Oxycodone for neuropathic pain and fibromyalgia in adults
(Review)

Gaskell H, Moore RA, Derry S, Stannard C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 6

http://www.thecochranelibrary.com

WILEY
**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>SUMMARY OF FINDINGS FOR THE MAIN COMPARISON</td>
<td>3</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>5</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>6</td>
</tr>
<tr>
<td>METHODS</td>
<td>6</td>
</tr>
<tr>
<td>RESULTS</td>
<td>9</td>
</tr>
<tr>
<td>Figure 1</td>
<td>10</td>
</tr>
<tr>
<td>Figure 2</td>
<td>11</td>
</tr>
<tr>
<td>Figure 3</td>
<td>12</td>
</tr>
<tr>
<td>Figure 4</td>
<td>13</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>14</td>
</tr>
<tr>
<td>AUTHORS’ CONCLUSIONS</td>
<td>15</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>15</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>16</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>20</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>27</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Oxycodone CR versus placebo, Outcome 1 Any adverse event.</td>
<td>27</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 Oxycodone CR versus placebo, Outcome 2 Serious adverse events.</td>
<td>28</td>
</tr>
<tr>
<td>Analysis 1.3. Comparison 1 Oxycodone CR versus placebo, Outcome 3 Adverse event withdrawals.</td>
<td>28</td>
</tr>
<tr>
<td>Analysis 1.4. Comparison 1 Oxycodone CR versus placebo, Outcome 4 Lack of efficacy withdrawals.</td>
<td>29</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>29</td>
</tr>
<tr>
<td>WHAT’S NEW</td>
<td>34</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>34</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>34</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>34</td>
</tr>
<tr>
<td>DIFFERENCES BETWEEN PROTOCOL AND REVIEW</td>
<td>35</td>
</tr>
</tbody>
</table>
Oxycodone for neuropathic pain and fibromyalgia in adults

Helen Gaskell¹, R Andrew Moore², Sheena Derry², Cathy Stannard³

¹Department of Clinical Geratology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, UK. ²Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. ³Pain Clinic, Macmillan Centre, Frenchay Hospital, Bristol, UK

Contact address: Helen Gaskell, Department of Clinical Geratology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headley Way, Oxford, Oxfordshire, OX3 9DU, UK. helen.gaskell@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2014.
Review content assessed as up-to-date: 6 November 2013.


Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background
This review is one of a series on drugs used to treat neuropathic pain and fibromyalgia. These conditions are estimated to affect 3 to 10% of adults, and are difficult to treat. Although they probably have different aetiologies, neuropathic pain and fibromyalgia can respond to the same therapies. There have been substantial changes in the standards of evidence considered necessary for assessment of interventions to treat chronic pain, to provide data that are more robust and clinically relevant. Oxycodone is a strong opioid agonist widely used to manage severe pain; this review assesses evidence for oxycodone using current standards of evidence designed to reduce bias.

Objectives
To assess the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain and fibromyalgia.

Search methods
On 6 November 2013, we searched CENTRAL, MEDLINE and EMBASE databases. We reviewed the bibliographies of all included studies and of reviews, and also searched two clinical trial databases, ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform, to identify additional published or unpublished data.

Selection criteria
We included randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer (although the emphasis of the review was on studies of eight weeks or longer) that used a placebo or active comparator.

Data collection and analysis
Two review authors independently extracted efficacy and adverse event data, examined issues of study quality, and assessed risk of bias. We performed analysis using three tiers of evidence. First tier evidence was derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, eight to 12 weeks duration, parallel design), second tier from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison, and third tier from data involving small numbers of participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both.
Main results

We included three studies with 254 participants; 204 had painful diabetic neuropathy and 50 postherpetic neuralgia. Study size ranged from 45 to 159 participants. Two studies used a cross-over design and one a parallel group design; study duration was four or six weeks. Controlled release oxycodone (oxycodone CR) was used in all three studies, with doses titrated up to a maximum of between 60 and 120 mg daily; mean doses achieved ranged between 37 and 45 mg daily. All studies used a placebo comparator, although in one study, an active placebo (benztropine) was used. All studies had one or more sources of potential major bias.

No study reported the proportion of participants experiencing at least 50% pain relief or who were very much improved, while one reported the proportion with at least 30% pain relief, two reported at least moderate pain relief, and one reported the number of participants who considered treatment to be moderately effective. No study provided first or second tier evidence for an efficacy outcome. Third tier evidence indicated greater pain intensity reduction and better patient satisfaction with oxycodone than with placebo in all three studies, but such evidence was derived mainly from group mean data, with last observation carried forward (LOCF) imputation or completer analysis, in small studies lasting less than eight weeks (very low quality evidence).

Adverse events were more common with oxycodone CR than with placebo. At least one adverse event was experienced by 86% of participants taking oxycodone CR and 63% taking placebo, and the number needed to treat for an additional harmful effect (NNH) was 4.3. The effect of oxycodone on serious adverse events reported was uncertain in comparison with placebo (oxycodone 3.4% versus placebo: 7.0%; RR 0.48 (95% confidence interval (CI) 0.18 to 1.23; very low quality evidence); one death was reported with oxycodone CR, but was not attributed to treatment. Adverse event withdrawals did not differ significantly between groups, occurring in 11% of participants with oxycodone CR and 6.4% with placebo (RR 1.69 (0.83 to 3.43); very low quality evidence). Withdrawals due to lack of efficacy were less frequent with oxycodone CR (1.1%) than placebo (11%), with an NNT to prevent one withdrawal of 10 (RR 0.12 (0.03 to 0.45); very low quality evidence).

We found no relevant studies in chronic neuropathic pain conditions other than painful diabetic neuropathy or postherpetic neuralgia, or in fibromyalgia.

Authors’ conclusions

No convincing, unbiased evidence suggests that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or postherpetic neuralgia. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. Adverse events typical of opioids appear to be common.

Plain Language Summary

Oxycodone for neuropathic pain and fibromyalgia in adults

Neuropathic pain is pain coming from damaged nerves. It differs from pain messages carried along healthy nerves from damaged tissue (as in a fall, a cut, or an arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines such as paracetamol and ibuprofen are not effective in neuropathic pain, while medicines that are sometimes used to treat epilepsy or depression can be very effective in some people with neuropathic pain. Our understanding of fibromyalgia (a condition of persistent, widespread pain and tenderness, sleep problems, and fatigue) is poor, but fibromyalgia can respond to the same medicines as neuropathic pain.

Oxycodone is used to treat acute and some forms of chronic pain, and so might be a useful medicine for neuropathic pain or fibromyalgia.

In 2013 we performed searches to look for clinical trials in which oxycodone was used to treat neuropathic pain or fibromyalgia. We found three studies of modest quality that tested oxycodone against placebo for several weeks. Almost all of the 254 people in the studies had painful limbs because of damaged nerves caused by diabetes.

Oxycodone was not convincingly shown to help relieve the pain (very low quality evidence). Compared with placebo, fewer people stopped taking oxycodone because they felt it was not effective, but more people experienced adverse effects (very low quality evidence).

