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[Intervention Review]

Oxycodone for pain in fibromyalgia in adults

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ABSTRACT

Background

This review replaces part of an earlier review that evaluated oxycodone for both neuropathic pain and fibromyalgia, which has now been split into separate reviews for the two conditions. This review will consider pain in fibromyalgia only.

Opioid drugs are commonly used to treat fibromyalgia, but they may not be beneficial for people with this condition. Most reviews have examined all opioids together. This review sought evidence specifically for oxycodone, at any dose, and by any route of administration.

Objectives

To assess the analgesic efficacy and adverse events of oxycodone for treating pain in fibromyalgia in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE for randomised controlled trials from inception to 25 July 2016. We also searched the reference lists of retrieved studies and reviews, and searched online clinical trial registries.

Selection criteria

We planned to include randomised, double-blind trials of eight weeks' duration or longer, comparing oxycodone (alone or in fixed-dose combination with naloxone) with placebo or another active treatment. We did not include observational studies.

Data collection and analysis

The plan was for two independent review authors to extract data and assess trial quality and potential bias. Where pooled analysis was possible, we planned to use dichotomous data to calculate risk ratio and numbers needed to treat for one additional event, using standard methods.

Main results

No study satisfied the inclusion criteria. Effects of interventions were not assessed as there were no included studies. We have only very low quality evidence and are very uncertain about estimates of benefit and harm.

Authors' conclusions

There is no randomised trial evidence to support or refute the suggestion that oxycodone, alone or in combination with naloxone, reduces pain in fibromyalgia.

PLAIN LANGUAGE SUMMARY

Oxycodone for pain in fibromyalgia in adults

Bottom line

There is no good evidence to support or refute the suggestion that oxycodone, alone or in combination with naloxone, reduces pain in fibromyalgia.

Background

Fibromyalgia is a complex disorder characterised by widespread pain, fatigue, poor sleep, low mood, and other bodily symptoms. Common pain-relieving medicines such as paracetamol and ibuprofen are not usually considered effective. Opioid painkillers are commonly used to treat fibromyalgia, but there is uncertainty over how good they are.

Opioid painkillers are drugs like morphine. Morphine is derived from plants, but many opioids are also made by chemical synthesis rather than being extracted from plants. Oxycodone is a semi-synthetic opioid, manufactured from the opioid alkaloid thebaine, and is widely available.

This review replaces part of a review originally published in 2014, which examined how well oxycodone worked in pain in fibromyalgia and some other medical conditions. In this review, we examined only pain in fibromyalgia. In the previous review, we did not find any evidence that oxycodone is, or is not, of value in treating pain in fibromyalgia.

Study characteristics

In July 2016, we searched for clinical trials where oxycodone, either alone or in a fixed-dose combination with naloxone, was used to treat pain due to fibromyalgia in adults. We did not find any studies that met the requirements for this review.

Key results

There was no information from randomised controlled trials on the benefits or harms of oxycodone when used to treat pain in fibromyalgia.

Quality of the evidence

We rated the quality of the evidence as very low because there were no studies. Very low quality evidence means that we are very uncertain about the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oxycodone compared with placebo for fibromyalgia

Oxycodone compared with placebo for fibromyalgia

Patient or population: adults with fibromyalgia

Settings: community

Intervention: oxycodone

Comparison: placebo

Outcomes	Probable out- come with intervention	Probable out- come with comparator	RR (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Moderate benefit: At least 30% reduction in pain, or PGIC much or very much improved	No data	No data	Not calculated	No data	Very low	No trials found
Substantial benefit: At least 50% reduction in pain, or PGIC much improved	No data	No data	Not calculated	No data	Very low	No trials found
Lack of efficacy withdrawal	No data	No data	Not calculated	No data	Very low	No trials found
Adverse event withdrawal	No data	No data	Not calculated	No data	Very low	No trials found
Serious adverse events	No data	No data	Not calculated	No data	Very low	No trials found
Deaths	No data	No data	Not calculated	No data	Very low	No trials found

CI: confidence interval; **PGIC:** Patient Global Impression of Change; **RR:** risk ratio

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

The protocol for this review is based on a template for reviews of drugs used to relieve 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; Appendix 1).

