribing of opioids for neuropathic pain, we conducted a systematic review of published randomized controlled trials (RCTs) to answer two questions.

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

2) What is the nature and occurrence 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 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 differentiated.

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: orally, rectally, transdermally, intravenously, intramuscularly, or subcutaneously. 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; or if tramadol was used as the active drug, because, although tramadol interacts to some degree with opioid receptors, it is not regarded as a pure opioid agonist. The efficacy of tramadol in relieving neuropathic pain has recently been reviewed (Hollingshead 2005).

Types of outcome measures
We extracted data on the following outcomes from each trial report included in the review: pain intensity using a visual analog scale (VAS); type and amount of opioid and control used; and incidence of adverse effects during treatment with opioid or control.
We normalized pain intensity data assessed by means other than a zero to 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 zero to ten scale) or by assigning values on a zero to 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 second point was scored as 50 on a zero to 100 scale (0 = no pain, 1 = 25, 2 = 50, 3 = 75, 4 = 100).

Search methods for identification of studies
We searched for pertinent articles in any language using the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2005) and MEDLINE (1966 to June, week 2, 2005), and the reference lists of reviews and retrieved articles. We then searched EMBASE (1980 to 2005, Week 27) for additional articles. We did not contact authors for original data unless data were missing or unclear. We did not consider abstracts or unpublished reports. We combined nine search terms for RCTs with 32 terms for opioids and 15 terms for neuropathic pain. Our MEDLINE search strategy can be found in Appendix 1. The MEDLINE search strategy was adapted to the EMBASE and CENTRAL databases.

Data collection and analysis

Data extraction
We extracted information on study design, methods, interventions, pain outcomes, and adverse effects from each article. In addition, two independent investigators (EE and EM), who were not blinded to study authors, extracted diagnoses, participant inclusion and exclusion criteria, numbers enrolled and completing the study, and functional assessments, placing this information into a standardized table. 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 effects. When possible we normalized all data to a zero to 100 mm VAS. We made no attempt to convert surrogate outcomes (e.g. global evaluations or preferences, amount of rescue medication used) to a VAS. For studies in which surrogate outcomes were the only results available, we describe them herein 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 or dropouts if described.

Assessment of methodological quality
We graded studies that met inclusion criteria for methodological quality using the Oxford Quality Scale as reported by Jadad et al (Jadad 1996). Scores are based on the description of randomization, blinding, and withdrawals, and can range from zero to five; higher scores indicate better methodological quality.

Statistical analysis
We performed statistical analyses of included trials using the Cochrane Collaboration’s Review Manager software (RevMan), version 4.2.7 (Oxford, England: Cochrane Collaboration). Whenever possible, we combined results from the trials to calculate differences in postintervention pain intensity or pain relief and also to calculate numbers-needed-to-treat-to-harm (NNH) for adverse effects.
effects, along with 95% confidence intervals (CIs). We evaluated heterogeneity between and within trials using both the chi square (12) test and the I^2 test. The X^2 test assesses whether observed differences in results are compatible with chance alone. A low P-value (or a large X^2 statistic relative to its degrees of freedom) provides evidence of heterogeneity of treatment effects (variation in effect estimates beyond chance). The X^2 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 I^2 statistic, I^2 = [(Q - df)/Q] x 100%, where Q is the X^2 statistic and df is its degrees of freedom (Green 2005; Higgins 2003). The I^2 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 (Green 2005). Since visual inspection of both forest plots, and I^2 and X^2 statistics suggested that results were homogeneous, a fixed-effect model was used for all analyses. P-values less than 0.05 were considered significant.

RESULTS

Description of studies

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

The literature search yielded 3823 potential studies (CENTRAL, 945; MEDLINE, 1531; EMBASE 1347), of which 46 were selected for retrieval. Our EMBASE search produced no additional relevant articles but did, as a form of internal positive control, yield the 22 included trials derived from the original MEDLINE search.

Included studies

Twenty-three of the 46 articles met the inclusion criteria and provided data on 727 people with neuropathic pain who were treated with opioids. 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 the median duration was sufficiently long to make firm conclusions about chronic administration of opioids. The first group consisted of 14 short-term trials (Arner 1988; Atall 2002; Dellemijn 1997; Eide 1994; Eide 1995; Jadad 1992; Jorum 2003; Kupers 1991a; Kupers 1991b; Leung 2001; Max 1988; Max 1995; Rabben 1995; Rowbotham 1991; Wu 2002a; Wu 2002b) 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, seven 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 1991a central; Kupers 1991b peripheral). In another study changes in phantom limb pain and stump pain were assessed separately (Wu 2002a phantom limb pain; Wu 2002b stump pain). 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 randomized trials (Benedetti 1998; Kalman 2002; Maier 2002) of opioids for neuropathic pain failed to meet one or more of the inclusion criteria. 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 effects of the two types of pain were combined into a single outcome, thereby precluding separate analyses of data for the two subgroups. That study was therefore excluded. 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 µ receptor agonist, with different pharmacological properties to members of the full µ opioid agonist class.

Risk of bias in included studies

The quality of the short- and intermediate-term studies as judged by the Oxford Quality Scale is presented in the table of included studies. The median overall score was four (range, two to five), indicating generally good methodological quality. The Oxford Quality Scales for intermediate-term studies were non-significantly higher than those of short-term studies (median, five versus four). Inadequate description of the randomization process (in eight tri-
als) was the most common shortfall in the short-term trials. In the intermediate-term trials, seven scored five points, one scored three (Huse 2001), and one scored two (Harke 2001). Inadequate description of adverse events, reasons for dropout, methods of randomization, and blinding led to the lower scores of the latter two studies.

Effects of interventions

Short-term studies

Fourteen RCTs using a crossover design provided adequate data regarding efficacy of acute exposure to opioids in 267 people with neuropathic pain. Drugs were administered intravenously in 12 trials, orally in one (Max 1988), and intramuscularly in one (Rabben 1999). The duration of treatment varied from seconds (i.e. a single intramuscular injection) to eight hours, but was less than one hour in ten trials. The tested drug was morphine in seven trials, alfentanil in four, and fentanyl, meperidine, or codeine in one trial each. Placebo was used as a control in 12 trials. The diagnosis was specified in all trials: three trials included people with posther- petic neuralgia (PHN) only (Eide 1994; Max 1988; Rowbotham 1991); two involved people with post-traumatic neuralgia (Jorum 2001a; Max 1995); in five, participants with mixed neuropathies were studied (Arner 1988; Dellemijn 1997; Jadad 1992; Kupers 1991a; Kupers 1991b; Leung 2001); 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 2002a; Wu 2002b). Considerable variation between studies in dosage, duration of treatment, and method of pain assessment allowed only limited quantitative synthesis of data.

A change in spontaneous pain intensity was the primary outcome measure in all 14 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). Six trials showed greater efficacy of the tested opioid than of placebo (Dellemijn 1997; Eide 1995; Jorum 2003; Leung 2001; Rowbotham 1991; Wu 2002a; Wu 2002b). 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 1991a; Kupers 1991b).

We combined data for meta-analysis from four articles (comprising six trials) enrolling a total of 90 participants (Attal 2002; Kupers 1991a; Kupers 1991b; Rowbotham 1991; Wu 2002a; Wu 2002b) (Comparison 01 01) because these reported means and standard deviations for pain intensity after active drug or placebo. The result of the t2 test for heterogeneity was 0.38 (P = 0.99), and the I² was 0%, indicating a high degree of homogeneity between and within studies. Opioid treatment was superior to placebo in all trials, but reached statistical significance in only three. The overall mean difference in the last measured pain intensity for active treatment versus placebo was -16 (on a zero to 100 VAS) (95% CI -23 to -9; P < 0.001). Data from two trials concerning a total of 21 participants with central pain and from four trials involving 69 people with peripheral neuropathic pain were combinable for further meta-analysis (Comparison 01 01). For peripheral pain, the final pain intensity following opioid administration was 15 points lower than that after placebo (95% CI -23 to -7; P < 0.001), whereas, for central pain, the difference was 18 points (95% CI -30 to -5; P = 0.006). When 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) (Comparison 01 02), although the total number of participants (n = 19) was low.