Oxycodone has not been shown to work as a pain medicine in diabetic neuropathy or postherpetic neuralgia. No studies have examined its use in other types of neuropathic pain, or in fibromyalgia.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**Oxycodone compared with placebo for neuropathic pain**

**Patient or population:** adults with neuropathic pain (two studies in peripheral diabetic neuropathy and one study in postherpetic neuralgia)

**Settings:** community

**Intervention:** oxycodone CR, 37 to 45 mg daily

**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Probable outcome with intervention</th>
<th>Probable outcome with comparator</th>
<th>RR (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 50% reduction in pain or equivalent</td>
<td>No data</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td>Downgraded due to small numbers of events and participants, and bias from imputation or completer analysis</td>
</tr>
<tr>
<td><strong>‘Moderate’ benefit</strong></td>
<td>37/82 (450 in 1000)</td>
<td>20/77 (260 in 1000)</td>
<td>not calculated</td>
<td>159 participants (1 study)</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>At least 30% reduction in pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion below 30/100 mm on VAS</td>
<td>No data</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Global Impression of Change much or very much improved</td>
<td>22/38 (579 in 1000)</td>
<td>7/38 (184 in 1000)</td>
<td>not calculated</td>
<td>38 participants (1 study)</td>
<td>Very low</td>
<td>Downgraded due to small numbers of events and participants, and bias from imputation or completer analysis</td>
</tr>
<tr>
<td>Adverse event withdrawals</td>
<td>19/177</td>
<td>11/172</td>
<td>RR 1.69 (0.83, 3.43)</td>
<td>254 participants (349 treatment phases due to cross-over studies) (3 studies)</td>
<td>Very low</td>
<td>Downgraded due to small numbers of events and participants, and bias from imputation or completer analysis</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Cases in Treatment</td>
<td>Cases in Placebo</td>
<td>RR (95% CI)</td>
<td>Number of participants (Number of treatment phases due to cross-over studies)</td>
<td>GRADE Working Group grades of evidence</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>6/177</td>
<td>12/172</td>
<td>RR 0.48 (0.18, 1.23)</td>
<td>254 participants (349)</td>
<td>Very low quality; Downgraded due to small numbers of events and participants, and bias from imputation or completer analysis</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1/177</td>
<td>0/172</td>
<td></td>
<td>254 participants (349)</td>
<td>Only a single event, and not judged related to study medication</td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio; VAS: visual analogue scale

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.
BACKGROUND

This review is one of a series looking at drugs used to relieve neuropathic pain and fibromyalgia. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Moore 2012b; Appendix 1). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so. Fibromyalgia is a less clearly defined condition both in clinical presentation and understanding of pathophysiology. The condition is characterised by widespread pain and a number of other bodily symptoms. Central sensitisation and other neuroadaptive sequelae are observed in fibromyalgia and drugs used for neuropathic pain are the mainstay of pharmacotherapy for the condition. Because of the limitations in the number of available clinical trials, it is convenient to consider fibromyalgia together with neuropathic pain. We make no presumption to pool data across individual neuropathic pain conditions or fibromyalgia, but will consider each condition separately.

Opioids for neuropathic pain is the subject of a previous Cochrane review (McNicol 2013). The current review is part of a move to evaluate individual opioid drugs in separate reviews according to dose and individual pain conditions.

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is “pain caused by a lesion or disease of the somatosensory system” (Jensen 2011) based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the central nervous system (CNS) (Moissert 2007). Neuropathic pain tends to be chronic and may be present for months or years. It is complex (Apkarian 2011; Tracey 2011), and neuropathic pain features can be found in patients with joint pain (Soni 2013). Fibromyalgia is a widespread pain disorder characterised by a number of other symptoms including poor sleep, fatigue and cognitive impairment. Early diagnostic criteria required demonstration of specified tender points on examination (Wolfe 1990) but current definitions relate to presence of widespread pain and symptom severity (Wolfe 2010). The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Moreover, patients with neuropathic pain and those with fibromyalgia experience similar sensory phenomena (Koroschetz 2011), and peripheral nerve fibre changes seen in neuropathic pain also occur in fibromyalgia (Oaklander 2013; Üçeyler 2013). Many people with these conditions are significantly disabled with moderate or severe pain for many years. In primary care in the United Kingdom (UK), the incidences per 100,000 person-years’ observation have been reported as 28 (95% confidence interval (CI) 27 to 30) for postherpetic neuralgia, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for painful diabetic neuropathy (Hall 2008). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katsusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person-years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007). The prevalence of neuropathic pain was reported as 3.3% in Austria (Gustorff 2008), 6.9% in France (Boulhassira 2008) and as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). The incidence of some forms of neuropathic pain, such as diabetic neuropathy and postherpetic neuralgia, is increasing (Hall 2013). Fibromyalgia is common, especially in women, with an all-age prevalence of 12%, and a female-to-male ratio of 6:1 (McNally 2006). Neuropathic pain and fibromyalgia are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical and/or cognitive interventions. Conventional analgesics are usually not effective. Some patients with neuropathic pain may derive some benefit from topical lidocaine patch or low concentration topical capsicain, although evidence of benefit is uncertain (Derry 2012; Khalilq 2007). High concentration topical capsicain may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is more usually provided by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011a). The proportion of patients who achieve worthwhile pain relief (typically defined as at least 50% pain intensity reduction (Moore 2013b)) is small, typically 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNTs) usually between 4 and 10 (Moore 2013c).

Description of the intervention

Oxycodone is a strong opioid agonist, developed in the early 20th century, and chemically related to codeine (Olkkola 2013). It is considered to be comparable to morphine for efficacy, and similar for adverse events, with the exception of hallucinations, which tend
to occur rarely with oxycodone (Poyhia 1993). Like morphine, it can be administered via a variety of routes including oral or rectal, and intramuscular, intravenous, or subcutaneous injection. Its analgesic potency makes it useful for the management of severe pain, usually acute postoperative, post-traumatic, or cancer pain. In acute postoperative pain, oxycodone 15 mg alone compared with placebo, had an NNT for at least 50% pain relief of 4.6 (2.9 to 11) (Gaskell 2009).

Various strands of evidence, mainly from studies in rodents, indicate that oxycodone may exert its opioid effects through the mu-opioid receptor and the kappa-opioid receptor (Kalso 2007). Oral oxycodone is widely used to treat cancer pain and chronic noncancer pain, and individual titration of doses to effect is indicated, especially in older people, as pharmacokinetics may be age-dependent and highly individual (Olkkola 2009).

Repeated administration of oxycodone can cause dependence and tolerance, and its potential for abuse is well known. Regulation of supply varies between countries, but in many, all oxycodone preparations are controlled substances. There have been indications that oxycodone is abused, and some reformulation to prevent crushing may reduce this (Butler 2013). There are other general concerns about long-term use of opioids, cognitive impairment and immune and endocrine effects (Brennan 2013), as well as mortality (Dhalla 2009).

**How the intervention might work**

Opioids like oxycodone bind to specific opioid receptors in the nervous system and other tissues; there are three principal classes of receptors (mu, kappa, and delta) though others have been suggested, and subtypes of receptors are considered to exist. Binding of opioid agonists like oxycodone to receptors brings about complex cellular changes, outcomes of which include decreased perception of pain, decreased reaction to pain, and increased pain tolerance. Opioids from plant sources have been used for thousands of years to treat pain.

**Why it is important to do this review**

Weak and strong opioids were used frequently for treating neuropathic pain in a UK survey (Hall 2013), and were used by 26% of people with fibromyalgia in a German survey (Häuser 2012). The standards used to assess evidence in chronic pain trials have changed substantially since about 2010, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to using the number of patients who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the reference guide for pain studies (AUREF 2012) and reflect what patients with chronic pain want from treatment (Moore 2013a).

This Cochrane review assessed evidence in ways that make both statistical and clinical sense, using developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed met a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 500 participants in a comparison in which the (NNT) is four or more (Moore 1998)). This approach does set high standards and marks a departure from how reviews have been done previously.

This is particularly important for opioids in chronic noncancer pain. Opioids in clinical trials in noncancer pain are associated with very high withdrawal rates of up to 60% over about 12 weeks (Moore 2010b). Many withdrawals occur within the first few weeks, when patients experience pain relief but cannot tolerate the drug. The common practice of using the last observed results carried forward to the end of the trial many weeks later (last observation carried forward (LOCF)) can therefore produce results based largely on patients no longer in the trial, and who in the real world could not achieve pain relief because they could not take the tablets. The newer standards, outlined in Appendix 1, would not allow this and can produce very different results. For example, oxycodone was judged effective in a large analysis of pooled data from trials in osteoarthritis and chronic low back pain conducted over about 12 weeks; an analysis of the same data using the new patient-centred standards showed oxycodone to be significantly worse than placebo (Lange 2010).

