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Fentanyl for neuropathic pain in adults (Review)

Derry S, Stannard C, Cole P, Wiffen PJ, Knaggs R, Aldington D, Moore RA

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[Intervention Review]

Fentanyl for neuropathic pain in adults

Sheena Derry[1], Cathy Stannard[2], Peter Cole[3], Philip J Wiffen[4], Roger Knaggs[5], Dominic Aldington[6], R Andrew Moore[7]

[1]Oxford, UK. [2]NHS Gloucestershire CCG, Brockworth, UK. [3]Oxford Pain Relief Unit, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK. [4]Thame, UK. [5]School of Pharmacy, University of Nottingham, Nottingham, UK. [6]Royal Hampshire County Hospital, Winchester, UK. [7]Plymouth, UK

Contact: Sheena Derry, Oxford, Oxfordshire, UK. sheena.derry@retired.ox.ac.uk.

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ABSTRACT

Background

Opioid drugs, including fentanyl, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for fentanyl, at any dose, and by any route of administration. Other opioids are considered in separate reviews.

Objectives

To assess the analgesic efficacy of fentanyl for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to June 2016, together with the reference lists of retrieved articles, and two online study registries.

Selection criteria

We included randomised, double-blind studies of two weeks' duration or longer, comparing fentanyl (in any dose, administered by any route, and in any formulation) with placebo or another active treatment in chronic neuropathic pain.

Data collection and analysis

Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality and potential bias. We did not carry out any pooled analyses. We assessed the quality of the evidence using GRADE.

Main results

Only one study met our inclusion criteria. Participants were men and women (mean age 67 years), with postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain. They were experiencing inadequate relief from non-opioid analgesics, and had not previously taken opioids for their neuropathic pain. The study used an enriched enrolment randomised withdrawal design. It was adequately blinded, but we judged it at unclear risk of bias for other criteria.

Transdermal fentanyl (one-day fentanyl patch) was titrated over 10 to 29 days to establish the maximum tolerated and effective dose (12.5 to 50 µg/h). Participants who achieved a prespecified good level of pain relief with a stable dose of fentanyl, without excessive use of rescue medication or intolerable adverse events ('responders'), were randomised to continue with fentanyl or switch to placebo for 12 weeks, under double-blind conditions. Our prespecified primary outcomes were not appropriate for this study design, but the measures reported do give an indication of the efficacy of fentanyl in this condition.

In the titration phase, 1 in 3 participants withdrew because of adverse events or inadequate pain relief, and almost 90% experienced adverse events. Of 258 participants who underwent open-label titration, 163 were 'responders' and entered the randomised withdrawal phase. The number of participants completing the study (and therefore continuing on treatment) without an increase of pain by more than 15/100 was 47/84 (56%) with fentanyl and 28/79 (35%) with placebo. Because only 63% responded sufficiently to enter the randomised withdrawal phase, this implies that only a maximum of 35% of participants entering the study would have had useful pain relief and tolerability with transdermal fentanyl, compared with 22% with placebo. Almost 60% of participants taking fentanyl were 'satisfied' and 'very satisfied' with their treatment at the end of the study, compared with about 40% with placebo. This outcome approximates to our primary outcome of moderate benefit using the Patient Global Impression of Change scale, but the group was enriched for responders and the method of analysis was not clear. The most common adverse events were constipation, nausea, somnolence, and dizziness.

There was no information about other types of neuropathic pain, other routes of administration, or comparisons with other treatments.

We downgraded the quality of the evidence to very low because there was only one study, with few participants and events, and there was no information about how data from people who withdrew were analysed.

Authors' conclusions

There is insufficient evidence to support or refute the suggestion that fentanyl works in any neuropathic pain condition.

PLAIN LANGUAGE SUMMARY

Fentanyl for neuropathic pain in adults

Bottom line

There is no good evidence to support or refute the suggestion that fentanyl works in any neuropathic pain condition.

Background

Neuropathic pain is pain coming from a damaged nervous system. It is different from pain messages that are carried along healthy nerves from damaged tissue (e.g. from a fall or cut, or an arthritic knee). Neuropathic pain is often treated by different medicines (drugs) from those used for pain from damaged tissue, which we often think of as painkillers. There are different types of neuropathic pain, with different causes. Some medicines that are used to treat depression or epilepsy can be very effective in some people with neuropathic pain. Sometimes opioid painkillers are used to treat neuropathic pain.

Opioid painkillers are drugs such as morphine. Morphine is derived from plants, but many opioids are also made by chemical synthesis rather than being extracted from plants. Fentanyl is one of these synthetic opioids. It is available in numerous countries for use as a painkiller and, when used to treat chronic pain, is usually given through an adhesive patch, so it is taken into the body through the skin.

Study characteristics

In January 2016 we searched for clinical trials where fentanyl was used to treat neuropathic pain in adults. We found one small study that did this and met our requirements for the review. The study had a complicated design. Study participants first received fentanyl (as one-day skin patches) for one month. Those who responded to therapy (achieved a predetermined level of pain relief) were then randomly allocated to continue receiving fentanyl or placebo for 12 weeks. The participants had one of three different types of neuropathic pain and had not taken opioids before. There were only 163 people in the 12-week comparison with placebo.

Key results

The study found that more people taking fentanyl had pain relief than those taking placebo. About 1 in 7 participants stopped taking fentanyl because of side effects, and 1 in 5 did not get a good level of pain relief in the first part of the study. Almost half of those who continued into the second part of the study also stopped. The most common side effects were constipation, nausea (feeling sick), somnolence (feeling sleepy), and dizziness. These are typical side effects with opioids such as fentanyl. There was so little information from this single study that we concluded there was no convincing evidence to support or reject a meaningful benefit for fentanyl over placebo.

Quality of the evidence

We rated the quality of the evidence as very low because there was only one study, with few participants and events, and an unusual design. Very-low-quality evidence means that we are very uncertain about the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Transdermal fentanyl compared with placebo for neuropathic pain

Patient or population: Adults with chronic neuropathic pain

Settings: Community

Intervention: Fentanyl 1-day adhesive patch 12.5 to 50 µg/h

Comparison: Placebo patch

Outcomes	Probable outcome with intervention	Probable outcome 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	Pain treatment: satisfied, very satisfied 49/84	Pain treatment: satisfied, very satisfied 32/79	Not calculated	1 study, 163 participants, 81 events	Very low	Downgraded three times: single study, few participants and events, approximates to prespecified outcome, imputation for withdrawals not specified, unusual mix of pain conditions
Substantial benefit: at least 50% reduction in pain, or PGIC much improved	No data	No data	-	-	-	-
Lack of efficacy withdrawal in randomised double-blind phase	19/84	39/79	Not calculated	1 study, 163 participants, 81 events	Very low	Downgraded three times: single study, few participants and events
Adverse event withdrawal in randomised double-blind phase	14/84	4/79	Not calculated	1 study, 163 participants, 81 events	Very low	Downgraded three times: single study, few participants and events
Serious adverse events	13/258 during titration phase	4/79 in randomised double-blind phase	Not calculated	Titration: 1 study, 258 participants, 13 events Randomised double-blind phase: 1	Very low	Downgraded three times: single study, few participants and events

	8/84 in randomised double-blind phase			study, 163 participants, 12 events		
Deaths	None	None	-	1 study, 258 participants, 0 events	Very low	Downgraded three times: estimated incidence not more frequent than 1 in 86[1]

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.