Intermediate-term studies

Nine trials provided data on 460 people treated with opioids. The number per treatment group ranged from 12 to 82 and the duration of treatment varied from eight days to ten weeks (median, 28 days). Six trials had a crossover design and three had a parallel design. Four drugs were tested: morphine in four trials, oxycodone in three trials; methadone in one article comprising two trials; and levorphanol in one trial. Placebo was used as a control in all but one trial (Rowbotham 2003). Three trials included, for comparison, additional study groups in which participants were administered non-opioid active drugs: carbamazepine in one trial (Harke 2001), the tricyclic antidepressants nortriptyline and desipramine in another (Raja 2002), and gabapentin in one other (Gilron 2005). Two trials compared different dosages of an opioid: one of these compared two different dosages of methadone (Morley 2003) and the other compared two different dosages of levorphanol (Rowbotham 2003). Five trials enrolled participants with one specific pain syndrome: diabetic neuropathy (Gimbel 2003; Watson 2003), PHN (Raja 2002; Watson 1998), and phantom pain (Huse 2001). The other four studies enrolled people with neuropathic pain of diverse etiologies. All trials reported that opioids were efficacious in reducing spontaneous neuropathic pain by demonstrating either superiority over placebo or a dose-dependent analgesic response. Seven of the nine
studies provided data suitable for pooling based on data on pain intensity after active drug and placebo treatments. Neither the $X^2$ test, nor the $F^2$ test suggested that the data were heterogeneous ($X^2 = 7.54, P = 0.27; F^2 = 20.4\%$). The meta-analysis included 307 opioid-treated and 301 placebo-treated participants and showed the overall mean pain intensity to be 13 points lower in opioid-treated people than in those treated with placebo (95% CI -16 to -9; $P < 0.00001$; Comparison 02 01). A post hoc subanalysis of the highest-quality trials was performed, excluding one study (Huse 2001) with an Oxford Quality Scale score of three. The new estimate of the difference between VAS values in the opioid and placebo groups for the remaining six studies was -13 (95% CI -17 to -10).

A dose-dependent analgesic effect was found 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 high 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.

Evoked pain was measured in only two studies (Watson 1998; Watson 2003). In both these trials oxycodone was significantly superior to placebo in reducing allodynia, categorized as ‘skin pain’ (Comparison 02 02).

Two studies compared mean VAS pain scores for opioids versus active controls (Gilron 2005; Raja 2002). The first (Gilron 2005) showed a non-significant superiority in participants administered morphine versus those receiving gabapentin. The second (Raja 2002) demonstrated a similar non-significant superiority in people administered either morphine or methadone versus those administered the tricyclic antidepressants nortriptyline or desipramine. In combination, these two trials achieved statistical significance (Comparison 03 01), although the total number of participants ($n = 120$) was low.

Seven of the nine trials measured the effects of opioids on secondary outcome parameters, such as disability, sleep, cognition, and depression. However, because of the use of 20 different measurement tools, the data could not be quantitatively combined. Both the physical and mental health components of the Short Form-36 were improved by oxycodone treatment to a greater degree than by placebo in people with diabetic neuropathy in one study (Watson 2003) but not in another (Gimbel 2003). The ‘role-physical’, ‘bodily pain’ and ‘mental health’ scales of the Short Form-36 were improved in a group of participants with mixed neuropathies when receiving morphine in comparison to placebo (Gilron 2005). In people with PHN, neither the Multidimensional Pain Inventory (Raja 2002) nor the Categorical Disability Scale (Watson 1998) showed improvement with oxycodone treatment. Thus, no consistent reduction in disability was found. Depression, measured by the Beck Depression Inventory and by the Profile of Mood States questionnaire, failed to improve with oxycodone treatment in people with PHN (Watson 1998). 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). However, those with either diabetic neuropathy or PHN showed an improvement in the Beck Depression Inventory when administered morphine in comparison to placebo (Gilron 2005).

**Adverse events and withdrawals due to adverse events**

Although we extracted data on the prevalence of common opioid-related adverse effects from all studies, we obtained the majority of the information from six intermediate-term placebo-controlled trials (Gilron 2005; Gimbel 2003; Harke 2001; Morley 2003; Raja 2002; Watson 2003) and a lesser amount from two additional studies (Rowbotham 2003; Watson 1998). Another study (Huse 2001) reported adverse events on a VAS, precluding determination of the numbers of affected participants. Whenever possible, we calculated the NNH (Cook 1995) for each of the common opioid adverse effects. To avoid the possibility that the NNH could have been biased because of the selective dropout of participants experiencing adverse effects, we included only studies in which the adverse event that led to the withdrawal was specified.

The most common adverse events were nausea (33% opioid versus 9% control; NNH 4.2; 95% CI 3.2 to 5.6) and constipation (33% opioid versus 10% control; NNH 4.2; 95% CI 3.3 to 5.9), followed by drowsiness (29% opioid versus 12% control: NNH 6.2; 95% CI 4.3 to ten), dizziness (21% opioid versus 6% control: NNH 7.1; 95% CI five to 11.1), and vomiting (15% opioid versus 3% control: NNH 8.3; 95% CI 5.6 to 14.3). Data on cognitive impairment as well as on other adverse effects were insufficient to allow calculation of the NNH. Both the $X^2$ and $F^2$ tests for each adverse event analyzed suggested that heterogeneity existed between 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.

When opioid therapy is initiated, there is always a possibility that recipients will abandon treatment because of adverse events. Of the nine intermediate-term RCTs reviewed, four provided comparable information regarding the number of dropouts due to adverse events (Gilron 2005; Gimbel 2003; Morley 2003; Watson 2003). In total, 23 (11%) of 212 participants in these four studies withdrew because of adverse events during opioid therapy versus nine (4%) of 202 receiving placebo (NNH 16.7; 95% CI 9.1 to 100).
DISCUSSION

The results of this study can be divided into two categories according to the duration of included trials. Short-term trials yielded mixed results with respect to the analgesic efficacy of opioids. Intermediate-term trials demonstrated consistent opioid analgesic efficacy in reducing spontaneous neuropathic pain that was statistically significant when the results were pooled. These larger trials are more clinically relevant than the shorter ones because they assess the benefits and risks associated with opioid treatments for weeks to months. Were we to exclude the short-term trials, therefore, the heterogeneity of results would diminish. However, it is important to present these trials. A clinician who looks to individual trials for guidance may be unaware that their duration has a bearing on outcome.

This study included trials that assessed outcomes using diverse scales and often presented them in ways that made accurate extraction of raw data impossible. Because of this, many results, in particular of the short-term studies, could not be included in our quantitative analyses. The problem of heterogeneity of outcomes in the published literature on pain (Carr 2004), including neuropathic pain (Stanton-Hicks 2002), has been described and has compelled authors of systematic reviews of analgesic interventions to adopt a ‘best available evidence’ approach (Mailis 2005; McNicol 2004). Any conclusions from our meta-analyses of short-term trials should be interpreted with caution because they are based on only four of 14 studies (and only 90 of 267 participants), all of which showed positive results.

In contrast with the short-term trials, the meta-analysis of the intermediate-term studies was based on most of the available trials and included the majority of those treated. Furthermore, the two studies not included in the meta-analysis because of non-comparable data also found benefit from opioids over placebo. Hence, we conclude that intermediate-term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain for up to eight weeks of treatment and that the magnitude of this opioid effect is a 13-point difference in pain intensity at study end compared with placebo. A 13-point difference out of 100 points can be compared with that achieved by other commonly used treatments for neuropathic pain. For example, the equivalent pain intensity at study end with gabapentin treatment would be 12 points lower than placebo (39 versus 51) in people with painful diabetic neuropathy (Backonja 1998). To achieve this effect, 67% of the participants in the gabapentin study 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. The dose-dependent analgesic effect shown in two of the opioid studies (Morley 2003; Rowbotham 2003) suggests that higher doses of opioids may have the potential to produce a greater magnitude of pain reduction in people with neuropathic pain. Yet, for the most part, the trials participants received opioids within a relatively narrow range of fixed doses. It is possible, therefore, that, were opioids to be administered in a manner that more closely reflected clinical practice, they may be shown to be more effective than other treatments. Our meta-analysis suggests that a goal of future studies in this area should be to evaluate the true efficacy of opioids for neuropathic pain by means of trials using wider dose ranges rather than fixed-dose studies.

A challenging question is whether an average decline of 13 points on a scale of zero to 100 is meaningful for people suffering pain. The mean initial pain intensity was recorded for the participants in five of the intermediate-term trials and ranged from 46 to 69. The 13-point difference therefore corresponds to a 20% to 30% greater reduction of neuropathic pain with opioids than with placebo. Analysis of data from large randomized clinical trials has shown that a 30% reduction in pain intensity may be the threshold for people to describe a reduction in chronic pain as meaningful (Cepeda 2003; Farrar 2000; Farrar 2001). Therefore, for people presenting with severe initial pain, a reduction in pain intensity of 13 points would not be considered clinically significant. However, in the context of a meta-analysis, reduction in pain intensity may follow a bimodal distribution, i.e. many participants will have a greater than 13-point difference (conversely, many will have less). Because of a lack of reported data we were unable to quantify absolute numbers of participants reporting a clinically significant reduction in pain, or to identify which subset received most benefit within a single trial.