A previous Cochrane review demonstrated the limitations of our knowledge about opioids in neuropathic pain, except in short duration studies of 24 hours or less (McNicol 2013), and a review specific to oxycodone, one of the most widely used opioids, is timely.

**OBJECTIVES**

To assess the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain and fibromyalgia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
We included studies if they were randomised controlled trials (RCTs) with at least 10 participants per treatment arm and reported double-blind assessment of participant outcomes following two weeks of treatment or longer, although the emphasis of the review was on studies of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised studies of experimental pain, case reports and clinical observations.

Types of participants
Studies had to include adult participants aged 18 years and older. Participants could have one or more of a wide range of chronic neuropathic pain conditions including, but not limited to:
- cancer-related neuropathy;
- central neuropathic pain;
- complex regional pain syndrome (CRPS) Type II;
- human immunodeficiency virus (HIV) neuropathy;
- painful diabetic neuropathy;
- phantom limb pain;
- postherpetic neuralgia;
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- trigeminal neuralgia;
and
- CRPS Type I;
- fibromyalgia.

We would have included studies of participants with neuropathic pain associated with more than one condition, with analysis according to the primary condition, but the included studies enrolled participants with only one pain condition.

Types of interventions
Oxycodone at any dose, by any route, administered for the relief of neuropathic pain or fibromyalgia and compared with placebo or any active comparator. Oxycodone in fixed dose combination with naloxone was not considered.

Types of outcome measures
We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain intensity reduction over baseline (moderate), at least 50% pain intensity reduction over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (O’Brien 2010).

We have included a Summary of findings table as set out in the author guide (AUREF 2012). The Summary of findings table (Summary of findings for the main comparison) reports on the outcomes of at least 50% and at least 30% pain intensity reduction, PGIC, adverse event withdrawals, serious adverse events, and death.

Primary outcomes
- Patient-reported pain intensity reduction of 30% or greater.
- Patient-reported pain intensity reduction of 50% or greater.
- Patient-reported global impression of clinical change (PGIC) much or very much improved.
- Patient-reported global impression of clinical change (PGIC) very much improved.

Secondary outcomes
- Any pain-related outcome indicating some improvement.
- Participants experiencing any adverse event.
- Participants experiencing any serious adverse event.
- Specific adverse events, particularly somnolence and dizziness.
- Withdrawals due to adverse events.
- Withdrawals due to lack of efficacy

Search methods for identification of studies

Electronic searches
We searched the following databases.
- Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Issue 7 of 12, 2013.
- MEDLINE 1946 to 6 November 2013 (via Ovid).
- EMBASE 1974 to 6 November 2013 (via Ovid).

See Appendix 2, Appendix 3, and Appendix 4 for the MEDLINE, EMBASE and CENTRAL search strategies. There were no language or date restrictions.

Searching other resources
We searched www.clinicaltrials.gov and apps.who.int/trialsearch/ in November 2013 to identify additional completed or ongoing studies. We reviewed the bibliographies of any randomised trials and review articles identified, and contacted the authors and
known experts in the field, to identify additional published or unpublished data.

**Data collection and analysis**

**Selection of studies**

We determined eligibility by reading the title and abstract of all studies identified by the search. Studies that clearly did not satisfy inclusion criteria were eliminated, and we obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement on inclusion by discussion. We did not anonymise the studies in any way before assessment. We have included a PRISMA study flow diagram (Liberati 2009) to document the screening process, as recommended in Part 2, Section 11.2.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

**Data extraction and management**

Review authors independently extracted data using a standard form and checked for agreement before entry into RevMan 5 (RevMan 2012) or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event).

**Assessment of risk of bias in included studies**

We used the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that, as a minimum, were randomised and double-blind.

Two review authors independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) were excluded.
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). Studies that did not conceal allocation (e.g. open list) were excluded.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved). Studies that were not double-blind were excluded.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (< 10% of participants did not complete the study and/or used ‘baseline observation carried forward’ analysis); unclear risk of bias (used ‘last observation carried forward’ analysis); high risk of bias (used ‘completer’ analysis).
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

**Measures of treatment effect**

We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CIs) using a fixed-effect model unless significant statistical heterogeneity was found (see below). We planned to calculate numbers needed to treat to benefit (NNTs) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT became the number needed to treat to harm (NNH) and was calculated in the same manner. We did not use continuous data in analyses.

**Unit of analysis issues**

The unit of analysis was the individual participant. In the event of a study having more than one active treatment arm, in which data were not combined for analysis, we planned to split the control treatment arm between active treatment arms. For cross-over studies, we planned to use only the first period, if this was available. Where only combined data for both periods were reported, we treated the study as if it was a parallel study, drawing attention to the potential bias that this confers, and interpreting the results accordingly.
**Dealing with missing data**

When possible we used intention-to-treat (ITT) analysis, where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Missing participants were assigned zero improvement, where possible, and information about any imputation method was collected. Where ITT data were not available, we have commented.

**Assessment of heterogeneity**

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L’Abbé 1987) and with the use of the I² statistic.

**Assessment of reporting biases**

The aim of this review was to use dichotomous data of known utility (Moore 2010d). The review did not depend on what authors of the original studies chose to report or not report, although clearly difficulties arose due to studies failing to report any dichotomous results of interest. We extracted continuous data, which probably poorly reflect efficacy and utility, where useful, for illustrative purposes only.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect that would be required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or more in these conditions) (Moore 2008). This was not possible since no pooled analyses were carried out.

**Data synthesis**

We considered individual painful conditions separately because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). We planned to use a fixed-effect model for meta-analysis, but no pooling of data was possible. We have included a Summary of Findings table according to recommendations described in Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

We analysed data for each painful condition in three tiers, according to outcome and freedom from known sources of bias.

- The first tier uses data meeting current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation methods for dropouts, report an ITT analysis, last eight weeks or more, have a parallel group design, and have at least 200 participants (preferably at least 400) in the comparison (Moore 2010a; Moore 2012b). These top-tier results are reported first.
- The second tier uses data from at least 200 participants but where one or more of the above conditions is not met (for example reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
- The third tier of evidence relates to data from fewer than 200 participants, or where there are expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there is major heterogeneity between studies, or where there are shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

**Subgroup analysis and investigation of heterogeneity**

We planned to analyse separately data for different pain conditions and dosing regimens.

**Sensitivity analysis**

No sensitivity analyses were planned.
**Included studies**

We included three studies, with 254 participants (Gimbel 2003; Watson 1998; Watson 2003) using oxycodone in neuropathic pain conditions. Another report (Jensen 2006) described additional results from the study by Gimbel 2003. Participants took oral controlled-release oxycodone (oxycodone CR) for up to four (Watson 1998; Watson 2003) or six (Gimbel 2003) weeks.

We did not identify any studies using oxycodone to treat fibromyalgia.

Studies enrolled adult participants of mean age ranging between 59 and 70 years, with no upper age limits, and there were similar numbers of men and women. All participants had experienced at least moderate pain for three months or more, associated with either postherpetic neuralgia (Watson 1998) or diabetic neuropathy (painful symmetrical distal polyneuropathy) in participants with stable diabetes (Gimbel 2003; Watson 2003). There were no included studies of oxycodone for neuropathic pain of other etiology. Study recruitment was from a chronic pain specialist or through newspaper advertising in one study (Watson 1998), and not reported in the other studies. One study was multi-centred (Gimbel 2003). Chronic pain of other aetiology, a history of substance or alcohol abuse, or both, were exclusion criteria in all studies, but the extent of other exclusion criteria varied between studies. Oxycodone CR was compared with a placebo (Gimbel 2003; Watson 1998) or an “active” placebo (benztropine) (Watson 2003). One study used a parallel group design (Gimbel 2003); the other two were cross-over studies (Watson 1998; Watson 2003), and neither reported data from the first phase separately.