[1] Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. BMJ 1995;311(7005):619-20.

BACKGROUND

This review is based on a template for reviews of drugs used to relieve neuropathic pain. 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).

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), and is based on a definition agreed at 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 (Moisset 2007). The origin of neuropathic pain is complex (Baron 2010; Baron 2012; Tracey 2011; von Hehn 2012), and neuropathic pain features can be found in people with joint pain (Soni 2013).

Many people with neuropathic pain conditions are significantly disabled with moderate or severe pain for many years. Chronic pain 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 and employment, and increased healthcare costs (Moore 2014a).

Neuropathic pain is usually divided according to the cause of nerve injury. There may be many causes, but some common causes of neuropathic pain include diabetes (painful diabetic neuropathy (PDN)), shingles (postherpetic neuralgia (PHN)), amputation (stump and phantom limb pain), neuropathic pain after surgery or trauma, stroke or spinal cord injury, trigeminal neuralgia, and HIV infection. Sometimes the cause is unknown.

In systematic reviews, the overall prevalence of neuropathic pain in the general population is reported to be between 7% and 10% (van Hecke 2014), and about 7% in a systematic review of studies published since 2000 (Moore 2014a). In individual countries, prevalence rates have been reported as 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006). Some forms of neuropathic pain, such as PDN and postsurgical chronic pain (which is often neuropathic in origin), are increasing in prevelance (Hall 2008).

Estimates of incidence vary between individual studies for particular origins of neuropathic pain, often because of small numbers of cases. In primary care in the UK, between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for PDN (Hall 2008). Others have estimated an incidence of 4 in 100,000 per year (Katusic 1991; Rappaport 1994) for trigeminal neuralgia, and of 12.6 per 100,000 person-years for trigeminal neuralgia and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009). One systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as PDN, can be more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, combining pharmacological interventions with physical or cognitive (or both) interventions. Conventional analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs are not thought to be effective, but are frequently used (Di Franco 2010; Vo 2009). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2013).

Treatment is often by so-called 'unconventional analgesics', such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics (gabapentin or pregabalin; Moore 2009; Moore 2014b; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2013b). Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

One overview of treatment guidelines pointed out some general similarities between recommendations, but guidelines are not always consistent with one another (O'Connor 2009). The current National Institute for Health and Care Excellence (NICE) guidance suggests offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (with the exception of trigeminal neuralgia), with switching if the first, second, or third drugs tried are not effective or not tolerated (NICE 2013).

Description of the intervention

Fentanyl was first synthesised in the 1950s and was found to be significantly more potent than commonly used opioids, such as morphine. It was initially used for intravenous anaesthesia and analgesia in the 1960s and became a mainstay of intraoperative and perioperative analgesia and both conscious and deep sedation in the in-hospital setting. Peak analgesic effects of intravenous fentanyl last for 30 to 60 minutes, but onset of analgesia is rapid. Fentanyl is approximately 80 to 100 times more potent than morphine, is highly lipophilic, and binds strongly to plasma proteins (Trescot 2008). Fentanyl is associated with possible hypoxaemia (low oxygen levels in the blood) after surgery (McQuay 1979).

Fentanyl undergoes extensive metabolism in the liver, and is subject to first-pass metabolism in the liver and possibly small intestine, though hepatic extraction from blood may be more complicated (Bullingham 1984). Various formulations of fentanyl have been studied, including a rapid transmucosal formulation for buccal absorption or intranasal sprays for acute breakthrough pain, and transdermal formulations for chronic pain (Lötsch 2013; Nelson 2009). The transdermal formulation has a lag time of 6 to 12 hours to onset of action after application, and typically reaches steady state in three to six days. When a patch is removed, a subcutaneous reservoir remains, and drug clearance may take up to 24 hours.

Fentanyl patches are available as generic formulations, and brand names include Fentalis®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, Victanyl®, Durogesic®, and DTrans®. They are available as 12, 25, 50,

75, and 100 µg/h transdermal patches. The 25, 50, 75, and 100 µg/h patches were first licensed in 1994, and a 12 µg patch followed in 2005. Transdermal fentanyl provides 'rate controlled' drug delivery over 72 hours, although shorter and longer delivery periods are under development. A 24-hour patch has been licensed for some pain conditions in Japan. Surface area exposed, skin permeability, and local blood flow determine absorption (Heiskanen 2009). Absorption was impaired in 10 cachectic (weak and underweight) compared with 10 normal weight cancer patients, (Heiskanen 2009). The 'reservoir patch' is being phased out and replaced with a matrix design, as it was likely to leak if damaged or cut. Trials have demonstrated no difference in pain intensity reduction or overall adverse effects between the reservoir and matrix patches. Satisfaction was improved, and wearability, adhesion, and comfort were improved with the matrix patches (Cachia 2011).

Fentanyl patches have been suggested to have some benefits over more traditional opioids such as oral morphine. There is a favourable safety profile in people with renal insufficiency, as this does not affect fentanyl elimination, while renal insufficiency or failure cause a build-up of active metabolites of opioids such as morphine. Fentanyl is also considered to cause less constipation than morphine. However, fentanyl patches are not generally recommended in clinical practice for people who are opioid naïve. Moreover, exposure to heat through fever, sunbathing, hot showers or baths, and warm weather can cause more fentanyl to be released into the skin and cause serious, or even fatal, adverse events.

How the intervention might work

Opioids such as fentanyl 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 such as fentanyl to receptors brings about complex cellular changes, the 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

One UK survey found that weak and strong opioids were used frequently for treating neuropathic pain (Hall 2013). Fentanyl patches can be useful in people who cannot tolerate oral opioids. Titrating the dose of fentanyl patches can be difficult and it is probably better to convert from a dose of morphine or other oral opioid that is effective but not tolerated. Since the early 2000s, a marked increase in prescribing of opioids for non-cancer pain in general, despite a relatively modest evidence base, has in some countries led to widespread diversion with consequent abuse, misuse, and mortality (Franklin 2014; Weisberg 2014; Zin 2014). There were 1.2 million prescriptions for fentanyl in primary care in England in 2014 at a cost of almost GBP57 million (PCA 2015) and the amount of fentanyl prescribed has been rising substantially (Zin 2014), although not all this prescribing will be for neuropathic pain.

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 neuropathic pain than previously assumed.

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 in treatment, ideally in trials of 8 to 12 weeks' duration or longer. A 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 (PaPaS) Author and Referee Guidance* for pain studies (PaPaS 2012).