The earlier review of 'Oxycodone for neuropathic pain and fibromyalgia in adults' has been split into separate reviews (Gaskell 2014). This review looked at oxycodone for pain in fibromyalgia, and a separate review has looked at oxycodone for neuropathic pain (Gaskell 2016). These two reviews will serve to update the original.

Description of the condition

Fibromyalgia was defined by the American College of Rheumatology (ACR) 1990 classification criteria as widespread pain lasting for longer than three months with tenderness on palpation at 11 or more of 18 specified tender points (Wolfe 1990). Chronic widespread pain is frequently associated with other symptoms such as poor sleep, fatigue, and depression (Wolfe 2014), and the prevalence of chronic widespread pain in the general population (one component of fibromyalgia) was estimated to be 11% (Mansfield 2016). Fibromyalgia symptoms can be assessed by self report, using the fibromyalgia criteria and severity scales for clinical and epidemiological studies, a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia (so-called Fibromyalgia Symptom Questionnaire) (Wolfe 2011). For a clinical diagnosis, the ACR 1990 classification criteria (Wolfe 1990) and the ACR 2010 Preliminary Diagnostic Criteria (Wolfe 2010) are now used. Lacking a specific laboratory test, diagnosis is established by a history of the key symptoms and the exclusion of somatic diseases sufficiently explaining the key symptoms (Wolfe 2010). The indexing of fibromyalgia within the international classification of diseases is under debate. While some rheumatologists have thought of it as a specific pain disorder and central sensitivity syndrome (Clauw 2014; Yunus 2008), recent research points at small fibre pathology in a subgroup of patients with fibromyalgia that may be of pathophysiological importance (Oaklander 2013; Üçeyler 2013a). In psychiatry and psychosomatic medicine, fibromyalgia symptoms are categorised as a functional somatic syndrome, a bodily distress syndrome, a somatic symptom disorder, or a somatoform disorder (Häuser 2014a).

The cause, or causes, of fibromyalgia remain unknown. A model of interacting biological and psychosocial variables in the predisposition, triggering, and development of the chronicity of fibromyalgia symptoms has been suggested (Sommer 2012). Depression (Forseth 1999), genetics (Arnold 2013; Lee 2012), obesity combined with physical inactivity (Mork 2010), physical and sexual abuse in childhood (Häuser 2011), sleep problems (Mork 2010), and smoking (Choi 2010), have been shown to predict future development of fibromyalgia. Psychosocial stress (working place and family conflicts) and physical stress (infections, surgery, accidents) might trigger the onset of chronic widespread pain and fatigue (Clauw 2014; Sommer 2012). Depression and post-traumatic stress disorder worsen fibromyalgia symptoms (Häuser 2013a; Lange M 2010).

Several factors are associated with the pathophysiological changes of fibromyalgia, but their relationship is unclear. The changes include alteration of sensory processing in the

brain, reduced reactivity of the hypothalamus-pituitary-adrenal axis to stress, increased pro-inflammatory and reduced anti-inflammatory cytokine profiles (produced by cells involved in inflammation), disturbances in neurotransmitters such as dopamine and serotonin, and small fibre pathology (Oaklander 2013; Sommer 2012; Üçeyler 2013a). Prolonged exposure to stress, as outlined above, may contribute to these changes in predisposed individuals (Bradley 2009). There are similarities to, and differences from, neuropathic pain (Koroshetz 2011).

People with fibromyalgia often report high disability levels and poor quality of life along with extensive use of medical care (Häuser 2015a). Many people with fibromyalgia are significantly disabled, and experience moderate or severe pain for many years (Bennett 2007). Chronic painful conditions comprised 5 of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, lack of employment, and increased health costs (Moore 2014a).