All participants discontinued pre-study opioids with an appropriate washout period before the start of the study, but other stable medication (for example, including pain and antidiabetic medication) was continued unchanged. There was no washout between phases in the two cross-over studies. The dosage of oxycodone CR was progressively increased to a maximum of 60 to 120 mg daily, taken as a divided dose. The mean dosages achieved were similar in the three studies (37 mg to 45 mg daily).

**Excluded studies**

We excluded 14 studies after reading the full reports. Pain was not identified as being specifically, or predominantly, neuropathic in the majority of excluded studies, and oxycodone was combined with other drugs in four studies. Reasons for exclusion of individual studies are in the Characteristics of excluded studies table.

**Risk of bias in included studies**

Figure 2 and Figure 3 illustrate the Risk of bias assessments by category for each included study.
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
Figure 3. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

**Allocation**
All studies were randomised. Random sequence generation and allocation concealment were of low risk in Gimbel 2003 and Watson 2003; in Watson 1998 the details of randomisation and completeness of allocation concealment were unclear.

**Blinding**
All studies were double-blind. Two studies (Gimbel 2003; Watson 1998) adequately described the method used to achieve double-blinding, while the other (Watson 2003) did not. Watson 2003 also carried out a “Test of blinding” by participants and investigators at the end of the study, but details were not reported.

**Incomplete outcome data**
Gimbel 2003 reported that LOCF was used for participants who withdrew from the study, while Watson 1998 and Watson 2003 reported efficacy data only for participants who provided data for both phases of the cross-over (completer analysis).

**Other potential sources of bias**
None of the studies randomised sufficient numbers of participants to minimise the bias associated with small studies. One study (Gimbel 2003) just exceeded our threshold of 50 participants per treatment arm (77 participants) and was judged at unclear risk of bias. Another study (Watson 1998) reached the threshold, but reported on only 38 participants, and the other (Watson 2003) was below that threshold (45 participants); both studies were judged at high risk of bias.

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

**Efficacy**
All included studies reported at least one pain-related outcome indicating some improvement with oxycodone CR compared with placebo, details of data from individual studies are shown in Appendix 5. There was no first or second tier evidence of efficacy.

**Third tier evidence**
Using a responder analysis with participant-reported pain relief and LOCF imputation, Jensen 2006 (Gimbel 2003) reported that 37/82 participants experienced pain intensity reduction of 33% or greater for the item “intense pain” with oxycodone CR and 20/77 with placebo. Gimbel 2003 reported a statistically significant difference in change from baseline in three fields in the Brief Pain Inventory (current pain, pain relief, and sleep) after 42 days of treatment. In the ITT population there was a statistically significant difference in average pain intensity over 28 days of treatment, and also in satisfaction with oxycodone CR compared with placebo over 42 days treatment. Participants taking oxycodone CR
had more days with mild pain than those taking placebo, and also a lower median time to achieve mild pain. Watson 1998 reported efficacy results only for the 38/50 participants who completed both phases of the cross-over study. The authors report that 58% of participants treated with oxycodone CR and 18% treated with placebo experienced at least moderate pain relief. We assume that this outcome is derived from weekly assessments of effectiveness of treatment, including ratings of “moderately effective” and “highly effective”. Group mean data showed a statistically significant improvement in pain relief, steady pain, allodynia and paroxysmal spontaneous pain with oxycodone CR, and global effectiveness and disability were better with oxycodone CR. More participants reported a preference for oxycodone CR than placebo (67% versus 11%, with 22% having no preference). Similar results were reported by Watson 2003, for both the “evaluable population” and the ITT population. Mean pain intensity and pain relief scores were significantly better with oxycodone CR than with placebo. Oxycodone CR was preferred by 88% of participants, considered at least moderately effective by 95% of those who completed the study, and 73% said they were satisfied with the treatment. There were no equivalent data reported for placebo. In Watson 2003, information on the number of participants who experienced at least moderate pain relief (using a non-standard 6-point scale) was not reported, but the authors did report an NNT for this outcome of 2.6. It is not clear whether this was calculated using the “evaluable population” (who completed both phases of the cross-over) or the ITT population, and it is not clear whether any imputation method was used.

Adverse events

Details of adverse events reported in individual studies are provided in Appendix 6. Two of the studies (Watson 1998; Watson 2003) used a cross-over design without reporting adverse events by period. We chose to combine the analyses from cross-over studies, as reported, with those of the single parallel group study (Gimbel 2003).

Participants experiencing any adverse event

All studies contributed data from participants experiencing an adverse event. An active placebo was used in one study (Watson 2003).

- The proportion of participants experiencing any adverse event with oxycodone CR was 86% (153/177, range 76% to 98%).
- The proportion of participants experiencing any adverse event with placebo was 63% (109/172, range 48% to 73%). An active placebo was used in one study (Watson 2003).
- The risk ratio for participants experiencing any adverse event with oxycodone CR compared with placebo was 1.4 (95% CI 1.2 to 1.5); the NNH was 4.3 (3.1 to 7.0) (Figure 4).

![Figure 4. Forest plot of comparison: 1 Oxycodone CR versus placebo, outcome: 1.1 Any adverse event.](image)

To exclude possible adverse events arising from the active placebo used in one study (Watson 2003), we carried out a sensitivity analysis excluding this study; the NNH was not significantly changed (3.4 (2.5 to 5.1)).

Participants experiencing any serious adverse event

Two studies (Gimbel 2003, Watson 2003) reported on participants experiencing a serious adverse event. Although not specifically reported, we have assumed that there were no serious adverse events in the third included study (Watson 1998). None of the serious adverse events were judged to be linked to taking oxycodone CR.

- The proportion of participants experiencing any serious adverse event with oxycodone CR was 3.4% (6/177, range 0% to 6.1%).
- The proportion of participants experiencing any serious adverse event with placebo was 7.0% (12/172, range 0% to 12%).
- The risk ratio for participants experiencing any serious adverse event with oxycodone CR versus placebo was 0.49 (95% CI 0.24 to 0.94) (Figure 4).
adverse event with oxycodone CR compared with placebo was 0.48 (0.18 to 1.2); the NNH was not calculated (Analysis 1.2).

Deaths
One death was reported in a participant taking oxycodone CR (Gimbel 2003), but was not judged to be linked to treatment.

Particular adverse events
Somnolence was reported by 33/82 (40%) (Gimbel 2003) and 9/45 (20%) (Watson 2003) participants taking oxycodone CR, and by 1/77 (1.3%) and 11/45 (24%) participants respectively taking placebo. Sedation was reported by 3/50 (6.0%) of participants taking oxycodone CR (Watson 1998), but there were no corresponding data reported for placebo in this study.

Dizziness was reported by 26/82 (32%) (Gimbel 2003) and 7/45 (16%) (Watson 2003) participants taking oxycodone CR, and by 8/77 (10%) and 3/45 (6.6%) participants respectively taking placebo.

Constipation was reported by 35/82 (43%) (Gimbel 2003) and 13/45 (29%) (Watson 2003) participants taking oxycodone CR, and by 11/77 (14%) and 4/45 (8.9%) participants respectively taking placebo. Constipation was reported by 5/50 (10%) participants taking oxycodone CR (Watson 1998), but there were no corresponding data reported for placebo in this study.

Other adverse events affecting ≥ 8% of participants taking oxycodone CR included nausea, vomiting, and pruritus.

Withdrawals
Details of withdrawals reported in individual studies are in Appendix 6.

Withdrawals due to adverse events
All studies reported withdrawals due to adverse events.