Correlations between the response to a brief exposure to local anesthetics and N-methyl-D-aspartate receptor antagonists and long-term response to their oral analogues have been reported (Attal 2004; Cohen 2004; Galer 1996). The difference in outcomes between short-term and intermediate-term opioid studies does not support a similar use of short-term opioid administration as a predictive tool to decide whether to initiate intermediate-term opioid therapy.

The debate regarding the differential efficacy of opioids for central versus peripheral 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.

This review also included a quantitative analysis of common opioid-related adverse effects (McNicol 2003). Although the analysis is based on a relatively large number of people 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. Only four papers reported treatment emergent participants withdrawals. We do not have data on dropout rates for other active treatments for...
neuropathic pain in similar participants for comparison. Therefore, the clinical significance of an 11% withdrawal rate can only be estimated.

Two other limitations of this systematic review result from the design of the included studies. First, study duration was at most ten weeks. Therefore, we do not have data on the efficacy or adverse event rate of opioids in the treatment of neuropathic pain over months to years. Second, the available 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, it is reasonably likely that the recruitment of people with apparent abuse or addiction potential (Danbar 1996) into such studies would often be avoided. The need to further assess the risk of abuse and addiction continues to be important.

Finally, the management of any form of chronic pain requires not only a reduction in pain intensity but also an improved quality of life in dimensions such as sleep, mood, work, social, and recreational capacities (Wittink 2005). Unfortunately, because of the use of a large number of measurement tools in the included trials, these results could not be quantitatively combined and no consistent improvement in quality of life could be demonstrated.

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 for neuropathic pain, which is likely to be clinically important. 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 intermediate-term opioid therapy. Although our review demonstrated clinically significant efficacy of opioids 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 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 meta-analysis takes an initial and necessary first step of showing efficacy for spontaneous pain during opioid treatment for up to two 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.

ACKNOWLEDGEMENTS

None known

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Kupers 1991b [published data only]


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Eisenberg 2005

*Indicates the major publication for the study
## Characteristics of included studies  [ordered by study ID]  

### Aner 1988

| Methods | QS = 3 (R = 1, DB = 2, W = 0)  
Crossover - at least four test infusions with active drug or placebo given |
|---------|--------------------------------------------------------------------------------|
| Participants | Study arms enrolled/completed: 8/8  
Neuropathic pain diagnosis: Mixed deafferentation. |
| Interventions | Morphine: 15 mg IV over 15 min  
Placebo |
| Outcomes | No numerical data available  
One participant described as having ‘partly positive’ response to opioid test;  
all others ‘negative’ |
| Notes | Adverse events: nature - opioid vs control (n/N or continuous data); withdrawals: not reported |

### Risk of bias

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### Attal 2002

| Methods | QS = 4 (R = 1, DB = 2, W = 1)  
Crossover, single doses, separated by at least two weeks |
|---------|--------------------------------------------------------------------------------|
| Participants | Study arms enrolled/completed: 15/15  
Neuropathic pain diagnosis: central: SC (n = 9), post stroke pain (n = 6) |
| Interventions | Morphine IV: 9 to 30 mg (mean 166), previously individually titrated to maximum dose tolerated, over 20 min  
Placebo |
| Outcomes | Initial pain intensity: 62 ± 17 opioid arm vs 69 ± 17 placebo arm  
Final pain intensity: 33 ± 23 opioid arm vs. 52 ± 19 placebo arm |
| Notes | Adverse events: nature - opioid vs control (n/N or continuous data); withdrawals: somnolence, nausea and headache most common in morphine arm. Total - 9/15 vs 6/15; no withdrawals. Mean number of side effects greater in morphine arm (P = 0.005) |
### Dellemijn 1997

**Methods**

\[ QS = 5 \ (R = 2, \ DB = 2, \ W = 1) \]

Crossover, single doses (fentanyl vs saline or fentanyl vs diazepam)

**Participants**

Study arms enrolled/completed: 53/50

Neuropathic pain diagnosis: peripheral (n = 50), central (n = 3)

**Interventions**

- Fentanyl: 5 µg/kg/min for maximum of 5 h
- Diazepam: 0.2 µg/kg/min for maximum of 5 h
- Saline

**Outcomes**

Maximum VAS % pain reduction: 66 (CI 53 to 80) opioid arm vs 23 (CI 12 to 35) diazepam arm; 50 (CI 36 to 63) opioid arm vs 12 (CI 4 to 20) saline arm.

**Notes**

Adverse events: total number of episodes including nausea, vomiting, hiccups, shortness of breath, light-headedness, feeling warm, clouded vision, dry mouth, trembling, strange floating feelings, or itching more frequent in fentanyl group vs diazepam or saline groups (8.50 vs 3.58 and 9.00 vs 2.54 respectively, \( P < 0.0001 \)).

90% of fentanyl infusions vs 46% diazepam infusions vs 8% saline infusions stopped early due to adverse events

No withdrawals due to adverse events

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### Eide 1994

**Methods**

\[ QS = 3 \ (R = 1, \ DB = 1, \ W = 1) \]

Crossover, single doses, separated by one week

**Participants**

Study arms enrolled/completed: 8/8

Neuropathic pain diagnosis: PHN

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**Risk of bias**

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Interventions | Morphine IV: 0.075 mg/kg over 10 min  
Ketamine IV: 0.15 mg/kg over 10 min  
Placebo  

Outcomes | Median global pain relief % VAS reduction: 7 (zero to 60, interquartile range) morphine group vs zero (zero to 38) saline group vs 50 (20 to 88) ketamine group  
Ketamine vs saline, P < 0.03  
All other results NS  

Notes | Adverse events: nature - opioid vs control (n/N or continuous data): fatigue, dizziness, nausea, etc., 6/8 morphine group vs 8/8 ketamine group vs 1/8 saline group  

Risk of bias

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Eide 1995

Methods | QS = 4 (R = 2, DB = 1, W = 1)  
Crossover, single doses, separated by 2 h  

Participants | Study arms enrolled/completed: 9/9  
Neuropathic pain diagnosis: central SC  

Interventions | Alfentanil IV: 7 µg/kg over 5 min + 0.6 µg/kg/min for 17 to 21 min  
Ketamine IV: 60 µg/kg over 5 min + 6 µg/kg/min for 17 to 21 min  
Placebo  

Outcomes | Median % reduction in VAS continuous pain intensity: 20 (four to 50, interquartile range) alfentanil arm vs zero (zero to eight) saline arm vs 38 (26 to 73) ketamine arm  
Both interventions P < 0.05 vs placebo  
Data extracted from figure  

Notes | Adverse events: nature - opioid vs control (n/N or continuous data): nausea, fatigue, dizziness, etc., 6/9 alfentanil arm vs 5/9 ketamine arm vs 0/9 saline arm  
Ketamine produced more severe side effects than alfentanil  

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**Gilron 2005**

**Methods**  
QS = 5 (R = 2, DB = 2, W = 1)  
Crossover, each arm 5 weeks (including titration and washout).

**Participants**  
Study arms enrolled/completed: 57/41 (patients receiving all four treatments)  
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 three weeks, maintained at maximum tolerated dose for one week, then tapered and 3-day washout on fifth week.

**Outcomes**  
Baseline pain intensity: 5.720.23 (mean on a 0-10 scaleSE)  
Pain intensity at maximum tolerated dose: 3.700.34 morphine arm vs. 4.150.33 gabapentin arm vs. 3.060.33 combination arm vs. 4.490.34 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. All other comparisons NS.

**Notes**  
Adverse events; withdrawals: At maximal tolerated dose combination arm higher frequency of constipation than gabapentin arm (p = 0.006) and higher frequency of dry mouth than morphine arm (p = 0.03); morphine arm, n = 5 vs. gabapentin arm, n = 4 vs. combination arm, n = 6 vs. placebo arm, n = 1.