This Cochrane review assessed evidence using methods that make both statistical and clinical sense, and used developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). To be included, trials 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 2010b). Many withdrawals occur within the first few weeks, when participants 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 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 2010).

One 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). These limitations were confirmed by reviews specific to buprenorphine and oxycodone (Gaskell 2014; Wiffen 2015). A review specific to fentanyl is timely.

OBJECTIVES

To assess the analgesic efficacy of fentanyl for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials with double-blind assessment of participant outcomes following two weeks or more of treatment, although the emphasis of the review was on studies

with a duration 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

We included studies involving adults aged 18 years and above with one or more chronic neuropathic pain condition including (but not limited to):

1. cancer-related neuropathy;
2. central neuropathic pain;
3. complex regional pain syndrome (CRPS) Type II;
4. human immunodeficiency virus (HIV) neuropathy;
5. painful diabetic neuropathy (PDN);
6. phantom limb pain;
7. postherpetic neuralgia (PHN);
8. postoperative or traumatic neuropathic pain;
9. spinal cord injury;
10. trigeminal neuralgia.

Where studies included participants with more than one type of neuropathic pain, we planned to analyse results according to the primary condition.

Types of interventions

Fentanyl at any dose, by any route, administered for the relief of neuropathic pain and compared with placebo or any active comparator.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with most studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity (where higher numbers indicate more pain) or pain relief (where higher numbers indicate more 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 benefit);
2. at least 50% pain relief over baseline (substantial benefit);
3. much or very much improved on Patient Global Impression of Change scale (PGIC; moderate benefit); and
4. very much improved on PGIC (substantial benefit).

These outcomes are different from those used in most 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 2013a; O'Brien 2010).

We have included a 'Summary of findings' table as set out in the PaPaS author guide (PaPaS 2012), to include outcomes of at least 30% and at least 50% pain intensity reduction, much or very much improvement on PGIC, withdrawals due to adverse events, serious adverse events, and death. We used the GRADE approach to assess the quality of evidence related to each of the key outcomes listed below (Chapter 12, Higgins 2011), as appropriate.

Primary outcomes

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

Secondary outcomes

1. Any pain-related outcome indicating some improvement
2. Withdrawals due to lack of efficacy, adverse events, and for any cause
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. 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)) to 14 June 2016.
2. MEDLINE (via Ovid) from 1946 to 14 June 2016.
3. Embase (via Ovid) from 1974 to 14 June 2016.

The search strategies for CENTRAL, MEDLINE, and Embase are listed in Appendix 2, Appendix 3, and Appendix 4, respectively.

Searching other resources

We reviewed the bibliographies of relevant studies and review articles, and searched two clinical trial registries, (ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)), to identify additional published or unpublished data. We contacted Janssen-Cilag Ltd who were able to clarify the publication status of the included study shortly before full publication. We did not contact investigators or other study sponsors.

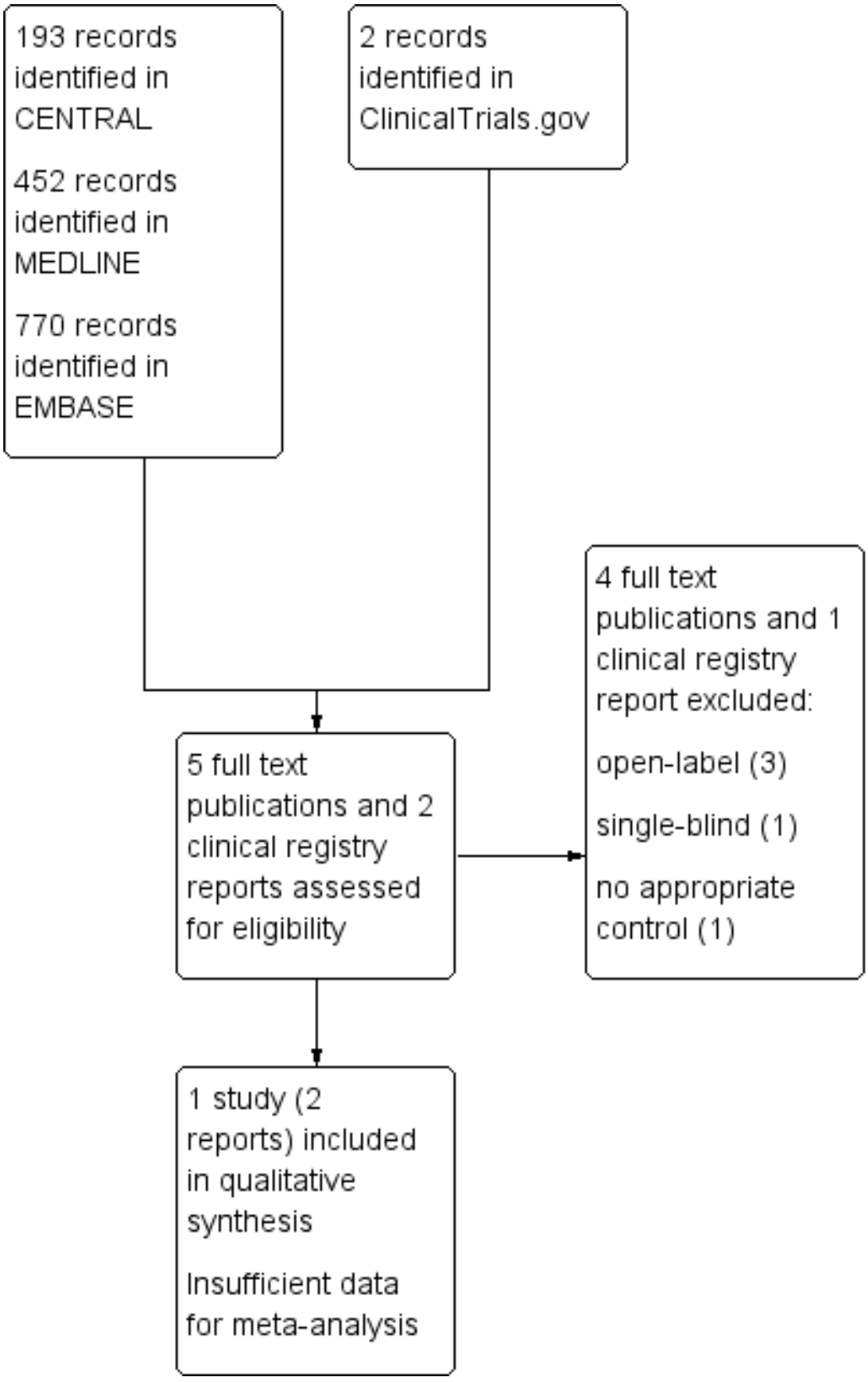
Data collection and analysis

We planned to perform separate analyses according to particular neuropathic pain conditions, combining different neuropathic pain conditions in analyses for exploratory purposes only.

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors made the decisions, reading these studies independently and reaching agreement by discussion. We did not anonymise the studies in any way before assessment. We have included a PRISMA flow chart (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors extracted data independently using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 2014) or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, control intervention, study design, 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 as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, 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.