- The proportion of participants who withdrew due to an adverse event with oxycodone CR was 11% (19/177, range 8.5% to 16%).
- The proportion of participants who withdrew due to an adverse event with placebo was 6.4% (11/172, range 5.2% to 11%).
- The risk ratio for withdrawal with oxycodone CR compared with placebo was 1.7 (0.83 to 3.4); the NNH was not calculated (Analysis 1.3).

Withdrawals due to lack of efficacy
All studies contributed data from participants withdrawing due to lack of efficacy.

- The proportion of participants who withdrew due to lack of efficacy with oxycodone CR was 1.1% (2/177, range 0% to 2.2%).
- The proportion of participants who withdrew due to lack of efficacy with placebo was 11% (19/172, range 2.0% to 16%).
- The risk ratio for withdrawal with oxycodone CR compared with placebo was 0.12 (0.03 to 0.45); the NNH was 10 (6.7 to 20) (Analysis 1.4).

Discussion
Summary of main results
The review found three studies testing 254 participants with chronic neuropathic pain in two conditions: painful diabetic neuropathy (painful symmetrical distal polyneuropathy) and postherpetic neuralgia. No first or second tier evidence was available. Third tier evidence indicated some improvement in pain relief with oxycodone CR compared with placebo, but this is derived from group mean data, completer analyses, and LOCF (or unspecified) imputation (Appendix 1) in small, short duration studies, where major bias is possible. Participants taking oxycodone CR experienced more adverse events (but not serious adverse events) than did participants taking placebo. In one study, an active placebo was used to help maintain blinding, which influences interpretation of data on adverse events in this case. See Summary of findings for the main comparison.

There were no relevant studies in chronic neuropathic pain in other conditions, or in fibromyalgia.

Overall completeness and applicability of evidence
Overall completeness and applicability of evidence were poor. Oxycodone CR was tested only in painful diabetic neuropathy and postherpetic neuralgia. The usefulness of the available evidence was limited because reporting quality was poor by current standards. RCTs of up to six weeks duration do not necessarily provide information about longer term use, which is important in treatment of a chronic condition. In particular, concern has been raised about the lack of evidence on potential problems with long-term use of opioids in the treatment of neuropathic pain (such as safety issues, addiction and misuse) (Dworkin 2007; Stannard 2013).

Quality of the evidence
While all the included studies were randomised and double-blind, none provided data that met predefined criteria for first or second
All the studies were small (the largest treatment group consisted of 82 participants) and, in particular, there were very few data from participants with postherpetic neuralgia. The studies were of short duration (maximum treatment period six weeks) and two were of cross-over design without separate reporting of first period data. One study used LOCF imputation for withdrawals, and two reported efficacy only for participants completing both phases of a cross-over.

Potential biases in the review process
The absence of publication bias (unpublished trials showing no benefit of oxycodone over placebo) can never be proved. We carried out a broad search of studies and feel it is unlikely that significant amounts of relevant data remain unknown to us.

The degree of exaggeration of treatment effects in cross-over trials compared to parallel group designs, as has been seen in some circumstances (Khan 1996), is unclear but is unlikely to be a source of major bias (Elbourne 2002). The two cross-over studies reported efficacy results only for those who completed both treatment periods, which is likely to overestimate efficacy.

Agreements and disagreements with other studies or reviews
The results of this review are in broad agreement with the relevant sections of European and United Kingdom guidelines on the use of oxycodone in the management of neuropathic pain (Attal 2010, NICE 2013). In a wider review on the use of opioids for neuropathic pain, McNicol 2013 identified the same three studies of oxycodone, but carried out no separate analyses for individual opioids. Other analyses of oxycodone in chronic pain have failed to find any beneficial effect except where LOCF imputation is used and where adverse event withdrawals are high (Lange 2010). A randomised trial that added low dose (10 mg/day) oxycodone to pregabalin did not report enhanced analgesic efficacy (Zin 2010). Evidence that uses current best standards relevant to clinical effectiveness does not suggest a benefit of opioids over placebo for the treatment of chronic neuropathic pain (Moore 2012b), and an analysis of a large number of participants in trials of osteoarthritis and back pain shows oxycodone to be ineffective (Lange 2010).

Implications for practice
Clinical trial evidence on the use of oxycodone in neuropathic pain conditions is limited to three small studies in painful diabetic neuropathy and postherpetic neuralgia, all of which we considered at substantial risk of bias and likely to overestimate efficacy. There is no convincing, unbiased evidence that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or postherpetic neuralgia. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. As with other opioids, some adverse events (particularly somnolence or sedation, and constipation) may limit its clinical usefulness.

Implications for research
It might be expected that, at best, only a few patients with neuropathic pain or fibromyalgia will benefit from long term use of oxycodone, and longitudinal cohort studies in fibromyalgia link opioid use to negative health related measures (Fitzcharles 2013).

To establish whether oxycodone has a place in the treatment of neuropathic pain and fibromyalgia would require very large, randomised, double-blind, parallel group studies, of adequate duration (> 12 weeks), with outcome measures that are more relevant to clinical practice (≥ 50% or ≥ 30% pain intensity reduction), and analysis that does not use LOCF imputation for withdrawals. Any comparisons should be made with placebo and other drugs with known efficacy, such as pregabalin. An alternative might be the use of registry studies in noncancer pain; preliminary suggestions for such a study have been published (Kim 2013).

A further area of research would be to identify characteristics that predict which individuals are likely to benefit from oxycodone, in order to target treatment more effectively, but this is extraordinarily difficult in the absence of any convincing evidence of efficacy from clinical trials.

Acknowledgements
Institutional support was provided by the Oxford Pain Relief Trust.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.
Oxycodone for neuropathic pain and fibromyalgia in adults (Review)

References to studies included in this review

Gimbel 2003  [published data only]


Waxton 1998  [published data only]

Waxton 2003  [published data only]

References to studies excluded from this review

Buynak 2010  [published data only]

Gatti 2009  [published data only]

Hale 1999  [published data only]

Hale 2005  [published data only]

Hanna 2008  [published data only]

He 2009  [published data only]

Lange 2010  [published data only]

Löwenstein 2009  [published data only]

Simpson 2008  [published data only]

Steiner 2011  [published data only]

Webster 2006  [published data only]

Wild 2010  [published data only]

Wörz 2003  [published data only]
Oxycodone for neuropathic pain and fibromyalgia in adults (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Zin 2010 [published data only]

Additional references

Apkarian 2011

Attal 2010

AUREF 2012

Bouhassira 2008

Brennan 2013

Butler 2013

Derry 2012

Derry 2013

Dhalla 2009

Dworkin 2007

Dworkin 2008

Elbourne 2002

Fitzcharles 2013

Gaskell 2009

Gustorff 2008

Hall 2008

Hall 2013

Higgins 2011
Oxycodone for neuropathic pain and fibromyalgia in adults (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Moore 2010a

Moore 2010b

Moore 2010c

Moore 2010d

Moore 2010e

Moore 2011a

Moore 2011b

Moore 2011c

Moore 2012a

Moore 2012b

Moore 2013a

Moore 2013b

NICE 2013

O’Brien 2010

Oaklander 2013

Olkkola 2009

Olkkola 2013

Poyhia 1993
## Characteristics of included studies [ordered by study ID]