**Risk of bias**

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**Gimbel 2003**

**Methods**  
QS = 5 (R = 2, DB = 2, W = 1)  
Parallel, six weeks

**Participants**  
Study arms enrolled/completed:  
Opioid group: 82/63  
Control group: 77/52  
Neuropathic pain diagnosis: Diabetic neuropathy

**Interventions**  
Oxycodone oral long-acting: ten to 60 mg twice daily (mean: 37 21)  
Placebo
| Outcomes | End point pain intensity: 41 27 oxycodone group vs 53 26 placebo group (P = 0.002)  
Oxycodone superior to placebo in satisfaction with medication, sleep quality & 9/14 Brief Pain Inventory parameters; median time to achieve mild pain: six vs 17 days (P = 0.017); % days with mild pain: 47 39 vs 29 37 (P = 0.007); NS difference in Rand Mental Health Inventory; Sickness Impact Profile; SF-36 |
| Notes | Adverse events: nature - opioid vs placebo (n):  
nausea/ vomiting: 30/17 vs 6/2  
Constipation: 35 vs 11  
Drowsiness/Somnolence: 33 vs one  
Dizziness: 26 vs eight  
Altered cognition: NR  
Withdrawals due to adverse events: seven vs four |
| Risk of bias | Item | Authors’ judgement | Description |
| Allocation concealment? | Yes | A - Adequate |

Harke 2001

| Methods | QS = 2 (R = 1, DB = 1, W = 0)  
Parallel, eight days |
| Participants | Study arms enrolled/completed:  
Morphine group: 21/20  
Placebo group I: 17/15  
Carbamazepine group: 22/19  
Placebo group II: 21/19  
Neuropathic pain diagnosis: Mixed peripheral |
| Interventions | Morphine oral long-acting: 30 mg three times daily  
Placebo  
Carbamazepine: 200 mg three times daily |
| Outcomes | NS differences between morphine & placebo.  
Carbamazepine reduced pain intensity and increased time without spinal cord stimulation vs placebo |
| Notes | Adverse events: nature - opioid vs placebo (n):  
nausea/ vomiting: 7/5 vs 1/1  
Constipation: two vs zero  
Drowsiness/Somnolence: NR  
Dizziness: four vs zero  
Altered cognition: NR |
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### Huse 2001

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<td>Crossover, four weeks</td>
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<th>Participants</th>
<th>Study arms enrolled/completed: 12/12</th>
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<td>Neuropathic pain diagnosis: Phantom limb</td>
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<tr>
<th>Interventions</th>
<th>Morphine oral long-acting: 70 to 300 mg/day</th>
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<td>Placebo</td>
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<tr>
<th>Outcomes</th>
<th>End point pain intensity: 3.3 1.6 vs 4.0 1.2 (zero to ten scale, P = 0.036)</th>
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<tr>
<td></td>
<td>50% reduction in VAS: 42% vs 8% (P &lt; 0.05)</td>
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<td></td>
<td>Electrical pain threshold (mA): 4.0 1.8 vs 4.0 1.5</td>
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<td></td>
<td>No correlation between reduction in VAS and Pain-Related Self-Treatment Scale, Brief Stress Scale or West Haven-Yale Multidimensional Pain Inventory; 'd2-test' (test for attention performance): 101 19 vs 106 18</td>
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<th>Notes</th>
<th>Adverse events: nature - opioid vs control: altered</th>
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<td>Cognition: worsened vs improved (n not reported)</td>
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<td>Withdrawals due to adverse events: NR</td>
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### Jadad 1992

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<td>Crossover, 8 h, separated by 24 h.</td>
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<th>Participants</th>
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<td>Neuropathic pain diagnosis: central (n = 1) peripheral (n = 6)</td>
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### Interventions
Morphine (low vs high dose): PCA up to 30 mg/h for up to 8 h, or up to 90 mg/h for up to 8 h

### Outcomes
% maximal total pain relief: 53.41 high-dose morphine vs 51.32 low-dose

### Notes
Adverse events: all participants experienced at least one adverse effect in at least one session drowsiness and dizziness most common. Total number of adverse effects: 31 high dose vs 36 low dose (NS)

### Risk of bias

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<td>C - Inadequate</td>
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### Jorum 2003

#### Methods
QS = 4 (R = 2, DB = 2, W = 0)
Crossover, single doses, separated by at least 2 h

#### Participants
Study arms enrolled/completed: 12/12
Neuropathic pain diagnosis: PTN (n = 11), PHN (n = 1)

#### Interventions
Alfentanil: 7 µg/kg over 5 min + 0.6 µg/kg/min over 20 min
Ketamine: 60 µg/kg over 5 min + 6 µg/kg/min over 20 min
Placebo

#### Outcomes
Median initial ongoing pain intensity: 3.8 (2.3 to 5.5, interquartile range) alfentanil arm vs 4.4 (three to 6.3) placebo arm vs 4.3 (2.4 to 6.8) ketamine arm
Median final ongoing pain intensity: 2.2 (0.3 to 3.6) alfentanil arm vs 4.3 (2.1 to 5.8) placebo arm vs 3.2 (0.2 to 4.3) ketamine arm.
Reduction in alfentanil and ketamine arms, baseline vs infusion end, P < 0.05. Data extracted from figure

#### Notes
Adverse events: mostly mild; disturbing side effects - alfentanil arm 5/12, ketamine arm 4/12

### Risk of bias

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</table>
Kupers 1991a

| Methods | QS = 3 (R = 1, DB = 2, W = 0)  
Crossover, 50 min, separated by at least 24 h |
|---------|--------------------------------------------------------------------------------|
| Participants | Study arms enrolled/completed: 6/6  
Neuropathic pain diagnosis: central |
| Interventions | Morphine: 0.3 mg/kg in five divided bolus doses every 10 min  
Placebo |
| Outcomes | Initial pain intensity: 62 13 morphine arm vs 58 26 placebo arm  
Final pain intensity: 43 13 vs 58 26  
Morphine reduced pain vs placebo (P < 0.001). Data extracted in part from figure Results refer to the “affective” component of pain |
| Notes | Adverse events: not reported |

**Risk of bias**

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Kupers 1991b

| Methods | QS = 3 (R = 1, DB = 2, W = 0)  
Crossover, 50 min, separated by at least 24 h |
|---------|--------------------------------------------------------------------------------|
| Participants | Study arms enrolled/completed: 8/8  
Neuropathic pain diagnosis: peripheral |
| Interventions | Morphine: 0.3 mg/kg in five divided bolus doses every 10 min  
Placebo |
| Outcomes | Initial pain intensity: 45 14 morphine arm vs 45 28 placebo arm  
Final pain intensity: 28 14 vs 40 28  
Morphine reduced pain vs placebo (P < 0.001)  
Data extracted in part from figure Results refer to the “affective” component of pain |
| Notes | Adverse events: not reported |

**Risk of bias**

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### Leung 2001

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#### Methods
- QS = 4 (R = 1, DB = 2, W = 1)
- Crossover, single doses, separated by one week

#### Participants
- Study arms enrolled/completed: 12/12
- 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 & 75 ng/ml
- **Ketamine**: 20 min infusion aimed at achieving plasma levels of 50, 100 & 150 ng/ml
- Placebo (diphenhydramine)

#### Outcomes
- % VAS reduction in spontaneous pain: 62 11 alfentanil arm (P < 0.05) vs 36 12 placebo arm (NS) vs 55 12 ketamine arm (NS) (values are maximal reductions)
- Data extracted from figures

#### Notes
- Adverse events: mean VAS (zero to 100, 100 = most severe) for lightheadedness, sedation and dry mouth low in all arms
- Two patients in alfentanil arm developed pruritus VAS > 30

#### Risk of bias

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### Max 1988

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#### Methods
- QS = 4 (R = 1, DB = 2, W = 1)
- Crossover, single doses, separated by at least 48 h

#### Participants
- Study arms enrolled/completed: 46/39
- 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 Mean 6 h summed pain relief (zero to four scale): 2.92 codeine arm vs 2.21 placebo arm vs 4.31 clonidine arm vs 1.79 ibuprofen arm
Only clonidine arm P < 0.05 vs placebo
No SD supplied

Notes Adverse events: sedation, dizziness, and other side effects more frequent after clonidine (74%) or codeine (69%) vs placebo (36%) or ibuprofen (28%) (significance not stated)

Risk of bias

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Max 1995

Methods QS = 4 (R = 1, DB = 2, W = 1)
Crossover, single infusions, separated by one day

Participants Study arms enrolled/completed: 8/8
Neuropathic pain diagnosis: PTN

Interventions Alfentanil: 1.5 µg/kg/min for 60 min; rate doubled as required at 60 and 90 min for a total of 2 h
Ketamine: 0.75 mg/kg/hr for 20 min; rate doubled as required at 60 and 90 min for a total of 2 h
Placebo

Outcomes % pain relief: 45 35 alfentanil arm vs 22 27 placebo arm vs 65 38 ketamine arm
SD calculated from data