1. 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, random number table, computer random number generator); unclear risk of bias (when the method used to generate the sequence is not clearly stated). We excluded 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 assessed the methods as: low risk of bias (telephone or central randomisation, consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when method was not clearly stated). We excluded 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 assessed 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 excluded 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 assessed the methods used to deal with incomplete data as: low risk of bias (fewer than 10% of participants did not complete the study, or used 'baseline observation carried forward' analysis (BOCF), 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 assessed 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 NNTs as the reciprocal of the absolute risk reduction (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 ratios (RRs) with 95% confidence intervals (CIs) 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 reflect efficacy and utility poorly, only if useful for illustrative purposes.

Unit of analysis issues

We accepted randomisation to the 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 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 would 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 with the use of the I^2 statistic. When the I^2 value was greater than 50%, we would consider possible reasons for this.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to patients with pain (Hoffman 2010; Moore 2010c; Moore 2010d; Moore 2010e; Moore 2013a). The review would not depend on what the authors of the original studies chose to report or not, though clearly difficulties would arise in studies that did not report any dichotomous results.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher; Moore 2008).

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. We planned to analyse data for each painful condition separately.

Quality of the evidence

We used the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 5; Chapter 12.2, Higgins 2011). Two

review authors independently rated the quality of evidence for each outcome.

We paid particular attention to:

1. inconsistency, where point estimates vary widely across studies, or CIs of studies show 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 a study used LOCF imputation in circumstances where there are 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 no data were reported for an outcome, we would report the level of evidence as very low quality (Guyatt 2013b).

'Summary of findings' table

We have included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we have included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of 'moderate' and 'substantial' benefit, withdrawal due to lack of efficacy, withdrawal due to adverse events, serious adverse events, and death.

Subgroup analysis and investigation of heterogeneity

We planned all analyses to be according to individual neuropathic pain conditions, because placebo response rates for the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009).

We did not plan subgroup analyses since our experience of previous reviews indicates that there would be too few data for any meaningful subgroup analysis (Gaskell 2014; McNicol 2013).

Sensitivity analysis

We planned no sensitivity analysis because the evidence base was known to be too small to allow reliable analysis. We planned to examine details of dose-escalation schedules in the unlikely situation that this could provide some basis for a sensitivity analysis, but this was not possible.

RESULTS

Description of studies

Results of the search

Searches identified 193 potentially relevant records in CENTRAL, 452 in MEDLINE, and 770 in Embase, and two in clinical trial registries. After deduplication and reading the titles and abstracts we obtained and read the full texts of five published records and two clinical trial registry reports. We excluded five studies, and included one (two reports) (Figure 1).

Included studies

We included one study, identified as a registry report (NCT01008553) and in a published pooled analysis (Arai 2015). This study used an enriched enrolment randomised withdrawal (EERW) design in which 258 participants underwent open-label titration over 10 to 29 days with fentanyl one-day patches to determine the maximum tolerated dose. It was not clear whether participants stopped or continued with previously inadequate medication.

Those who had pain intensity below 45/100 in the last three days of this open-label titration, an improvement from pre-treatment of at least 15/100, achieved a stable dosage of fentanyl, and required fewer than two doses per day of rescue medication, were classified as 'responders' (163 participants; 63% of those entering the open titration period) and were randomised to double-blind treatment with either the same dose of fentanyl or placebo for 12 weeks. Of 84 receiving fentanyl, 47 completed the 12 weeks, compared with 28/79 receiving placebo (Arai 2015).

Fentanyl was administered as a one-day patch, and all participants started with fentanyl 12.5 µg/h, increasing to a maximum of 50 µg/h over 10 to 29 days. Morphine hydrochloride was available as rescue medication (5 mg per fentanyl 12.5 µg/h).

Participants were opioid-naïve and had pain that was not adequately controlled with non-opioid analgesics. They were adults (mean age 67 years) with PHN (51%), CRPS (type not specified, 20%), or chronic postoperative pain (for a duration of 12 weeks or more, but no further details given; 29%). There were approximately equal numbers of men and women. Mean baseline pain intensity was 74/100 before treatment and 40/100 at the end of titration. For those entering the double-blind period, baseline pain was 30/100 in the fentanyl group and 28/100 in the placebo group.

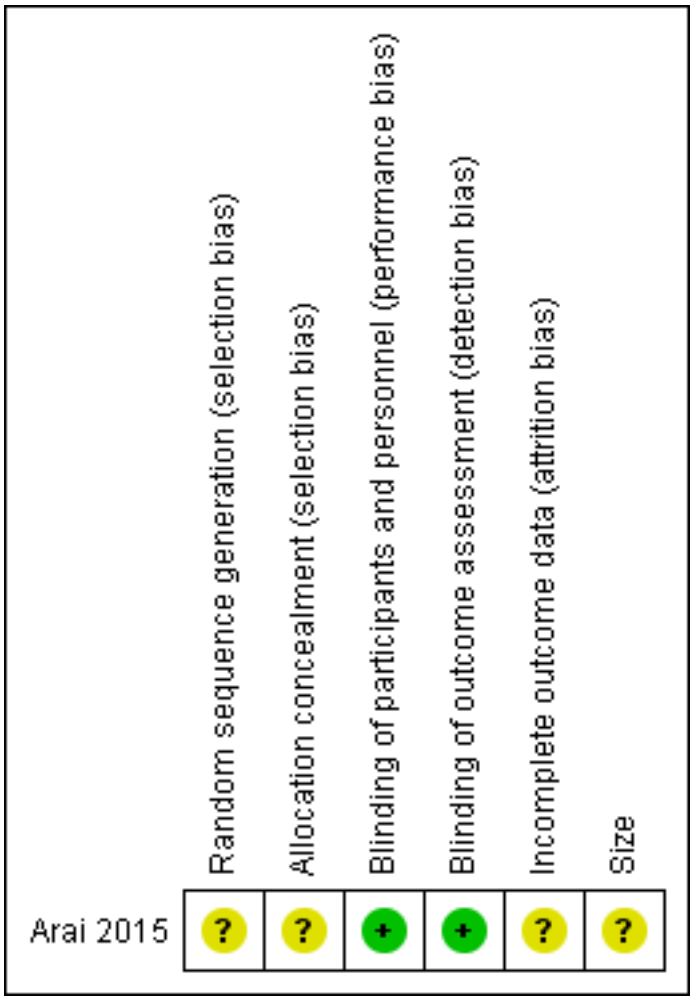
Excluded studies

We excluded five studies. Three were open-label studies, two of which were in mixed pain conditions, one was a single-blind study (ongoing), and one compared fentanyl with fentanyl plus gabapentin (no appropriate control). See the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 2 for a summary of our assessment of the risk of bias in the included study. Studies with EERW designs are likely to have additional sources of bias, or may require somewhat different assessments (Moore 2015), but we have not included those here.

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



Allocation

The study did not report the methods used to generate the randomisation sequence or to conceal allocation (unclear risk of bias).