**Gimbel 2003**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre, randomised, double-blind, placebo-controlled parallel group study Screening and washout for 3 to 7 days followed by 42 day treatment phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Diabetic with symmetrical, distal polyneuropathy Average pain intensity $\geq 5/10$ for $\geq 12$ hours/day for $\geq 3$ months, and $\geq$ moderate pain intensity in absence of opioid therapy Diabetes stable, with HbA1c $\leq 11%$ Exclusions: significant co-morbidities, pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse, pregnancy or breast feeding N = 159 Mean age 59 ($\pm$ 11) years M 83, F 76 Mean baseline pain intensity 7/10 ($\pm$ 1.4) Mean baseline HbA1c 7.8 ($\pm$ 1.4)</td>
</tr>
<tr>
<td>Interventions</td>
<td>All pre-study opioid drugs discontinued for $\geq 3$ days before starting study medication. Other stable analgesics and diabetic medications continued unchanged Oxycodone CR to maximum 120 mg/day, n = 82 Placebo, n = 77 Starting dose 10 mg, twice daily. Dose titrated upwards by 10 mg twice daily every 3 days. Optional 1 week taper at end Average daily dose: Oxycodone 37 ($\pm$ 21) mg Placebo 52 ($\pm$ 25) mg Mean daily dose in last 2 weeks for oxycodone 42 ($\pm$ 27) mg Dose reduction allowed if adverse events intolerable. No opioid rescue medication allowed</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Daily diary: 1. Average daily pain intensity (0 to 10) in last 24 hours (days 28 to 42), NPS Also scored for current pain, worst pain, satisfaction, sleep quality 2. BPI 3. Psychological state, physical functioning, mental health, SF-36 5. Days with mild pain (pain intensity $\leq 4/10$) 6. Adverse events LOCF for withdrawal Intermittent missing data not imputed ITT: all participants randomised and receiving $\geq 1$ dose study medication</td>
</tr>
</tbody>
</table>
Gimbel 2003  (Continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>Responder analysis of NPS items (Gimbel 2003 in Jensen 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxford Quality Score: R2, DB2, W1 Total = 5/5</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated by sponsor centrally</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Remotely packaged and shipped to sites Subject numbers assigned in ascending sequence as subjects qualified for randomisation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>“Matching placebo”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>“Matching placebo”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>LOCF for withdrawal Intermittent missing data not imputed</td>
</tr>
<tr>
<td>Size</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants per treatment arm</td>
</tr>
</tbody>
</table>

### Watson 1998

**Methods**

Single centre, randomised, double-blind, placebo-controlled, two-way cross-over study medication Washout period ≥ 7 days, then treatment phase of 2 periods of 4 weeks, without washout at cross-over

**Participants**

Postherpetic neuralgia for ≥ 3 months, with pain of at least moderate intensity for at least half of the day

Exclusions: pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse

N = 50
Mean age 70 (± 11) years
M 16, F 22 (in efficacy analysis)

**Interventions**

All pre-study opioid drugs discontinued ≥ 7 days before starting study medication

Other stable medications for pain (taken for 3 weeks or more) continued unchanged
Watson 1998  

Oxycodone CR to maximum 60 mg/day, n = 50  
Placebo, n = 50  
Starting dose 10 mg, twice daily. Dose titrated upwards at a maximum rate of 10 mg twice daily, at weekly visits over 4 weeks  
Mean daily dose during final week = 45 (± 17) mg

| Outcomes | Diary:  
1. Daily overall pain intensity (100 mm VAS and 5-point categorical scale)  
2. Daily overall pain relief (6-point categorical scale)  
3. Intensity of steady, brief, and skin pain over previous week (100 mm VAS and 5-point categorical scale)  
Weekly (investigator rated following participant interview):  
1. Disability (scale 0 to 3)  
2. Effectiveness (scale 0 to 4)  
3. Affective state (POMS, BDI)  
Adverse events assessed using "non-directed questionnaire"  
End of study:  
Treatment preference (assessed under double-blind conditions) |

| Notes | Oxford Quality Score: R1, DB2, W1 Total = 4/5 |

| Risk of bias |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Details of randomisation method not reported |
| Allocation concealment (selection bias) | Unclear risk | Assignment in opaque envelope, but not recorded if envelope sealed |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | “Matching placebo” |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | “Matching placebo”. “Overall treatment preference was assessed by the patient under double-blind conditions” at end of study |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Imputation method not reported. Completer analysis for efficacy data |
### Watson 1998  (Continued)

<table>
<thead>
<tr>
<th>Size</th>
<th>High risk</th>
<th>50 participants in each treatment arm, but only 38 provided data for analysis</th>
</tr>
</thead>
</table>

### Watson 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Two centre, randomised, double-blind, active placebo-controlled, cross-over study Washout 2 to 7 days then treatment phase of 2 periods of 4 weeks, without washout at crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Diabetic with symmetrical, distal sensory neuropathy At least moderate pain intensity (≥2/5) at screening for at least 3 months Stable glycaemic control Exclusions: pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse N = 45 Mean age 63 (± 9) years M 19, F 17 Mean baseline pain 67/100 (± 15)</td>
</tr>
<tr>
<td>Interventions</td>
<td>All pre-study opioid drugs discontinued 2 to 7 days before randomisation Other stable medications continued Oxycodone CR to maximum 80 mg/day, n = 45 Placebo (benztropine) to maximum 2 mg/day, n = 45 Starting dose oxycodone 10 mg, twice daily or benztropine 0.25 mg. Upward titration by 10 mg (oxycodone) or 0.25 mg (benztropine) twice daily every 2 to 7 days Rescue medication - paracetamol Mean daily dose in last week of study: Oxycodone 40 (± 19) mg Benztropine 1.2 (± 0.6) mg, (49 (± 24) mg placebo)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Successful treatment was defined as at least moderate pain relief (the top 3 categories) on a 6-point categorical scale (worse pain, no relief, slight, moderate, a lot, complete) Diary: 1. Daily overall pain intensity (100 mm VAS and 5-point categorical scale) 2. Daily overall pain relief (6-point categorical scale) 3. Intensity of steady, brief, and skin pain over previous week (100 mm VAS and 5-point categorical scale) 4. Rescue medication used Weekly: Disability (Pain Disability Index) At baseline, cross-over and end of study:</td>
</tr>
</tbody>
</table>
Watson 2003  (Continued)

<table>
<thead>
<tr>
<th>SF-36 Pain and sleep questionnaire</th>
<th>Adverse events reported spontaneously by participants or observed by investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the end of each phase, participants and investigators: Effectiveness (7-point categorical scale) Satisfaction with pain relief and tolerability (yes, no) Preference Blinding</td>
<td></td>
</tr>
</tbody>
</table>

Notes

Oxford Quality Score: R2, DB1, W1 Total = 4/5

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“Study medication prepackaged with assigned randomization numbers”, allocated using “consecutive numbers after screening to ensure balanced treatment at both centres”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>“Double-blind” but methods to achieve blinding of medication not reported</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>“Double-blind” but methods to achieve blinding of medication not reported. “Test of blinding” by participants and investigators at end of study, details not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Imputation method not reported. Completer analysis for efficacy data</td>
</tr>
<tr>
<td>Size</td>
<td>High risk</td>
<td>&lt; 50 participants per treatment arm</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; CR: Controlled release; DB: double blind; HbA1c: Glycosylated haemoglobin; ITT: intention-to-treat; LOCF: Last observation carried forward; NPS: Neuropathic Pain Scale; POMS: Profile of Mood States; R: randomisation; SF-36: 36-item short-form health survey; VAS: visual analogue scale; W: withdrawals
### Characteristics of excluded studies  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buynak 2010</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Gatti 2009</td>
<td>Open label study</td>
</tr>
<tr>
<td>Hale 1999</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Hale 2005</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Hanna 2008</td>
<td>Trial of oxycodone and gabapentin together</td>
</tr>
<tr>
<td>He 2009</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Lange 2010</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Löwenstein 2009</td>
<td>Trial of oxycodone and naloxone together</td>
</tr>
<tr>
<td>Simpson 2008</td>
<td>Trial of oxycodone and naloxone together</td>
</tr>
<tr>
<td>Steiner 2011</td>
<td>Enriched enrolment trial in which oxycodone was used as control during withdrawal; very small numbers of participants with low back pain of neuropathic origin</td>
</tr>
<tr>
<td>Webster 2006</td>
<td>Not specifically neuropathic pain</td>
</tr>
<tr>
<td>Wild 2010</td>
<td>Open label, and not specifically neuropathic pain</td>
</tr>
<tr>
<td>Wörz 2003</td>
<td>Not a randomised controlled trial</td>
</tr>
<tr>
<td>Zin 2010</td>
<td>Trial of oxycodone and pregabalin together</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. Oxycodone CR versus 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 Any adverse event</td>
<td>3</td>
<td>349</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.36 [1.20, 1.54]</td>
</tr>
<tr>
<td>2 Serious adverse events</td>
<td>3</td>
<td>349</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.48 [0.18, 1.23]</td>
</tr>
<tr>
<td>3 Adverse event withdrawals</td>
<td>3</td>
<td>349</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [0.83, 3.43]</td>
</tr>
<tr>
<td>4 Lack of efficacy withdrawals</td>
<td>3</td>
<td>349</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.12 [0.03, 0.45]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Oxycodone CR versus placebo, Outcome 1 Any adverse event.