Fibromyalgia is common. Numerous studies have investigated prevalence in different settings and countries. A review gave a global mean prevalence of potential cases of fibromyalgia of 2.7% (range 0.4% to 9.3%), with a mean in the Americas of 3.1%, in Europe of 2.5%, and in Asia of 1.7% (Queiroz 2013). Changes in diagnostic criteria do not appear to have significantly affected estimates of prevalence (Wolfe 2013). A large US survey using a modification of the 2010 ACR criteria found a prevalence of 1.8%, but 73% of these reported having been given a different diagnosis by their physician (Walitt 2015). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in those with repetitive strain injury; Queiroz 2013). When the 1990 ACR criteria are used for clinical surveys, women are more frequently diagnosed with the disorder. Using these criteria, the ratio of women to men has ranged from 8:1 to 30:1 in people who were studied in clinical institutions and surveys. However, with criteria that do not use tender point examination, the sex ratio can be close to equal. The sex ratio has ranged from 4:1 to 1:1 in studies that were conducted in the general population using the research criteria for fibromyalgia (Häuser 2015a; Queiroz 2013).

Fibromyalgia pain is known to be difficult to treat effectively, and is similar to other chronic pain conditions in that only a small proportion of trial participants have a good response to analgesic treatment (Moore 2013a). A multidisciplinary approach is recommended by evidence-based guidelines, combining pharmacological treatment with physical or cognitive training, or both. Interventions aim to reduce the key symptoms of fibromyalgia (pain, sleep problems, fatigue) and the associated symptoms (depression, disability) and to improve daily functioning (Eich 2012; Fitzcharles 2013a). Conventional analgesics are usually not effective. Treatment is often offered with antidepressants including serotonin and noradrenaline reuptake inhibitors (Häuser 2013b; Lunn 2014), tricyclic agents such as amitriptyline (Moore 2012a), or anticonvulsants such as gabapentin or pregabalin (Moore 2014b; Üçeyler 2013b; Wiffen 2013). The proportion of patients who achieve worthwhile pain relief (typically at least 50% reduction in pain intensity) is small (Moore 2014a), and generally reaches only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNTs) between 8 and 11. However, people who do experience good levels of pain relief also benefit from substantial reductions in other

symptoms, such as fatigue, function, sleep, depression, anxiety, and ability to work, with significant improvement in quality of life (Moore 2010b; Straube 2011).

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 (Pöyhä 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).

Oral oxycodone is widely used to treat cancer pain where it has similar efficacy to other opioids (Schmidt-Hansen 2015). It is sometimes used to treat chronic non-cancer pain. Individual titration of dose to effect is indicated, especially in older people, as pharmacokinetics may be age-dependent and highly individual (Olkkola 2009). A modified-release (MR) oral formulation has been developed for twice-daily dosing in chronic conditions. This formulation may be referred to as controlled-release or prolonged-release oxycodone. The peak plasma concentration is reached in about three hours, compared with one hour for the standard formulation.

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

How the intervention might work

Opioids such as oxycodone bind to specific opioid receptors in the nervous system and other tissues; there are three principal classes of receptors (μ , κ , and δ) 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, and oxycodone has been used since the early 20th century.

Various strands of evidence, mainly from studies in rodents, indicate that oxycodone may exert its opioid effects through the μ -opioid receptor and the κ -opioid receptor (Kalso 2007).

Why it is important to do this review

Since the early 2000s, there has been a marked increase in prescribing of opioids for non-cancer pain in general, despite a relatively modest evidence base. In some countries, this has been associated with widespread diversion, with consequent abuse, misuse, and mortality. Concurrently, suspicion has arisen

that opioid-induced hyperalgesia, together with tolerance to the analgesic effects of opioids, may in reality result in a lesser degree of benefit for opioids in chronic non-cancer pain than previously assumed. Ballantyne et al suggested that acute and end-of-life pain tends to respond well to opioids and follow a predictable course, but that chronic pain is different and not well managed with opioids (Ballantyne 2016). Guidelines recommend that opioid analgesics are not used for fibromyalgia in the long term, but observational studies (mainly health claims database studies) show that the practice is common, at least in the USA and Canada (Fitzcharles 2013a; Goldenberg 2016).