Blinding

Blinding was achieved by using a placebo patch that was indistinguishable from the fentanyl patch. There was a period of down-titration for the placebo group, which would help to maintain the blinding (low risk of bias).

Incomplete outcome data

Study did not mention how missing data were handled. The study's primary outcome (median time to withdrawal) appears robust, but other outcomes are unclear.

Other potential sources of bias

We judged the study to be at unclear risk of bias due to its size (84 and 79 participants in treatment arms for the randomised phase).

Effects of interventions

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

Since we identified only one study for inclusion, we were unable to carry out any analyses.

Efficacy

Details of efficacy outcomes are provided in Appendix 6.

Participants with at least 30% or at least 50% pain relief

These outcomes were not reported.

PGIC much or very much improved

The study reported the participants' assessment of 'treatment satisfaction for pain' on a five-point scale (very dissatisfied, dissatisfied, neither satisfied or dissatisfied, satisfied, very satisfied) after the double-blind phase. We judged that the categories of 'satisfied' and 'very satisfied' approximate to our PGIC outcome of moderate benefit. In the fentanyl group, 49/84 (58%) participants were either satisfied or very satisfied, and corresponding data in the placebo group were 32/79 (41%). It is not clear how data from participants who withdrew due to adverse events were analysed for this outcome, but some form of imputation must have been used for participants who withdrew as the numbers are greater than the number who completed the study.

Other pain-related outcomes

The primary outcome chosen in the study was median time to withdrawal from the double-blind phase, where withdrawal occurred when there was worsening of pain of 15/100 (mean increase over three consecutive days) from entry into this phase, use of three or more doses of rescue medication per day for five or more days, the participant requested it because of a lack of efficacy, or the participant requested an increase in study drug dosage. The median time to withdrawal for the placebo group was 45 days, but could not be estimated for the fentanyl group because fewer than half the participants withdrew over the 12 weeks; the assumption must be that the median time to withdrawal was greater than 42 days.

The study did not report the number of participants who remained 'responders' at the end of the 12-week double-blind treatment period as a treatment outcome. However, Arai 2015 reports the number of participants completing the study (and therefore continuing on treatment) without an increase in pain of more than 15/100. For fentanyl, this was 47/84 (56%) and for placebo it was 28/79 (35%). The implication, then, is that because only 63% responded sufficiently to enter the randomised withdrawal phase, only a maximum of 35% of participants entering the study would have useful pain relief and tolerability with transdermal fentanyl, compared with 22% with placebo.

The group mean change (increase) in pain intensity from randomisation to the end of the double-blind phase (mean of last three days) was 0.5/100 (from 30.1 to 29.6) in the fentanyl group, and 9.6/100 (from 27.5 to 37.1) in the placebo group. This mean change is unlikely to be of clinical significance, but probably masks larger changes in some individuals. It is not clear how data from participants who withdrew during treatment were analysed for this outcome.

We downgraded the quality of the evidence for efficacy to very low because there was only one study, with a small number of participants, low numbers of events, and there was no information about how participants who withdrew from the study were analysed (see Summary of findings for the main comparison).

Withdrawals

Details of withdrawals are provided in Appendix 7.

Withdrawals due to lack of efficacy

Following the titration period, 50/258 participants were classified as non-responders to fentanyl. During the double-blind period, one participant taking fentanyl withdrew because of perceived lack of efficacy, and a further 18/84 were withdrawn because they experienced a greater than 15/100 increase in pain intensity. With placebo, 4/79 withdrew because of perceived lack of efficacy, and a further 35/79 were withdrawn because they experienced a greater than 15/100 increase in pain intensity.

Withdrawals due to adverse events

During titration 39/258 participants withdrew due to adverse events. During the double-blind period 14/84 participants taking fentanyl and 4/79 taking placebo withdrew due to adverse events.

Other withdrawals

During titration 12/258 participants withdrew because of physician (2) or participant (6) decision, participant was determined to increase dosage (3), and participant was considered not appropriate for the study (1). During the double-blind period 4/84 participants taking fentanyl withdrew due to physician (1) or participant (2) decision, and an inability to perform required tests (1), and 8/79 taking placebo withdrew due to physician (2) or participant (2) decision, and excessive use of rescue medication (4).

We downgraded the quality of the evidence for withdrawals to very low because there was only one study, with a small number of participants per treatment arm in the randomised withdrawal phase, and low numbers of events.

Adverse events

Details of adverse events are provided in Appendix 7.

Any adverse event

During the titration phase, 231/258 (90%) participants experienced at least one adverse event. During the double-blind phase, 72/84 (86%) and 56/79 (71%) participants experienced at least one adverse event with fentanyl and placebo, respectively. Generally, participants experienced fewer adverse events during the double-blind period.

Most adverse events were of mild or moderate intensity.

Serious adverse events

During the titration phase, 13/258 participants experienced a serious adverse event. During the double-blind phase, 8/84 and 4/79 participants experienced a serious adverse event with fentanyl and placebo, respectively. No serious adverse event occurred in more than one participant, and no deaths were reported.

Specific adverse events

Constipation (124/258), nausea (103/258), somnolence (118/258), and dizziness (52/258) were the most common adverse events reported during the titration period. As would be expected, the rates of these events were lower in the double-blind period. Among the 84 participants taking fentanyl in the double-blind phase, 12 reported constipation, 12 nausea, 12 somnolence, and 6 dizziness, and among 79 taking placebo, 10 reported constipation, 10 nausea, 5 somnolence, and 3 dizziness.

A small number of participants experienced application-site reactions during titration: pruritus (15/258), erythema (8/258), dermatitis (4/258), rash (3/258). Few participants in either group reported these events during the double-blind period.

We downgraded the quality of the evidence for adverse events to very low because there was only one study, with a small number of participants per treatment arm in the randomised withdrawal phase, and low numbers of events.

DISCUSSION

Summary of main results

We found only one study to include in this review. The study assessed the efficacy of fentanyl, using the transdermal route of

administration, for the treatment of neuropathic pain in opioid-naïve participants; 258 participants entered the dose-titration period, and 163 'responders' entered the double-blind phase. The results indicated a reduction in pain intensity with open-label fentanyl that was better maintained with fentanyl than placebo in the randomised, double-blind withdrawal period. However, during titration, 1 in 3 (101/258) participants withdrew overall, mainly due to intolerable adverse events (1 in 7; 39/258) or not achieving a sufficiently good level of pain relief to proceed to the double-blind phase (1 in 5; 50/258). Of those who did enter the double-blind phase, only about 1 in 2 (37/84) in the fentanyl group and 2 in 3 (51/79) in the placebo group maintained good pain relief and were able to tolerate adverse events over 12 weeks.

Taking the pool of participants originally recruited, therefore, after 12 weeks treatment a maximum of about 3 in 10 would have maintained low pain and continued with the treatment, compared with 2 in 10 with placebo.