**Review:** Oxycodone for neuropathic pain and fibromyalgia in adults

**Comparison:** 1 Oxycodone CR versus placebo

**Outcome:** 1 Any adverse event

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oxycodeone CR n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel 2003</td>
<td>80/82</td>
<td>52/77</td>
<td>48.5 % 1.44 [1.23, 1.69]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson 1998</td>
<td>38/50</td>
<td>24/50</td>
<td>21.7 % 1.58 [1.14, 2.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>35/45</td>
<td>33/45</td>
<td>29.8 % 1.06 [0.84, 1.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td>172</td>
<td>100.0 % 1.36 [1.20, 1.54]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 153 (Oxycodeone CR), 109 (Placebo)

Heterogeneity: Chi² = 5.67, df = 2 (P = 0.06); I² = 65%

Test for overall effect: Z = 4.76 (P < 0.00001)

Test for subgroup differences: Not applicable

Favours oxycodone CR Favours placebo
Analysis 1.2. Comparison 1 Oxycodone CR versus placebo, Outcome 2 Serious adverse events.

Review: Oxycodone for neuropathic pain and fibromyalgia in adults

Comparison: 1 Oxycodone CR versus placebo

Outcome: 2 Serious adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oxycodone CR n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel 2003</td>
<td>5/82</td>
<td>9/77</td>
<td>75.6 % 0.52 [0.18, 1.49]</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Watson 1998</td>
<td>0/50</td>
<td>0/50</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>1/45</td>
<td>3/45</td>
<td>24.4 % 0.33 [0.04, 3.08]</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td>172</td>
<td>100.0 % 0.48 [0.18, 1.23]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Oxycodone CR), 12 (Placebo)
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Oxycodone CR versus placebo, Outcome 3 Adverse event withdrawals.

Review: Oxycodone for neuropathic pain and fibromyalgia in adults

Comparison: 1 Oxycodone CR versus placebo

Outcome: 3 Adverse event withdrawals

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oxycodone CR n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel 2003</td>
<td>7/82</td>
<td>4/77</td>
<td>37.1 % 1.64 [0.50, 5.39]</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>Watson 1998</td>
<td>5/50</td>
<td>3/50</td>
<td>27.0 % 1.67 [0.42, 6.60]</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>7/45</td>
<td>4/45</td>
<td>36.0 % 1.75 [0.55, 5.57]</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td>172</td>
<td>100.0 % 1.69 [0.83, 3.43]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19 (Oxycodone CR), 11 (Placebo)
Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable

Oxycodone for neuropathic pain and fibromyalgia in adults (Review) 28
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Analysis 1.4. Comparison 1 Oxycodone CR versus placebo, Outcome 4 Lack of efficacy withdrawals.

Review: Oxycodone for neuropathic pain and fibromyalgia in adults

Comparison: 1 Oxycodone CR versus placebo

Outcome: 4 Lack of efficacy withdrawals

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oxycodone CR</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Gimbel 2003</td>
<td>1/82</td>
<td>11/77</td>
<td>57.2 % 0.09 [ 0.01, 0.65 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson 1998</td>
<td>0/50</td>
<td>1/50</td>
<td>7.6 % 0.33 [ 0.01, 7.99 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson 2003</td>
<td>1/45</td>
<td>7/45</td>
<td>35.3 % 0.14 [ 0.02, 1.11 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>177</strong></td>
<td><strong>172</strong></td>
<td><strong>100.0 % 0.12 [ 0.03, 0.45 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Oxycodone CR), 19 (Placebo)
Heterogeneity: Chi$^2$ = 0.52, df = 2 ($P = 0.77$); $I^2 = 0.0$
Test for overall effect: $Z = 3.16$ ($P = 0.0016$)
Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria of what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with “any improvement”. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010b; Moore 2010c), arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.

Oxycodone for neuropathic pain and fibromyalgia in adults (Review)
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013c; Moore 2014; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.

4. Imputation methods like last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

5. Finally, individual patient analyses and other evidence indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010d; Moore 2013a).

Appendix 2. Search strategy for MEDLINE via Ovid

1. Oxycodone/
2. (oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percolone or Roxicodone or Supeudol or Tylox).mp.
3. 1 or 2
4. exp pain/
5. exp peripheral nervous system diseases
6. exp somatosensory disorders/
7. Fibromyalgia/
8. (pain* or fibromyalgia* or neuralgi* or analgesi* or discomfort*).mp.
9. 4 or 5 or 6 or 7 or 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 9 and 18

Appendix 3. Search strategy for EMBASE (via Ovid)

1. Oxycodone/
2. (oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percolone or Roxicodone or Supeudol or Tylox).mp.
3. 1 or 2
4. fibromyalgia/
5. exp neuralgia/
6. (pain* or fibromyalgia* or neuralgi* or analgesi* or discomfort*).mp.
7. 4 or 5 or 6
8. crossover-procedure/
9. double-blind procedure/
10. randomized controlled trial/
Appendix 4. Search strategy for CENTRAL

1. MeSH descriptor: [Oxycodone] this term only
2. oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percodone or Roxicodone or Supeudol or Tylox:ti,ab,kw
3. #1 and #2
4. MeSH descriptor: [Pain] explode all trees
5. MeSH descriptor: [Peripheral Nervous System Diseases] explode all trees
6. MeSH descriptor: [Somatosensory Disorders] explode all trees
7. MeSH descriptor: [Fibromyalgia] this term only
8. (pain* or fibromyalgia* or neuralgi* or analgesi* or discomfort*):ti,ab,kw
9. #4 or #5 or #6 or #7 or #8
10. #3 and #9

Appendix 5. Summary of efficacy in individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Pain outcome</th>
<th>Other efficacy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel 2003</td>
<td>Oxycodone CR to maximum 120 mg/day, n = 82 Placebo, n = 77 Titration over 42 days</td>
<td>Mean (SE) of average daily pain intensity (days 28 to 42): Oxycodone CR 4.1 (0.3) Placebo 5.3 (0.3) Median time to achieve mild pain: Oxycodone CR 6 days Placebo 17 days Mean (SD) days with mild pain: Oxycodone CR 20 (17) days Placebo 13 (16) days Mean percentage (SD) days with mild pain: Oxycodone CR 47 (39) % Placebo 29 (37) % Additional data (Jensen 2006 in Gimbel 2003): Responder analysis ≥33% reduction in pain intensity at 6 weeks: Oxycodone CR responder 37/82, nonresponder 45/82 Placebo responder 20/77, nonresponder 57/77</td>
<td>Oxycodone CR significantly better than placebo for all other outcomes except physical functioning, general health, and mental health of SF-36, and on subscales of Rand Mental Health Inventory</td>
</tr>
</tbody>
</table>
### Watson 1998
- Oxycodone CR to maximum 60 mg/day, n = 50
- Placebo, n = 50
- Titration in each of 2 periods of 4 weeks, without washout at cross-over