The standards used to assess evidence in chronic pain trials have evolved substantially in recent years, 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 mean pain scores, or mean change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue taking the treatment, ideally in trials of 8 to 12 weeks' duration or longer. Pain intensity reduction of 50% or more correlates with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the Cochrane Pain, Palliative and Supportive Care Group's (PaPaS) Author and Referee Guidance for pain studies (PaPaS 2012).

In this Cochrane review, we planned to assess evidence using methods that make both statistical and clinical sense, using developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). For inclusion and analysis, trials would have had to meet 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 4 or above; Moore 1998). This approach sets high standards for the demonstration of efficacy and marks a departure from how reviews were conducted previously.

Taking this newer, more rigorous approach is particularly important for opioids in chronic non-cancer pain. Opioids in clinical trials in non-cancer pain are associated with very high withdrawal rates of up to 60% over about 12 weeks (Moore 2010c). Many withdrawals occur within the first few weeks, when people experience pain relief but cannot tolerate the drug. The common practice of using the last observed results carried forward (last observation carried forward (LOCF)) to the end of the trial many weeks later can, therefore, produce results based largely on people who are 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, one large analysis of pooled data from trials in osteoarthritis and chronic low back pain conducted over about 12 weeks judged oxycodone effective, but an analysis of the same data using the new clinically meaningful standards showed it to be significantly worse than placebo (Lange B 2010).

An earlier version of this review, found only three studies involving about 250 participants with neuropathic pain, and no studies of oxycodone for pain in fibromyalgia (Gaskell 2014). An update to identify any new evidence for oxycodone, one of the most widely used opioids, is timely.

OBJECTIVES

To assess the analgesic efficacy and adverse events of oxycodone for treating pain in fibromyalgia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include 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 planned to exclude studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies had to include participants aged 18 years and older with pain in fibromyalgia, diagnosed using either ACR 1990 or ACR 2010 criteria (Wolfe 1990; Wolfe 2010).

Types of interventions

We sought studies using oxycodone at any dose, by any route, either alone or in fixed-dose combination with naloxone, administered for the relief of pain in fibromyalgia and compared with placebo or any active comparator.

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:

1. at least 30% pain relief over baseline (moderate);
2. at least 50% pain relief over baseline (substantial);
3. much or very much improved on Patient Global Impression of Change scale (PGIC; moderate);
4. very much improved on PGIC (substantial).

These outcomes are different from those used in many earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% pain intensity reduction, and ideally having no worse than mild pain (Moore 2013b; O'Brien 2010).

Primary outcomes

1. Participant-reported pain relief of 50% or greater.
2. Participant-reported pain relief of 30% or greater.
3. PGIC very much improved.
4. PGIC much or very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics or consequences.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.

Search methods for identification of studies

Electronic searches

We searched the following databases, without language restrictions.

1. Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Register of Studies Online database (CRSO)) on 25 July 2016.
2. MEDLINE (via Ovid) from 1946 to 25 July 2016.
3. EMBASE (via Ovid) from 1974 to 25 July 2016.

The search strategies for CENTRAL, MEDLINE, and EMBASE are listed in [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#), respectively.

Searching other resources

We searched www.clinicaltrials.gov and apps.who.int/trialsearch/ in April 2016 to identify additional completed or ongoing studies. We planned to review the bibliographies of any RCTs and review articles identified, and contacted known experts in the field, to identify additional published or unpublished data.

Data collection and analysis

Selection of studies

We planned to determine eligibility by reading the title and abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained a full copy of the remaining studies. Two review authors read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We have included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart ([Figure 1](#)).

Figure 1. Study flow diagram.

Data extraction and management

We planned that two review authors would independently extract data using a standard form and check for agreement before entry into Review Manager 5 (RevMan 2014) or any other analysis tool. We planned to include 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 planned to use the Oxford Quality Score as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors would have independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8.5, Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We planned to assess the following for each study.