Most (90%) participants experienced adverse events during the titration phase, and the majority continued to do so in the double-blind phase, although most participants experienced fewer events. Most adverse events were of mild or moderate intensity, and the most common were constipation, nausea, somnolence, and dizziness, which are typically associated with opioids.

Overall completeness and applicability of evidence

The amount of evidence we have is small, from a single study. Although participants had three different types of neuropathic pain, the study was underpowered to demonstrate a differential response. Participants were opioid-naïve at screening, so high numbers of adverse events and withdrawals are to be expected; lower levels might be seen in an unselected or opioid-tolerant population. Fentanyl patches are generally not recommended for opioid-naïve patients.

About half of participants had PHN, 20% had CRPS, and 29% had chronic postoperative pain at enrolment. The study did not specify CRPS type II as an inclusion criterion, and provided no further details about the nature of the surgery leading to postoperative pain. We have no information about the efficacy of fentanyl in other types of neuropathic pain, such as diabetic neuropathy, or about routes of administration other than transdermal, or comparisons with other active treatments. The particular formulation used in this study is not commonly used; in most countries a 72-hour (three-day) patch is available.

As best we know, there is insufficient evidence to support or refute the use of fentanyl for treating neuropathic pain. This is despite the fact that a UK survey found that weak and strong opioids were used frequently for treating neuropathic pain, either alone or in combination with other drugs (Hall 2013). The lack of evidence for long-term benefit with fentanyl reflects similar findings for oxycodone, buprenorphine, and other opioids (Gaskell 2014; McNicol 2013; Wiffen 2015). This lack of evidence of efficacy combined with substantial evidence of harm has led to calls for referral to a pain management specialist (ideally with expertise in opioid use) if daily dosing exceeds 80 to 100 mg morphine equivalents, particularly if pain and function are not substantially improved (Franklin 2014).

The number of participants in the single included study (258 screened, 163 in the randomised double-blind phase) contrasts with 1096 who participated in randomised open studies and 1393 in observational studies of various designs (Appendix 8). Despite there being 2489 participants in these studies, with chronic pain of mostly mixed origins, no useful conclusions can be drawn because of problems in design, in outcomes, and in comparators used. Although some people had useful pain relief with fentanyl, there is no additional evidence that the proportion would be any higher than with no treatment.

One study did provide a useful insight into the relative efficacy of transdermal fentanyl and oral pregabalin in neuropathic cancer pain (Raptis 2014). The study had a randomised but open parallel design and was conducted over four weeks with initial titration for both drugs; initial pain relief was high, about 7/10 on a numerical rating scale. Of 60 participants given transdermal fentanyl, 22 (37%) had pain intensity reduction of 30% or more. Of 60 participants given oral pregabalin, 44 (73%) had that degree of pain reduction. All-cause withdrawals were 10/60 for fentanyl and 3/60 for pregabalin. Pregabalin has a well-established evidence base in neuropathic pain (Moore 2009), and the evidence from this open, but otherwise well-conducted study, indicates fentanyl to be much less effective.

Quality of the evidence

The methods used in the included study are fundamentally sound, but the study is substantially underpowered, particularly for the randomised, double-blind, withdrawal phase, and does not specify the imputation method(s) used for withdrawals (Moore 2015). It does not report the most useful outcome from the double-blind phase, the number of participants who maintained therapeutic efficacy and were able to continue taking the medication (with tolerable adverse events), although we were able to estimate this.

These factors downgrade the evidence for all outcomes to very low quality, which means that further research is very likely to have an important impact on our confidence in our understanding of the effect.

Potential biases in the review process

We know of no potential biases in the review process. It is unlikely that there is a large body of unpublished evidence showing a large effect from fentanyl in neuropathic pain.

Agreements and disagreements with other studies or reviews

This review agrees with previous reviews and Cochrane reviews that there appears to be no body of good clinical studies assessing the efficacy of fentanyl, at any dose or in formulation, for neuropathic pain (McNicol 2013). The one study in this review was published after McNicol 2013. A recent review of all pharmacotherapy for neuropathic pain in adults did not mention fentanyl (Finnerup 2015).

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

There is insufficient evidence to support or refute the suggestion that fentanyl has any efficacy in any neuropathic pain condition.

For clinicians

There is insufficient evidence to support or refute the suggestion that fentanyl has any efficacy in any neuropathic pain condition.

For policy makers

There is insufficient evidence to support or refute the suggestion that fentanyl has any efficacy in any neuropathic pain condition. 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 insufficient evidence to support or refute the suggestion that fentanyl has any efficacy in any neuropathic pain condition. 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

Large, robust, randomised trials with patient-centred outcomes would be required to produce evidence to support or refute the efficacy of fentanyl in neuropathic pain. The necessary design of such trials is well established, but, for opioids in neuropathic pain, the main outcomes should be those of at least a 30% and at least a 50% reduction in pain intensity over baseline at the end of a trial of 12 weeks' duration in participants continuing on treatment. Withdrawal for any reason should be regarded as treatment failure, and LOCF analysis should not be used. The reason for this is that, in chronic pain, opioids frequently produce withdrawal rates of 50% or more, meaning that LOCF analysis can overstate treatment efficacy to a large extent. BOCF should be used in preference to LOCF as it provides a more relevant estimate of efficacy for the real world.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arai 2015

Methods	Study N02. Multicentre, EERW, open-label titration phase (10 to 29 days), and parallel group, double-blind withdrawal phase (12 weeks)
Participants	PHN, CRPS, postoperative pain syndrome > 12 weeks, mean PI > 50/100, opioid-naïve, inadequate PR with non-opioid analgesics Excluded: pain from other causes, asthma, bradyarrythmia, severe respiratory function disorders, hepatic dysfunction, renal impairment, hypersensitivity to fentanyl or other opioids N = 258 (titration phase) M 134, F 124 Mean age 67 years (SD 14) Mean baseline PI 74/100 (SD 13) N = 163 (double-blind phase) M 83, F 80 Mean age 67 years (SD 14) Mean baseline PI 29/100 (SD 11)
Interventions	Titration phase: fentanyl 1-day adhesive patch 12.5 µg/h for minimum 2 days. Increased by 12.5 µg/h based on VAS PI and use of rescue medication to maximum 50 µg/h, over 10 to 29 days Double-blind phase: Fentanyl 1-day adhesive patch 12.5 to 50 µg/h, n = 84 Placebo patch, n = 79 Patches applied to chest abdomen, upper arm or thigh, replaced every day for 12 weeks Rescue medication: morphine hydrochloride (5 mg per fentanyl 12.5 µg/h)
Outcomes	Participants responding during titration period Median time to withdrawal due to loss of analgesic efficacy Median change in PI from randomisation to last 3 days of double-blind period (VAS) Satisfaction scores
Notes	Oxford Quality Score: R1, DB2, W1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo patch indistinguishable from one-day adhesive transdermal patch containing fentanyl"

Arai 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Placebo patch indistinguishable from one-day adhesive transdermal patch containing fentanyl"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analyses used full analysis set, but no mention of imputation methods. Study's primary outcome seems robust, but other outcomes unclear
Size	Unclear risk	50 to 199 participants per treatment arm

CRPS: complex regional pain syndrome; DB: double-blind; EERW: enriched enrolment randomised withdrawal; F: female; M: male; N: number of participants in study; n: number of participants in treatment arm; PHN: postherpetic neuralgia; PI: pain intensity; PR: pain relief; R: randomised; SD: standard deviation; VAS: visual analogue scale; W: withdrawals.