For participants with data from both phases only
- Mean daily overall pain intensity in last week of study:
  - Oxycodone CR: 35 (±25)/100
  - Placebo: 54 (±25)/100
- Oxycodone CR better than placebo in categorical scores of pain intensity and pain relief

Oxycodone CR better than placebo for disability
No difference in mood factors of POMS or in BDI
Preference: Oxycodone CR 67%, Placebo 11%, No preference 22%

### Watson 2003
- Oxycodone CR to maximum 80 mg/day, n = 45
- Placebo (benztropine) to maximum 2 mg/day, n = 45
- Titration in each of 2 periods of 4 weeks, without washout at cross-over

Mean (SD) pain intensity in last week of phase:
- Oxycodone CR: 21.8 (20.7)
- Placebo: 48.6 (26.6)
- "Successful treatment" defined as at least moderate pain relief using 6 point scale, NNT 2.6 (no CI) reported, almost certainly based on "evaluable" population (n = 36) who completed ≥1 week of 2nd phase

All other results reported as group means. Oxycodone CR better than placebo, for all but a few domains of sleep, disability and SF-36

Oxycodone CR preferred by 88%, rated moderately or highly effective by 95%, and 73% were satisfied. No data for placebo

88% of participants and investigators correctly guessed treatment assignment

---

**BDI**: Beck Depression Inventory; **BPI**: Brief Pain Inventory; **CR**: controlled release; **NNT**: number needed to treat for an additional beneficial outcome; **POMS**: Profile of Mood States; **SD**: standard deviation; **SE**: standard error; **SF-36**: 36-item short-form health survey

### Appendix 6. Summary of adverse events and withdrawals in individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Adverse events</th>
<th>Withdrawals</th>
</tr>
</thead>
</table>
Watson 1998

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Titration</th>
<th>Any AE</th>
<th>SAE</th>
<th>LoE</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxycodone CR to maximum 60 mg/day</td>
<td>50</td>
<td>2 periods of 4 weeks, without washout</td>
<td>Oxycodone CR: 38/50</td>
<td>none reported</td>
<td>0/50</td>
<td>1/50</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>50</td>
<td></td>
<td>Placebo: 24/50</td>
<td></td>
<td>1/50</td>
<td></td>
</tr>
</tbody>
</table>

Watson 2003

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Titration</th>
<th>Any AE</th>
<th>SAE</th>
<th>LoE</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxycodone CR to maximum 80 mg/day</td>
<td>45</td>
<td>2 periods of 4 weeks, without washout</td>
<td>Oxycodone CR: 35/45</td>
<td>1/45</td>
<td>1/45</td>
<td>7/45</td>
</tr>
<tr>
<td></td>
<td>Placebo (benztropine) to maximum 2 mg/day</td>
<td>45</td>
<td></td>
<td>Placebo: 33/45</td>
<td></td>
<td>4/45</td>
<td></td>
</tr>
</tbody>
</table>

Continued

Participants
Constipation: Oxycodone CR 35/82; placebo 11/77
Somnolence: Oxycodone CR 33/82; Placebo 1/77
Nausea: Oxycodone CR 30/82; Placebo 6/77
Dizziness: Oxycodone CR 26/82; Placebo 8/77
Pruritus: Oxycodone CR 20/82; Placebo 6/77
Vomiting: Oxycodone CR 17/82; Placebo 2/77
Dry mouth: Oxycodone CR 13/82; Placebo 2/77
Asthenia: Oxycodone CR 12/82; Placebo 5/77
Headache: Oxycodone CR 9/82; Placebo 18/77

Any AE:
Oxycodone CR: 38/50
Placebo: 24/50

SAE:
Oxycodone CR: none reported
Placebo: none reported

Deaths:
Oxycodone CR: none reported
Placebo: none reported

Most frequent AE with oxycodone: constipation (5/50), nausea (4/50), sedation (3/50)
No data reported for placebo

Watson 2003

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Titration</th>
<th>Any AE</th>
<th>SAE</th>
<th>LoE</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxycodone CR to maximum 80 mg/day</td>
<td>45</td>
<td>2 periods of 4 weeks, without washout</td>
<td>Oxycodone CR: 35/45</td>
<td>1/45</td>
<td>1/45</td>
<td>7/45</td>
</tr>
<tr>
<td></td>
<td>Placebo (benztropine) to maximum 2 mg/day</td>
<td>45</td>
<td></td>
<td>Placebo: 33/45</td>
<td></td>
<td>4/45</td>
<td></td>
</tr>
</tbody>
</table>

Continued

Participants
Constipation: Oxycodone CR 35/82; placebo 11/77
Somnolence: Oxycodone CR 33/82; Placebo 1/77
Nausea: Oxycodone CR 30/82; Placebo 6/77
Dizziness: Oxycodone CR 26/82; Placebo 8/77
Pruritus: Oxycodone CR 20/82; Placebo 6/77
Vomiting: Oxycodone CR 17/82; Placebo 2/77
Dry mouth: Oxycodone CR 13/82; Placebo 2/77
Asthenia: Oxycodone CR 12/82; Placebo 5/77
Headache: Oxycodone CR 9/82; Placebo 18/77

Any AE:
Oxycodone CR: 35/45
Placebo: 33/45

SAE:
Oxycodone CR: 1/45
Placebo: 3/45

Specific AE occurring in 5 or more participants:
Nausea: Oxycodone CR 16/45; Placebo 8/45
Somnolence: Oxycodone CR 9/45; Placebo 11/45
Constipation: Oxycodone CR 13/45; Placebo 4/45
Dry mouth: Oxycodone CR 12/45; Placebo 0/45
Diarrhoea: Oxycodone CR 4/45; Placebo 6/45

AE:
Oxycodone CR: 7/45
Placebo: 4/45

LoE:
Oxycodone CR: 1/45
Placebo: 7/45

Other:
Oxycodone CR: 2/45
Placebo: 0/45
Dizziness: Oxycodone CR 7/45; Placebo 3/45
Headache: Oxycodone CR 5/45; Placebo 3/45
Asthenia: Oxycodone CR 2/45; Placebo 5/45
Vomiting: Oxycodone CR 5/45; Placebo 2/45
Insomnia: Oxycodone CR 3/45; Placebo 4/45
Pruritus: Oxycodone CR 4/45; Placebo 1/45
Sweating: Oxycodone CR 4/45; Placebo 1/45

AE = adverse event; CR = controlled release; LoE = lack of efficacy; SAE = serious adverse event

WHAT’S NEW
Last assessed as up-to-date: 6 November 2013.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 July 2014</td>
<td>Amended</td>
<td>Source of support added</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS
SD and RAM wrote the protocol.
HG and SD searched for and selected studies for inclusion and carried out data extraction. All review authors were involved in the analysis and in writing the full review.

DECLARATIONS OF INTEREST
RAM and SD have received research support from charities, government, and industry sources at various times. RAM has consulted for various pharmaceutical companies and has received lecture fees from pharmaceutical companies related to analgesics and other health care interventions. HG and CS have no interests to declare.
SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.
General institutional support

External sources

- The National Institute for Health Research (NIHR), UK, UK.
NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the list of examples of neuropathic pain conditions to stress that the inclusion criteria were broad; however, few studies were identified, and data from only two conditions are included in the review.

We intended to use two tiers to assess evidence, depending on quality criteria. The lower tier has now been split in two, making three separate tiers.

Entry criteria for the first tier are high and we were concerned that evidence of widely varying quality would (necessarily) all be grouped together in the lower of a two-tier hierarchy. To make best use of such second tier evidence, it seems appropriate to use three rather than two tiers. The revised criteria are described in the Methods section. Unfortunately, only third tier evidence is available for this review.