Notes Dose limiting side effects: alfentanil: sedation (n = 7), nausea (n = 4), cyanosis (n = 2), visual hallucination (n = 1); ketamine: sedation (n = 3), dissociative reaction (n = 2), muteness (n = 2), nausea (n = 2), dizziness (n = 2)

Risk of bias

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</table>
### Morley 2003

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<th>Methods</th>
<th>QS = 5 (R = 2, DB = 2, W = 1) Crossover, 20 days</th>
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</table>
| Participants | Study arms enrolled/completed:  
Low dose arm: 19/18  
High dose arm: 17/11  
Neuropathic pain diagnosis: Mixed |
| Interventions | Methadone oral: 5 mg twice daily alternating with placebo on odd days & rest on even days  
Methadone oral: 10 mg twice daily alternating with placebo on odd days & rest on even days |
| Outcomes | Low dose methadone arm vs placebo:  
Pain intensity: maximal: 69 vs 74 13 NS; average: 60 20 vs 64 19 NS  
Pain relief: 23 vs 19 15 16 NS  
High dose methadone arm vs placebo:  
pain intensity: maximal: 64 vs 74 16; average: 57 26 vs 64 22  
Pain relief: 32 vs 23 21 |
| Notes | Adverse events: nature - low dose vs placebo (n); high dose vs placebo (n):  
Nausea/ vomiting: 7/4 vs 4/1; 8/1 vs 4/1  
Constipation: two vs one; three vs one  
Drowsiness/Somnia: two vs two; three vs two  
Dizziness: six vs zero; three vs one  
Altered cognition: one vs zero; zero vs one  
Withdrawals due to adverse events: one vs zero; three vs three |

### Risk of bias

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### Rabben 1999

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<tr>
<th>Methods</th>
<th>QS = 4 (R = 2, DB = 1, W = 1) Crossover, single doses, separated by one week</th>
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</table>
| Participants | Study arms enrolled/completed: 30/26  
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 |
### Rabben 1999 (Continued)

| Outcomes | Pain intensity post intervention: “Non responder” subgroup: 84% 23 vs 99 2  
| “Long-term” effect subgroup: 48% 34 vs 9 7  
| “Short-term” effect subgroup: 77% 22 vs 37 34  
| Values are percentage of initial pain at best time point ( = maximal response), meperidine vs ketamine  
| Three different subgroups of response were defined |

| Notes | Adverse events: nature - opioid vs control; withdrawals: sensory disturbances and general feeling of inso-briety more common in ketamine arm; n = 3 withdrew from trial due to nausea after meperidine injection |

### Risk of bias

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</table>

### Raja 2002

| Methods | QS = 5 (R = 2, DB = 2, W = 1)  
| Crossover, eight weeks each arm |

| Participants | Study arms enrolled/completed:  
| Opioid arm: 76/56  
| Control arm: 76/70  
| Placebo arm: 76/75  
| Neuropathic pain diagnosis: PHN |

| Interventions | Morphine oral: 15 to 240 mg/day or methadone oral five to 80 mg/day (means 91.49.3 & 15.2.0)  
| Nortriptyline or desipramine: ten to 160 mg/day (means 89 27.1 & 63 3.6 )  
| Placebo |

| Outcomes | Pain intensity: 4.4 2.4 opioid arm vs 5.1 2.3 antidepressant arm vs 6.0 2.0 placebo arm (zero to ten scale)  
| % pain reduction: 38.2 32.2 opioid arm vs 31.9 30.4 antidepressant arm vs 11.2 19.8 placebo arm  
| Cognitive function slightly worsened with antidepressants; sleep improved from baseline with opioids and antidepressants; all other multidimensional pain inventories unchanged |

| Notes | Adverse events: nature - opioid vs. control (n):  
| Nausea: 30 vs five  
| Constipation: 23 vs eight  
| Drowsiness/Somnolence: 23 vs 11  
| Dizziness: 14 vs five  
| Altered cognition: normal in both groups  
| Withdrawals due to adverse events: seven vs NR |
### Risk of bias

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#### Rowbotham 1991

**Methods**

QS = 4 (R = 1, DB = 2, W = 1)  
Crossover, single infusions, separated by at least 48 h

**Participants**

Study arms enrolled/completed: 19/19  
Neuropathic pain diagnosis: PHN

**Interventions**

Morphine: 0.3 mg/kg (max 25 mg) over 1 h  
Lidocaine: 5 mg/kg (max 450 mg) over 1 h  
Placebo

**Outcomes**

Initial pain intensity: 47 29 morphine arm vs. 52 31 placebo arm (lidocaine arm not listed, but difference between all groups NS, P > 0.3).  
Final pain intensity: 33 33 morphine arm vs. 44 29 placebo arm vs 30 24 lidocaine arm (both drugs p < 0.05 vs placebo, NS differences between active drug arm)  
Pain relief: 45 36 morphine arm vs 22 33 placebo arm vs 38 41 lidocaine arm (morphine vs placebo, P < 0.01; morphine vs lidocaine NS)

**Notes**

Adverse events: Morphine arm: emesis 7/19, no patient became excessively sedated or experienced respiratory compromise; Lidocaine arm: one session terminated due to nausea and lightheadedness

#### Risk of bias

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</table>

#### Rowbotham 2003

**Methods**

QS = 5 (R = 2, DB = 2, W = 1)  
Parallel, eight weeks

**Participants**

Study arms enrolled/completed:  
Levorphanol high-dose group: 43/29  
Levorphanol low-dose group: 38/30  
Neuropathic pain diagnosis: Mixed
### Rowbotham 2003 (Continued)

| Interventions | Levorphanol: 0.75 mg (one to seven capsules) three times daily (mean 8.9 mg/day)  
Levorphanol: 0.15 mg (one to seven capsules) three times daily (mean 2.7 mg/day) |
|---------------|------------------------------------------------------------------|
| Outcomes      | End point pain intensity: 42 26 (36% reduction from baseline) high-dose group vs. 53 25 (-21%) low dose group \(P = 0.02\) high vs low dose \(P = 0.02\)  
Categorical Pain Relief Scale: NS differences between groups \(P = 0.02\) high vs low dose \(P = 0.02\)  
Profile of Mood States Questionnaire unchanged; Symbol-Digit Modalities Test & Multidimensional Pain Inventory improved in both groups |
| Notes         | Adverse events: nature opioid vs control (n): \(Dizziness: two vs zero\) \(Dizziness: two vs zero\)  
Withdrawals due to adverse events: 12 vs three \(Withdrawals due to adverse events: 12 vs three\) |

### Risk of bias

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### Watson 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>QS = 5 (R = 2, DB = 2, W = 1) (Crossover, four weeks)</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Study arms enrolled/completed: 50/38 (Neuropathic pain diagnosis: PHN)</td>
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<tr>
<td>Interventions</td>
<td>Oxycodone oral long-acting: ten to 30 mg twice daily (mean: 45 17) (Placebo)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Daily pain intensity: 35 25 oxycodone arm vs 54 25 placebo arm (Daily categorical pain scale: 1.7 0.7 oxycodone arm vs 2.3 0.7 placebo arm (zero to four scale)) (Daily categorical pain relief scale: 2.9 1.1 vs 1.9 1.0 (zero to five scale)) (Allodynia weekly intensity: 32 27 oxycodone arm vs 50 30 placebo arm) (Allodynia weekly categorical pain scale: 1.6 1.0 oxycodone arm vs 2.0 1.1 placebo arm (zero to four scale)) (Categorical disability scale: 0.3 0.8 vs 0.7 1.0 (zero to three scale)) (Effectiveness rating: 1.8 1.1 vs 0.7 1.0 (zero to three scale)) (Profile of Mood States Questionnaire &amp; Beck Depression Inventory: NS difference - not specified whether between or within groups)</td>
</tr>
<tr>
<td>Notes</td>
<td>Adverse events oxycodone group: nausea (n = 4), constipation (n = 5), drowsiness/somnolence (n =3). (Adverse events in placebo group not listed) (Withdrawals due to adverse events: n = 5 oxycodone arm vs n = 3 placebo arm)</td>
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Watson 1998  (Continued)