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

Study	Reason for exclusion
Canneti 2013	Open-label study
Ding 2014	Compares fentanyl with fentanyl + gabapentin
Kalso 2007	Open-label, mixed conditions, secondary analysis of Allan 2005
NCT01127100	Single-blind (outcomes assessor), ongoing study
Park 2010	Open-label cohort, mixed conditions

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may report only participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, 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 the 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 2010d), and arthritis (Moore 2010e), 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.
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 of less than 12 weeks' duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010d); 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 2010e; Moore 2013b; Moore 2014c; Straube 2008; Sultan 2008). One 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 reasons for doing so.

4. Individual patient analyses 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 2010c; Moore 2014a).
5. 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).

Appendix 2. Search strategy for CENTRAL via CRSO

1. MESH DESCRIPTOR Neuralgia EXPLODE ALL TREES (610)
2. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES (2590)
3. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (710)
4. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)):TI,AB,KY (3306)
5. ((neur* or nerv*) adj6 (compress* or damag*)):TI,AB,KY (635)
6. 1 OR 2 OR 3 OR 4 OR 5 (6357)
7. MESH DESCRIPTOR Fentanyl EXPLODE ALL TREES (3897)
8. (fentanyl or fentanil* or Abstral or Actiq or DTrans or Durogesic or Fentalis or Matrifen or Mezolar or Osmanil or Sublimaze or Tilofyl or Victanyl):TI,AB,KY (9907)
9. 6 AND 9 (193)

Appendix 3. Search strategy for MEDLINE via Ovid

1. exp NEURALGIA/ (15118)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (124585)
3. exp SOMATOSENSORY DISORDERS/ (17961)
4. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (43123)
5. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (52215)
6. 1 or 2 or 3 or 4 or 5 (200106)
7. Fentanyl/ (11986)
8. (fentanyl or fentanil* or Abstral or Actiq or DTrans or Durogesic or Fentalis or Matrifen or Mezolar or Osmanil or Sublimaze or Tilofyl or Victanyl).mp. (17707)
9. 7 or 8 (17707)
10. randomized controlled trial.pt. (417624)
11. randomized.ab. (309508)
12. placebo.ab. (159698)
13. drug therapy.fs. (1862631)
14. randomly.ab. (219030)
15. trial.ab. (322047)
16. groups.ab. (1378466)
17. 10 or 11 or 12 or 13 or 14 or 15 or 16 (3483323)
18. 6 and 9 and 17 (452)

Appendix 4. Search strategy for Embase via Ovid

1. exp NEURALGIA/ (81076)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (55241)
3. exp SOMATOSENSORY DISORDERS/ (72226)
4. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (80613)
5. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (73746)
6. 1 or 2 or 3 or 4 or 5 (294021)
7. Fentanyl/ (50046)
8. (fentanyl or fentanil* or Abstral or Actiq or DTrans or Durogesic or Fentalis or Matrifen or Mezolar or Osmanil or Sublimaze or Tilofyl or Victanyl).mp. (54103)
9. 7 or 8 (54103)
10. random*.ti,ab. (1042778)
11. factorial*.ti,ab. (26694)

12.(crossover* or cross over* or cross-over*).ti,ab. (79506)
13.placebo*.ti,ab. (230284)
14.(doubl* adj blind*).ti,ab. (163796)
15.assign*.ti,ab. (276944)
16.allocat*.ti,ab. (99797)
17.RANDOMIZED CONTROLLED TRIAL.sh. (390913)
18.DOUBLE-BLIND PROCEDURE.sh. (127382)
19.CROSSOVER PROCEDURE.sh. (45369)
20.10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1482600)
21.6 and 9 and 20 (770)

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

- **High**: randomised trials; or double-upgraded observational studies.
- **Moderate**: downgraded randomised trials; or upgraded observational studies.
- **Low**: double-downgraded randomised trials; or observational studies.
- **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

1. limitations in the design and implementation of available studies suggesting high likelihood of bias;
2. indirectness of evidence (indirect population, intervention, control, outcomes);
3. unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
4. imprecision of results (wide confidence intervals);
5. high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

1. large magnitude of effect;
2. all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
3. dose-response gradient.

Appendix 6. Summary of outcomes: efficacy

Study	Treatment	Pain outcome	Other efficacy outcome
Arai 2015	**Titration**: Fentanyl 1-day patch, 12.5 to 50 µg/h **Randomised withdrawal**: (1) Fentanyl patch (titrated dose) (2) Placebo (down-titration)	**Titration**: 163/258 completed Mean PI reduced from 73.5 (SD 12.8) to 39.5 (20.0) (mean of last 3 days) (scale 0 to 100) **Randomised withdrawal**: Mean change in PI from randomisation to last 3 days of double-blind period (scale 0 to 100) (1) 0.5 (30.1, SD 11.5 to 29.6, SD 21.7) (2) 9.6 (27.5, SD 11.2 to 37.1, SD 20.2) PGIC (satisfied, very satisfied with pain treatment; 5-point scale) (1) 49/84 (2) 32/79	**Randomised withdrawal**: Median time to withdrawal due to insufficient analgesic efficacy (1) not estimated (2) 45 days Use of rescue medication (mean doses/day) (1) 0.4 (SD 0.68) (2) 0.7 (SD 0.86) Measures of health disability using SF-36 did not change substantially during treatment

(Continued)

PGIC: Patient Global Impression of Change; PI: pain intensity; SD: standard deviation; SF-36: Short-Form 36-Item Health Survey

Appendix 7. Summary of outcomes: adverse events and withdrawals

Study	Treatment	Adverse events	Serious AEs	Withdrawals
Arai 2015	**Titration**: Fentanyl 1-day patch, 12.5 to 50 µg/h **Randomised withdrawal**: (1) Fentanyl patch (titrated dose) (2) Placebo (down titration)	**Titration**: Any AE 231/258 (most mild or moderate) Most common were: constipation (124/258), nausea (103/258), somnolence (118/258), and dizziness (52/258) Application-site reactions during titration: pruritus (15/258), erythema (8/258), dermatitis (4/258), rash (3/258) **Randomised withdrawal**: (1) 72/84 (2) 56/79 Most mild or moderate Fentanyl: 12 reported constipation, 12 nausea, 12 somnolence, and 6 dizziness Placebo: 10 reported constipation, 10 nausea, 5 somnolence, and 3 dizziness Few participants in either group reported application site reactions during the double-blind period	No deaths reported **Titration**: 13/258 **Randomised withdrawal**: (1) 8/84 (2) 4/79	**Titration**: AE: 39/258 Participant decision: 6/258 Physician decision: 2/258 Participant determined to increase dose: 3/258 Participant not appropriate for study: 1/258 Non-responders: 50/258 **Randomised withdrawal**: Fentanyl: 37/84 AE: 14/84 LoE: 1/84 > 15/100 increase in PI: 18/84 Physician or participant decision: 3/84 Other: 1/84 Placebo: 51/79 AE: 4/79 LoE: 4/79 > 15/100 increase in PI: 35/79 Physician or participant decision: 4/79 Other: 4/79