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

Measures of treatment effect

We planned to calculate numbers needed to treat for one additional beneficial outcome (NNTs) as the reciprocal of the absolute risk reduction (ARR; [McQuay 1998](#)). For unwanted effects, the NNT becomes the number needed to treat for an additional harmful outcome (NNH) and is calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless we found significant statistical heterogeneity (see [Assessment of heterogeneity](#)). We planned not to use continuous data in analyses, and intended to extract and use continuous data, which probably reflects efficacy and utility poorly, only if useful for illustrative purposes only.

Unit of analysis issues

We planned to accept randomisation to individual participant only. We planned to split the control treatment arm between active

treatment arms in a single study if the active treatment arms were not combined for analysis.

Dealing with missing data

We planned to use an 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. We planned to assign zero improvement to missing participants wherever possible.

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 using the I^2 statistic.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility ([Moore 2010a](#)). The review did not depend on what authors of the original studies chose to report or not report, although clearly difficulties could arise if studies failed to report any dichotomous results of interest. We planned to extract 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 planned to use a fixed-effect model for meta-analysis. We would have used a random-effects model for meta-analysis if there was significant clinical heterogeneity and it was considered appropriate to combine studies. In the event, no pooling of data was possible.

We planned to analyse data 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 drop-outs, 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](#)).
- The second tier uses data from at least 200 participants but where one or more of the above conditions is not met (e.g. 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.

Quality of the evidence

We planned to use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to assess the quality of the evidence related to the key outcomes listed in [Types of outcome measures](#), as appropriate ([Appendix 5](#); Chapter 12, [Higgins 2011](#)). In the event, there was no evidence to assess.

We paid particular attention to:

1. inconsistency, where point estimates vary widely across studies or CIs of studies showed minimal or no overlap ([Guyatt 2011](#));
2. potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant ([Moore 2008](#)).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines ([Guyatt 2013a](#)). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if studies used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In circumstances where there were no data reported for an outcome, we planned to report the level of evidence as very low quality ([Guyatt 2013b](#)).

'Summary of findings' table

We have included 'Summary of findings' table as set out in the PaPaS author guide ([PaPaS 2012](#)), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 11, [Higgins 2011](#)). The table includes, where possible, outcomes equivalent to moderate or substantial benefit of at least 30% and at least 50% pain intensity reduction, PGIC (possibly at least substantial improvement and at least moderate improvement) ([Dworkin 2008](#)), withdrawals due to lack of efficacy, withdrawals due to adverse events, serious adverse events, and death (a particular serious adverse event).

Subgroup analysis and investigation of heterogeneity

We did not plan any subgroup analysis, since the evidence base was thought likely to be small.

Sensitivity analysis

We did not plan any sensitivity analyses.

RESULTS

Description of studies

Results of the search

Updated searches identified 550 studies in CENTRAL, 448 in MEDLINE, and 1643 in EMBASE. After screening titles and abstracts, we obtained the full text of one potentially relevant study. We did not find any additional studies in clinical trial registries or the reference lists of relevant reviews.

We did not find any studies that satisfied our inclusion criteria ([Figure 1](#)).

Included studies

There were no included studies.

Excluded studies

We excluded one study ([Lux 2014](#)). It did not include any participants with pain in fibromyalgia.

Risk of bias in included studies

There were no studies to evaluate.

Effects of interventions

See: [Summary of findings for the main comparison Oxycodone compared with placebo for fibromyalgia](#)

There were no studies to evaluate. See [Summary of findings for the main comparison](#).

DISCUSSION

Summary of main results

There were no relevant studies in fibromyalgia.

Several observational studies have found evidence that the use of opioids is common but associated with worse clinical outcomes. Opioids are often discontinued early ([Halpern 2015](#)). Patients with fibromyalgia in Germany reported very negatively about high adverse event rates of opioids in a consumer report ([Häuser 2012](#)). Two longitudinal US studies in relatively large numbers have shown that outcomes in fibromyalgia in opioid-treated participants were worse than those treated with non-opioid drugs ([Fitzcharles 2013a](#); [Peng 2015](#)). A minority of people with chronic pain conditions may obtain benefit from opioids over the longer term ([Häuser 2015b](#)), a feature of several chronic pain interventions where efficacy in clinical trials is either not available, or occasionally where trials show no benefit over placebo.