### Risk of bias

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<td>Participants: Study arms enrolled/completed: Opioid arm: 45/35</td>
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<td>Active placebo arm: 45/36 Neuropathic pain diagnosis: Diabetic neuropathy</td>
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<td>Interventions: Oxycodone oral long-acting: ten to 40 mg twice daily (mean: 40.0 18.5)</td>
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<td>Benztpine: 0.25 to 1.0 mg twice daily (mean: 1.2 0.6)</td>
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<td>Outcomes: Daily pain intensity: 26.3 24.7 oxycodone group vs 46.7 26.9 placebo group.</td>
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<td>Daily categorical pain scale: 1.3 0.9 vs 1.9 0.9</td>
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<td>Categorical pain relief scale: 1.8 1.4 vs 2.7 1.2 (relief measured on a zero to five scale; lower score = more relief)</td>
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<td>“Skin pain”: 14.3 20.4 vs 43.2 31.3</td>
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<td>Oxycodone superior to placebo for overall Pain and Sleep. Questionnaire, Pain Disability Index, SF-36; NNT for moderate pain relief = 2.6</td>
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<td>Notes: Adverse events: nature - opioid vs placebo (n): Nausea/ vomiting: 16/5 vs 8/2</td>
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<td>Constipation: 13 vs four Drowsiness/Somnolence: nine vs 11</td>
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<td>Dizziness: seven vs three Altered cognition: NR Withdrawals due to adverse events: seven vs one</td>
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Watson 2003

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<td>Participants: Study arms enrolled/completed: Opioid arm: 45/35</td>
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<td>Active placebo arm: 45/36 Neuropathic pain diagnosis: Diabetic neuropathy</td>
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<td>Dizziness: seven vs three Altered cognition: NR Withdrawals due to adverse events: seven vs one</td>
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## Wu 2002a

### Methods
QS = 5 (R = 2, DB = 2, W = 1)  
Crossover, single infusions, separated by 24 h

### Participants
Study arms enrolled/completed: 20/20  
Neuropathic pain diagnosis: Phantom limb pain

### Interventions
- **Morphine:** 0.05 mg/kg bolus + 0.2 mg/kg over 40 min  
- **Lidocaine:** 1.0 mg/kg bolus + 4.0 mg/kg over 40 min  
- **Active placebo (diphenhydramine):** 10 mg bolus + 40 mg over 40 min

### Outcomes
- **Initial pain intensity:** 46 ± 18 morphine arm vs 44 ± 18 placebo arm (lidocaine data not available, but NS differences between all arms)  
  Final pain intensity: 30 ± 22 morphine arm vs 46 ± 22 placebo arm (lidocaine data not available, but morphine P < 0.001 vs placebo, lidocaine P > 0.05 vs placebo)  
- **% pain reduction:** 48 ± 38 morphine arm vs 3 ± 10 placebo arm vs 26 ± 31 lidocaine group (P < 0.01 morphine vs. placebo, NS difference morphine vs. lidocaine)  
  Data on initial and end VAS extracted from figures. SD data received from direct communication with one of the authors

### Notes
- **Adverse events:** nature - opioid vs control (n/N or continuous data); withdrawals: No adverse events reported. Mean sedation scores not different between placebo, morphine, and lidocaine; n = 1 withdrawn because of no pain before treatment

### Risk of bias

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## Wu 2002b

### Methods
QS = 5 (R = 2, DB = 2, W = 1)  
Crossover, single infusions, separated by 24 h

### Participants
Study arms enrolled/completed: 22/22  
Neuropathic pain diagnosis: Stump pain

### Interventions
- **Morphine:** 0.05 mg/kg bolus + 0.2 mg/kg over 40 min  
- **Lidocaine:** 1.0 mg/kg bolus + 4.0 mg/kg over 40 min  
- **Active placebo (diphenhydramine):** 10 mg bolus + 40 mg over 40 min

### Outcomes
- **Initial pain intensity:** 52 ± 19 morphine arm vs 53 ± 22 placebo arm (lidocaine data not available, but NS differences between all arms)  
  Final pain intensity: 33 ± 18 morphine arm vs 50 ± 25 placebo arm vs 36.5 ± 23.5 lidocaine arm (morphine and lidocaine P < 0.01 vs placebo)
% pain reduction: 45 vs 35 morphine arm vs 8 vs 16 placebo arm vs 33 vs 34 lidocaine group (P < 0.01 morphine vs placebo, P < 0.02 lidocaine vs placebo, NS difference morphine vs lidocaine)
Data on initial and end VAS extracted from figures
SD data received from direct communication with one of the authors

| Notes | Adverse events: nature - opioid vs control (n/N or continuous data); withdrawals: No adverse events reported
Mean sedation scores not different between placebo, morphine, and lidocaine; n = 1 withdrawn because of no pain before treatment |

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CI = 95% confidence interval; IV = intravenous; NNT = number needed to treat; NNH = number need to harm; NR = not reported; NS = non significant (P > 0.05); PCA = patient controlled analgesia; PHN = post-herpetic neuralgia; PTN = post-traumatic neuralgia; QS = Oxford quality score; RSD = reflex sympathetic dystrophy; SC = spinal cord; SD = standard deviation; SE = standard error; VAS = visual analog scale; n/N = number of events/total participants
Outcomes presented as zero to 100 visual analog scale, mean +/- SD unless specified

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Arkinstall 1995</td>
<td>Non-neuropathic pain</td>
</tr>
<tr>
<td>Benedetti 1998</td>
<td>Opioid studied - buprenorphine - is not a full mu receptor agonist</td>
</tr>
<tr>
<td>Bohme 2002</td>
<td>Opioid studied - buprenorphine - is not a full mu receptor agonist</td>
</tr>
<tr>
<td>Cathelin 1980a</td>
<td>Opioid studied - buprenorphine - is not a full mu receptor agonist</td>
</tr>
<tr>
<td>Cathelin 1980b</td>
<td>Presented in abstract form only</td>
</tr>
<tr>
<td>Gustorff 2005</td>
<td>Only five participants had neuropathic pain (information provided by contacting author); data not presented separately</td>
</tr>
<tr>
<td>Heiskanen 2002</td>
<td>Morphine plus placebo versus morphine plus dextromethorphan</td>
</tr>
</tbody>
</table>
Kalman 2002  | Non-randomized and single-blinded study
Katz 2000   | Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
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
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
Price 1982 | Study group had mixed pain syndromes - both neuropathic and nociceptive; results not presented independently
Sheather 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
Worz 2003 | Opioid studied - buprenorphine - is not a full mu receptor agonist
## Data and Analyses

### Comparison 1. Short-term Efficacy Studies: Opioid vs. Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain intensity post opioid/placebo</td>
<td>6</td>
<td>180</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-15.96 [-22.70, -9.21]</td>
</tr>
<tr>
<td>1.1 Peripheral Pain</td>
<td>4</td>
<td>138</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-15.22 [-23.19, -7.24]</td>
</tr>
<tr>
<td>1.2 Central Pain</td>
<td>2</td>
<td>42</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-17.81 [-30.48, -5.15]</td>
</tr>
<tr>
<td>2 % pain reduction post opioid/placebo</td>
<td>2</td>
<td>38</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>25.78 [16.91, 34.65]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain intensity post opioid/placebo</td>
<td>7</td>
<td>608</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-12.77 [-16.41, -9.13]</td>
</tr>
<tr>
<td>2 Evoked pain intensity post opioid/placebo</td>
<td>2</td>
<td>148</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-23.85 [-32.63, -15.06]</td>
</tr>
</tbody>
</table>

### Comparison 3. Intermediate-term Efficacy Studies: Opioid vs. Active Control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain intensity post opioid/active control</td>
<td>2</td>
<td>240</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-6.02 [-11.84, -0.19]</td>
</tr>
</tbody>
</table>
Comparison 4. Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Patients reporting nausea</td>
<td>6</td>
<td>546</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.24 [0.18, 0.31]</td>
</tr>
<tr>
<td>2 Patients reporting constipation</td>
<td>6</td>
<td>546</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.24 [0.17, 0.30]</td>
</tr>
<tr>
<td>3 Patients reporting vomiting</td>
<td>5</td>
<td>395</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.12 [0.07, 0.18]</td>
</tr>
<tr>
<td>4 Patients reporting drowsiness/somnolence</td>
<td>5</td>
<td>508</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.16 [0.10, 0.23]</td>
</tr>
<tr>
<td>5 Patients reporting dizziness</td>
<td>6</td>
<td>546</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.14 [0.09, 0.20]</td>
</tr>
<tr>
<td>6 Patients withdrawing</td>
<td>4</td>
<td>414</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.06 [0.01, 0.11]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid N</th>
<th>Mean(SD)</th>
<th>Placebo N</th>
<th>Mean(SD)</th>
<th>Mean Difference (M-H, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Mean Difference (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Peripheral Pain</td>
<td>8</td>
<td>28 (14)</td>
<td>8</td>
<td>40 (28)</td>
<td>9.7 %</td>
<td>9.7 %</td>
<td>-12.00 [ -33.69, 9.69 ]</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>32.6 (33.2)</td>
<td>19</td>
<td>43.6 (29.3)</td>
<td>11.5 %</td>
<td>11.5 %</td>
<td>-11.00 [ -30.91, 8.91 ]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>30 (22.4)</td>
<td>20</td>
<td>46 (22.4)</td>
<td>23.6 %</td>
<td>23.6 %</td>
<td>-16.00 [ -29.88, -2.12 ]</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>32.6 (18)</td>
<td>22</td>
<td>50.1 (25.5)</td>
<td>26.8 %</td>
<td>26.8 %</td>
<td>-17.50 [ -30.54, -4.46 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td>71.6 %</td>
<td>71.6 %</td>
<td>-15.22 [ -23.19, -7.24 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.39, df = 3 (P = 0.94); I² =0.0%
Test for overall effect: Z = 3.74 (P = 0.00018)