AE: adverse event; LoE: lack of efficacy; PI: pain intensity

Appendix 8. Details of studies of fentanyl not included in this review

Study	Participants	Design and duration	Number	Intervention	Efficacy data	Adverse event data
Randomised open studies						
Allan 2001	CNCP requiring strong opioids Moderate control	Randomised, open, cross-over	N = 256	TD fentanyl compared with CR morphine	212/251 assessed for preference: fentanyl 65%	More withdrawals (38 vs 22) and AE withdrawals (27 vs 10) with fentanyl More nausea, less constipation with fentanyl

(Continued)

	with oral opioids	2 x 4 weeks			morphine 28% no preference 7% Mean pain score lower with fentanyl (58/100 vs 63/100) Better satisfaction with fentanyl	
Allan 2005	CLBP naïve to strong opioid	Randomised, open, parallel 13 months	N = 680	TD fentanyl compared with CR morphine	Similar pain relief, less constipation with fentanyl	Similar numbers completed (48% vs 53%) AE withdrawals: 125 fentanyl, 104 morphine LoE withdrawals: 18 fentanyl, 15 morphine
Canneti 2013	Peripheral neuropathic pain with advanced AIDS	Randomised, open, parallel 12 months	N = 40	TD fentanyl compared with TD buprenorphine	Mean PI reduced significantly in both groups Buprenorpine slightly better	Both well tolerated
Raptis 2014	Neuropathic cancer pain	Randomised, open, parallel 4 weeks	N = 120	TD fentanyl compared with pregabalin Increasing doses over 4 weeks	≥ 30% PI reduction: pregabalin 73%, fentanyl 37% % mean change from baseline: pregabalin 46%, fentanyl 22% Participant satisfaction more frequent with pregabalin	AEs more frequent with fentanyl (34 vs 16) Most common: nausea, somnolence, dizziness with fentanyl, nausea, somnolence with pregabalin AE withdrawals: fentanyl 10/60, pregabalin 3/60
Observational studies						
Agarwal 2007	Peripheral neuropathic pain, CRPS type I, postamputation pain PI ≥ 3/10	Open, cohort 16 weeks	N = 53 51 entered titration 44 entered maintenance 40 completed	TD fentanyl (3-day) 6-week titration 25-150 µg/h 8-week maintenance Stable, non-opioid medicines continued, opioid wash out	> 30% pain reduction: 30/53 > 50% pain reduction: 21/53 Mean reduction in PI (0 to 10): 2.94 ± 0.27 % pain relief: 34 ± 14% (48% in completers) Increase in average daytime activity: 37%	Drowsiness (47%) Nausea/vomiting (28%) Constipation (9%) Skin reactions (9%) Withdrawals due to AEs
Dellemijn 1998	Neuropathic pain - mixed	Open-label extension 24 months	N = 48	TD fentanyl - titrated over 12 weeks to max 100 µg/h or max tolerated Then tapered by 25 µg/h weekly, and		12-week dose escalation period: 16 withdrawals due to LoE, AEs 17/30 who completed chose not to continue with extension (AEs not justified by benefit (13), pain relief persisted (4))

(Continued)

				substituted with morphine SR 60 mg/d, tapering over 10 days 2 weeks with no opioid, then offered 2-year extension		3 discontinued in first year, 1 in second year Sedation, nausea, constipation most frequent AEs
Franco 2002	CNCP	Open-label, observational 6 months	N = 236 (120 neuropathic pain)	TD fentanyl	34% participants had PI < 3/10 after 6 months. Greatest reduction in PI in first 3 months	Somnolence, vomiting, dizziness most common AEs
Milligan 2001	CNCP moderate or severe	Open-label, observational 12 months	N = 532 *103 participated in Allan 2001	TD fentanyl	67% had ≥ moderate pain control on treatment Global satisfaction 42%	231 withdrew: 130 due to AEs, 39 LoE (most in first few months) Nausea, constipation, somnolence most common
Mitra 2011	Persistent pain - mixed	Open-label, observational 12 months	N = 46	TD fentanyl vs TD buprenorphine	Equivalent for efficacy Tolerance after 6 months	More AE withdrawals with fentanyl early on, buprenorphine later
Mystakidou 2003	CNCP	Open-label, observational Long-term - up to 4 years for a few participants	N = 529	TD fentanyl	Improvements in pain and QoL Median duration of effective pain management 10 months No difference between NP and nociceptive	55 withdrew, all but one within 4 weeks. 24 AE withdrawals, 24 LoE withdrawals Constipation, nausea, sleepiness most common
Park 2011	CNCP (most NP), requiring opioids PI moderate or severe	Open-label, observational	N = 65 41 evaluated	TD fentanyl titrated 12 weeks	Mean PI decreased by 62% (6.7/10 to 2.6/10)	24 withdrawals: 1 LoE, 18 AE Nausea, dizziness, drowsiness, constipation, vomiting most common

AE: adverse event; CLBP: chronic low back pain; CNCP: chronic non-cancer pain; CR: controlled release; CRPS: complex regional pain syndrome; LoE: lack of efficacy; N: number of participants in study; NP: neuropathic pain; PI: pain intensity; QoL: quality of life; SR: sustained release TD: transdermal

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol.

SD and PC 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

SD: none known.

CS: none known. She is a specialist pain physician and manages patients with chronic pain.

PC received support from Boston Scientific (2014) for travel and accommodation at a scientific meeting; Boston Scientific does not market drugs. PC is a specialist pain physician and manages patients with chronic pain.

PW: none known.

RK has consulted for Grunenthal Ltd (2014-15) and MundiPharma Research (2015), and received lecture fees from Grunenthal Ltd (2013-14) and Pfizer Ltd (2013-14). He is an Associate Professor in Clinical Pharmacy Practice and Advanced Pharmacy Practitioner.

DA has received lecture fees from Grünenthal (2013, 2014, 2015) and Pfizer (2013, 2016). He is a specialist pain physician and manages patients with chronic pain.

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 about the design of network meta-analyses (2014), and RB on understanding the pharmacokinetics of drug uptake (2015).

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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

In the protocol the inclusion criteria included both CRPS types I and II as a diagnosis of neuropathic pain. We have now removed CRPS type I because it is no longer considered to be neuropathic pain. We identified no studies in CRPS type I.

NOTES

No new studies likely to change the conclusions are expected. 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.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Fentanyl [*therapeutic use]; Neuralgia [*drug therapy]; Pain Measurement; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male