Potential biases in the review process

We carried out extensive searches of major databases using broad search criteria, and also searched two large clinical trial registries. We feel that is unlikely that we have missed significant studies.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no reviews (or even studies) evaluating oxycodone for pain in fibromyalgia, apart from the earlier version of this review. Guidelines from Europe and North America recommend other pharmacological and non-pharmacological treatments for fibromyalgia, and advise strongly against using opioids ([Fitzcharles 2013b](#); [Franklin 2014](#); [Häuser 2014b](#); [Lee 2014](#); [Macfarlane 2016](#); [Moisset 2016](#)). Despite this, observational studies (mainly health claims database studies) show that the use of opioids to treat pain in fibromyalgia is common, at least in the USA and Canada ([Fitzcharles 2013a](#); [Goldenberg 2016](#); [Halpern 2015](#)).

AUTHORS' CONCLUSIONS

Implications for practice

For people with pain in fibromyalgia

There is no evidence to support or refute the suggestion that oxycodone, either alone or in fixed dose combination with naloxone, has any efficacy in pain in fibromyalgia.

For clinicians

There is no evidence to support or refute the suggestion that oxycodone, either alone or in fixed dose combination with naloxone, has any efficacy in pain in fibromyalgia.

For policy makers

There is no evidence to support or refute the suggestion that oxycodone, either alone or in fixed dose combination with naloxone, has any efficacy in pain in fibromyalgia. In the absence of any supporting evidence, it should probably not be recommended, except at the discretion of a pain specialist with particular expertise in opioid use.

For funders

There is no evidence to support or refute the suggestion that oxycodone, either alone or in fixed dose combination with naloxone, has any efficacy in pain in fibromyalgia. In the absence of any supporting evidence, it should probably not be recommended, except at the discretion of a pain specialist with particular expertise in opioid use.

Implications for research

To establish whether oxycodone has a place in the treatment of fibromyalgia would require very large, randomised, double-

blind, parallel group studies, of adequate duration (greater than 12 weeks), with outcome measures that are relevant to clinical practice (at least 50% or at least 30% reduction in pain intensity), 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. Such a study seems unlikely given the current thinking that opioids are not effective for chronic pain in the long term, and are likely to cause harm (Ballantyne 2016; Fitzcharles 2013a).

An alternative might be the use of registry studies in non-cancer pain; preliminary suggestions for such a study have been published (Kim 2013).

Abnormalities in endogenous opioid systems have been identified in fibromyalgia (Goldenberg 2016). Further research to confirm and characterise the underlying pathophysiology in pain in fibromyalgia could lead to development of treatment that is focused, effective, and well tolerated for this condition.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Lux 2014	No participants with fibromyalgia

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 2011a](#); [Moore 2011b](#)), back pain ([Moore 2010c](#); [Moore 2010e](#)), arthritis ([Moore 2010d](#)), and 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.
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 2010e](#)); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of people 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 2010d](#); [Moore 2013a](#); [Moore 2014c](#); [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 such as 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 people who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way ([Moore 2010b](#); [Moore 2014a](#)).