2 Central Pain

|                   | 15       | 33 (23)  | 15       | 52 (19)  | 20.0 %                             | 20.0 % | -19.00 [ -34.10, -3.90 ]           |
|                   | 6        | 43 (13)  | 6        | 58 (26)  | 8.4 %                               | 8.4 %  | -15.00 [ -38.26, 8.26 ]            |

Subtotal (95% CI) | 21       |          |           |          | 28.4 %                             | 28.4 % | -17.81 [ -30.48, -5.15 ]           |

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%
Test for overall effect: Z = 2.76 (P = 0.0058)

Total (95% CI) 90 100.0 % -15.96 [ -22.70, -9.21 ]

Heterogeneity: Chi² = 0.58, df = 5 (P = 0.99); I² =0.0%
Test for overall effect: Z = 4.63 (P < 0.00001)
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² =0.0%

Opioids for neuropathic pain (Review)

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### Review: Opioids for neuropathic pain

**Comparison:** Short-term Efficacy Studies: Opioid vs. Placebo

**Outcome:** Pain intensity post opioid/placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Peripheral Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kupers 1991b</td>
<td>8</td>
<td>28 (14)</td>
<td>8</td>
<td>40 (28)</td>
<td>9.7 %</td>
</tr>
<tr>
<td>Rowbotham 1991</td>
<td>19</td>
<td>32.6 (33.2)</td>
<td>19</td>
<td>43.6 (29.3)</td>
<td>11.5 %</td>
</tr>
<tr>
<td>Wu 2002a</td>
<td>20</td>
<td>30 (22.4)</td>
<td>20</td>
<td>46 (22.4)</td>
<td>23.6 %</td>
</tr>
<tr>
<td>Wu 2002b</td>
<td>22</td>
<td>32.6 (18)</td>
<td>22</td>
<td>50.1 (25.5)</td>
<td>26.8 %</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>69</td>
<td>69</td>
<td>71.6 %</td>
<td>-15.22 [ -23.19, -7.24 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 0.39, df = 3 ($P = 0.94$); I$^2$ = 0.0%

Test for overall effect: Z = 3.74 ($P = 0.00018$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Central Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attal 2002</td>
<td>15</td>
<td>33 (23)</td>
<td>15</td>
<td>52 (19)</td>
<td>20.0 %</td>
</tr>
<tr>
<td>Kupers 1991a</td>
<td>6</td>
<td>43 (13)</td>
<td>6</td>
<td>58 (26)</td>
<td>8.4 %</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>21</td>
<td>21</td>
<td>28.4 %</td>
<td>-17.81 [ -30.48, -5.15 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 0.08, df = 1 ($P = 0.78$); I$^2$ = 0.0%

Test for overall effect: Z = 2.76 ($P = 0.0058$)
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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung 2001</td>
<td>12</td>
<td>36 (12)</td>
<td>92.7 %</td>
<td>26.00</td>
<td>[ 16.79, 35.21 ]</td>
</tr>
<tr>
<td>Max 1995</td>
<td>7</td>
<td>22 (27)</td>
<td>7.3 %</td>
<td>7.30</td>
<td>[ -9.75, 55.75 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>19</td>
<td>19</td>
<td>100.0 %</td>
<td>25.78</td>
<td>[ 16.91, 34.65 ]</td>
</tr>
</tbody>
</table>

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

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

---


Review: Opioids for neuropathic pain

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

Outcome: 1 Pain intensity post opioid/placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>44</td>
<td>43</td>
<td>14.9 %</td>
<td>14.90</td>
<td>[ -17.33, 1.53 ]</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>82</td>
<td>77</td>
<td>19.5 %</td>
<td>19.50</td>
<td>[ -20.24, -3.76 ]</td>
</tr>
<tr>
<td>Huse 2001</td>
<td>12</td>
<td>12</td>
<td>10.3 %</td>
<td>10.30</td>
<td>[ -18.32, 4.32 ]</td>
</tr>
<tr>
<td>Morley 2003</td>
<td>19</td>
<td>19</td>
<td>8.6 %</td>
<td>8.60</td>
<td>[ -16.40, 8.40 ]</td>
</tr>
<tr>
<td>Raja 2002</td>
<td>76</td>
<td>76</td>
<td>26.9 %</td>
<td>26.90</td>
<td>[ -23.02, -8.98 ]</td>
</tr>
<tr>
<td>Watson 1998</td>
<td>38</td>
<td>38</td>
<td>10.5 %</td>
<td>10.50</td>
<td>[ -30.24, -7.76 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>307</td>
<td>301</td>
<td>100.0 %</td>
<td>12.77</td>
<td>[ -16.41, -9.13 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 7.54, \ df = 6 (P = 0.27); I^2 = 20\%

Test for overall effect: \( Z = 6.88 (P < 0.00001) \)
Analysis 2.2. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 2 Evoked pain intensity post opioid/placebo.

Review: Opioids for neuropathic pain
Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo
Outcome: 2 Evoked pain intensity post opioid/placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Watson 1998</td>
<td>38</td>
<td>32 (27)</td>
<td>38</td>
<td>50 (30)</td>
<td>-18.00 [-30.83, -5.17]</td>
</tr>
<tr>
<td>Watson 2003</td>
<td>36</td>
<td>14 (20)</td>
<td>36</td>
<td>43 (31)</td>
<td>-29.00 [-41.05, -16.95]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>74</td>
<td>74</td>
<td></td>
<td></td>
<td><strong>-23.85 [-32.63, -15.06]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 5.32 (P < 0.00001)


Review: Opioids for neuropathic pain
Comparison: 3 Intermediate-term Efficacy Studies: Opioid vs. Active Control
Outcome: 1 Pain intensity post opioid/active control

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Gilron 2005</td>
<td>44</td>
<td>37 (22.6)</td>
<td>44</td>
<td>41.5 (21.9)</td>
<td>-4.50 [-13.80, 4.80]</td>
</tr>
<tr>
<td>Raja 2002</td>
<td>76</td>
<td>44 (24)</td>
<td>76</td>
<td>51 (23)</td>
<td>60.8% -7.00 [-14.47, 0.47]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>120</td>
<td>120</td>
<td></td>
<td></td>
<td><strong>-6.02 [-11.84, -0.19]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0.0%
Test for overall effect: Z = 2.03 (P = 0.043)
### Analysis 4.1. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome:

- **Patients reporting nausea.**

#### Study or subgroup Opioid Placebo Risk Difference Weight Risk Difference

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H,Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>2/44</td>
<td>0/43</td>
<td>15.9 % 0.05 [-0.03, 0.12 ]</td>
<td></td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>30/82</td>
<td>6/77</td>
<td>29.1 % 0.29 [0.17, 0.41 ]</td>
<td></td>
</tr>
<tr>
<td>Harke 2001</td>
<td>7/21</td>
<td>1/17</td>
<td>6.9 % 0.27 [0.04, 0.51 ]</td>
<td></td>
</tr>
<tr>
<td>Morley 2003</td>
<td>7/19</td>
<td>4/19</td>
<td>7.0 % 0.16 [-0.13, 0.44 ]</td>
<td></td>
</tr>
<tr>
<td>Raja 2002</td>
<td>30/76</td>
<td>5/76</td>
<td>27.9 % 0.33 [0.21, 0.45 ]</td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>16/36</td>
<td>8/36</td>
<td>13.2 % 0.22 [0.01, 0.43 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>278</strong></td>
<td><strong>268</strong></td>
<td><strong>100.0 % 0.24 [0.18, 0.31 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 92 (Opioid), 24 (Placebo)
- Heterogeneity: $\chi^2 = 30.11$, df = 5 ($P = 0.00001$); $I^2 = 83$
- Test for overall effect: $Z = 7.52$ ($P < 0.000001$)

---

**Opioids for neuropathic pain**

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## Analysis 4.2. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome 2 Patients reporting constipation.

**Review:** Opioids for neuropathic pain

**Comparison:** 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

**Outcome:** 2 Patients reporting constipation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Risk Difference M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>17/44</td>
<td>2/43</td>
<td>-15.9 % [0.18, 0.50]</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>35/82</td>
<td>11/77</td>
<td>-29.1 % [0.15, 0.42]</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Harke 2001</td>
<td>2/21</td>
<td>0/17</td>
<td>-6.9 % [-0.06, 0.25]</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Morley 2003</td>
<td>2/19</td>
<td>1/19</td>
<td>7.0 % [-0.12, 0.22]</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Raja 2002</td>
<td>23/76</td>
<td>8/76</td>
<td>-27.9 % [0.07, 0.32]</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>13/36</td>
<td>4/36</td>
<td>13.2 % [0.06, 0.44]</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>278</strong></td>
<td><strong>268</strong></td>
<td>100.0 % [0.17, 0.30]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 92 (Opioid), 26 (Placebo)

Heterogeneity: Chi² = 10.22, df = 5 (P = 0.07); I² = 51%

Test for overall effect: Z = 7.12 (P < 0.00001)
### Analysis 4.3. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome

3 Patients reporting vomiting.

#### Review:
Opioids for neuropathic pain

#### Comparison:
4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

#### Outcome:
3 Patients reporting vomiting

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>0/44</td>
<td>0/44</td>
<td></td>
<td></td>
<td>22.3 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0 [ -0.04, 0.04 ]</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>17/82</td>
<td>2/77</td>
<td></td>
<td></td>
<td>40.3 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18 [ 0.09, 0.28 ]</td>
</tr>
<tr>
<td>Harke 2001</td>
<td>5/21</td>
<td>1/17</td>
<td></td>
<td></td>
<td>9.5 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18 [ -0.03, 0.39 ]</td>
</tr>
<tr>
<td>Morley 2003</td>
<td>4/19</td>
<td>1/19</td>
<td></td>
<td></td>
<td>9.6 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16 [ -0.05, 0.37 ]</td>
</tr>
<tr>
<td>Watson 2003</td>
<td>5/36</td>
<td>2/36</td>
<td></td>
<td></td>
<td>18.3 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08 [ -0.05, 0.22 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>202</strong></td>
<td><strong>193</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.12 [ 0.07, 0.18 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 31 (Opioid), 6 (Placebo)

Heterogeneity: $\chi^2 = 32.04$, df = 4 ($P<0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 4.33$ ($P = 0.000015$)
### Analysis 4.4. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome 4 Patients reporting drowsiness/somnolence.

#### Review: Opioids for neuropathic pain

#### Comparison: 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

#### Outcome: 4 Patients reporting drowsiness/somnolence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>7/44</td>
<td>6/43</td>
<td></td>
<td>17.1 %</td>
<td>0.02 [-0.13, 0.17]</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>33/82</td>
<td>1/77</td>
<td></td>
<td>31.3 %</td>
<td>0.39 [0.28, 0.50]</td>
</tr>
<tr>
<td>Morley 2003</td>
<td>2/19</td>
<td>2/19</td>
<td></td>
<td>7.5 %</td>
<td>0.0 [-0.20, 0.20]</td>
</tr>
<tr>
<td>Raja 2002</td>
<td>23/76</td>
<td>11/76</td>
<td></td>
<td>29.9 %</td>
<td>0.16 [0.03, 0.29]</td>
</tr>
<tr>
<td>Watson 2003</td>
<td>9/36</td>
<td>11/36</td>
<td></td>
<td>14.2 %</td>
<td>-0.06 [-0.26, 0.15]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>257</strong></td>
<td><strong>251</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.16 [0.10, 0.23]</strong></td>
</tr>
</tbody>
</table>

Total events: 74 (Opioid), 31 (Placebo)

Heterogeneity: $\chi^2 = 27.03$, df = 4 ($P = 0.00002$); $I^2 = 85$

Test for overall effect: $Z = 4.86$ ($P < 0.00001$)
### Analysis 4.5. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome

**5 Patients reporting dizziness.**

#### Review: Opioids for neuropathic pain

#### Comparison: 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

#### Outcome: 5 Patients reporting dizziness

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>0/44</td>
<td>0/43</td>
<td>15.9 %</td>
<td>0.07</td>
<td>0.0 [-0.04, 0.04]</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>26/82</td>
<td>8/77</td>
<td>29.1 %</td>
<td>0.21</td>
<td>0.09 [0.09, 0.33]</td>
</tr>
<tr>
<td>Harke 2001</td>
<td>4/21</td>
<td>0/17</td>
<td>6.9 %</td>
<td>0.19</td>
<td>0.01 [0.01, 0.38]</td>
</tr>
<tr>
<td>Morley 2003</td>
<td>6/19</td>
<td>0/19</td>
<td>7.0 %</td>
<td>0.32</td>
<td>0.10 [0.10, 0.53]</td>
</tr>
<tr>
<td>Raja 2002</td>
<td>14/76</td>
<td>5/76</td>
<td>27.9 %</td>
<td>0.12</td>
<td>0.01 [0.01, 0.22]</td>
</tr>
<tr>
<td>Watson 2003</td>
<td>7/36</td>
<td>3/36</td>
<td>13.2 %</td>
<td>0.11</td>
<td>0.05 [0.05, 0.27]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>278</strong></td>
<td><strong>268</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.14</strong></td>
<td><strong>0.09, 0.20</strong></td>
</tr>
</tbody>
</table>

Total events: 57 (Opioid), 16 (Placebo)

Heterogeneity: $\chi^2 = 46.29, df = 5 (P<0.00001); I^2 = 89%$

Test for overall effect: $Z = 5.18 (P < 0.00001)$

---

Opioids for neuropathic pain (Review)

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Analysis 4.6. Comparison 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo, Outcome 6 Patients withdrawing.

Review: Opioids for neuropathic pain

Comparison: 4 Adverse Events from Intermediate-term Studies: Opioid vs. Placebo

Outcome: 6 Patients withdrawing

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid n/N</th>
<th>Placebo n/N</th>
<th>Risk Difference M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Difference M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron 2005</td>
<td>5/49</td>
<td>1/44</td>
<td>22.4 % 0.08 [-0.02, 0.17]</td>
<td>2.37</td>
<td>100.0 % 0.06 [0.01, 0.11]</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>7/82</td>
<td>4/77</td>
<td>38.4 % 0.03 [-0.04, 0.11]</td>
<td>3.89</td>
<td></td>
</tr>
<tr>
<td>Morley 2003</td>
<td>4/36</td>
<td>3/36</td>
<td>17.4 % 0.03 [-0.11, 0.16]</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>7/45</td>
<td>1/45</td>
<td>21.8 % 0.13 [0.02, 0.25]</td>
<td>3.89</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>212</strong></td>
<td><strong>202</strong></td>
<td><strong>100.0 % 0.06 [0.01, 0.11]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 23 (Opioid), 9 (Placebo)
Heterogeneity: Chi² = 2.37, df = 3 (P = 0.50); I² = 0.0%
Test for overall effect: Z = 2.50 (P = 0.012)

APPENDICES

Appendix 1. MEDLINE search strategy

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. alldynia.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 oxydornorphine 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].

WHAT'S NEW

Last assessed as up-to-date: 6 April 2006.

6 November 2008  Amended  Further RevMan 5 changes made.

HISTORY

Review first published: Issue 3, 2006

22 April 2008  Amended  Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Elon Eisenberg: conceived the review and provided clinical perspective. Designed and coordinated review, organized retrieval of papers, screened retrieved papers against inclusion criteria, appraised quality of papers, extracted data from papers, compiled “table of included studies”, wrote the review.

Ewan McNicol: developed search strategy, organized retrieval of papers, screened retrieved papers against inclusion criteria, appraised quality of papers, extracted data from papers, entering data into RevMan, analysed data, compiled “table of included studies” and “table of excluded studies”. Converted and updated manuscript to Cochrane Review.

Daniel Carr: provided a methodological, clinical, policy and consumer perspective. He also provided general and editorial advice on the review and secured funding for the review.

Opioids for neuropathic pain (Review)
DECLARATIONS OF INTEREST

Dr Carr is also with Javelin Pharmaceuticals, Inc., a small specialty pharmaceutical company with no products yet marketed.

SOURCES OF SUPPORT

Internal sources

- Evenor Armington Fund, USA.
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- Rambam Medical Center, Israel.
- Technion-Israel Institute of Technology, Israel.

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