Appendix 2. Search strategy for CENTRAL

1. MESH DESCRIPTOR Pain EXPLODE ALL TREES (32214)
2. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (778)
3. MESH DESCRIPTOR Fibromyalgia (614)
4. MESH DESCRIPTOR Myofascial Pain Syndromes EXPLODE ALL TREES (374)
5. MESH DESCRIPTOR Polymyalgia Rheumatica EXPLODE ALL TREES (44)
6. ((pain* or discomfort*) and (central or complex or rheumat* or muscul* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):TI,AB,KY (21440)
7. (fibromyalgi* or fibrosi* or FM or FMS):TI,AB,KY (2151)
8. ((neur* or nerv*) and (compress* or damag*)):TI,AB,KY (2301)
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 (50120)
10. MESH DESCRIPTOR oxycodone EXPLODE ALL TREES (408)
11. (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):TI,AB,KY (940)
12. #10 OR #11 (940)
13. #9 AND #12 (550)

Appendix 3. Search strategy for MEDLINE via Ovid

1. exp PAIN/ (326072)
2. exp SOMATOSENSORY DISORDERS/ (17854)
3. FIBROMYALGIA/ (6870)
4. exp MYOFASCIAL PAIN SYNDROMES/ (6018)
5. POLYMYALGIA RHEUMATICA/ (2249)
6. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscul* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):mp. (69117)

7. (fibromyalgi* or fibrostri* or FM or FMS).mp. (22020)
8. 1 or 2 or 3 or 4 or 5 or 7 (361475)
9. Oxycodone/ (1578)
- 10.(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. (2338)
- 11.9 or 10 (2338)
- 12.randomized controlled trial.pt. (410079)
- 13.controlled clinical trial.pt. (90300)
- 14.randomized.ab. (307130)
- 15.randomly.ab. (217155)
- 16.12 or 13 or 14 or 15 (735485)
- 17.8 and 11 and 16 (448)

Appendix 4. Search strategy for EMBASE (via Ovid)

1. exp PAIN/ (966548)
2. exp SOMATOSENSORY DISORDERS/ (73706)
3. FIBROMYALGIA/ (15365)
4. exp MYOFASCIAL PAIN SYNDROMES/ (6919)
5. POLYMYALGIA RHEUMATICA/ (3408)
6. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp. (133815)
7. (fibromyalgi* or fibrostri* or FM or FMS).mp. (35188)
8. 1 or 2 or 3 or 4 or 5 or 7 (1021952)
9. Oxycodone/ (12226)
- 10.(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. (12988)
- 11.9 or 10 (12988)
- 12.crossover-procedure/ (46530)
- 13.double-blind procedure/ (129623)
- 14.randomized controlled trial/ (398899)
- 15.(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1431007)
- 16.12 or 13 or 14 or 15 (1515319)
- 17.8 and 11 and 16 (1643)

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning grade of evidence ([GRADEpro GDT 2016](#)).

- **High** = further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = 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** = any estimate of effect is very uncertain.

We decrease grade if we find:

- a serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- a high probability of reporting bias (-1).

We increase grade if we find:

- strong evidence of association - significant risk ratio of greater than 2 (less than 0.5) based on consistent evidence from two or more; observational studies, with no plausible confounders (+1);

- very strong evidence of association - significant risk ratio of greater than 5 (less than 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1);
- that all plausible confounders would have reduced the effect (+1).

WHAT'S NEW

Date	Event	Description
1 September 2016	Review declared as stable	See Published notes .

HISTORY

Review first published: Issue 9, 2016

Date	Event	Description
3 July 2014	Amended	Source of support added

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol.

For both the original review and this update, HG and SD carried out searches and made decisions about inclusion and exclusion.

All review authors were involved in writing the full review.

DECLARATIONS OF INTEREST

HG: none known.

RAM has received grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015).

SD: none known.

CS: none known. She is a specialist pain consultant and treats people with fibromyalgia.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.
General institutional support

External sources

- The National Institute for Health Research (NIHR), 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

This review differs from the protocol for the original review on oxycodone for neuropathic pain and fibromyalgia, in that we have now divided it into two reviews. We have considered only pain in fibromyalgia in this updated review. In addition, we have increased the scope of the review to include oxycodone in fixed dose combination with naloxone, as well as oxycodone alone.

We required that included studies should have at least 10 participants per treatment arm (which was not specified in the original protocol) in keeping with other reviews from this review group in acute and chronic pain. Small studies have been shown to overestimate treatment effects.

We have extended the description of the GRADE assessment for exceptional circumstances to explain possible decisions.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.