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Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults (Review)

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[Intervention Review]

Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults

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ABSTRACT

Background

Paracetamol, either alone or in combination with codeine or dihydrocodeine, is commonly used to treat chronic neuropathic pain. This review sought evidence for efficacy and harm from randomised double-blind studies.

Objectives

To assess the analgesic efficacy and adverse events of paracetamol with or without codeine or dihydrocodeine for chronic neuropathic pain in adults.

Search methods

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

Selection criteria

We included randomised, double-blind studies of two weeks' duration or longer, comparing paracetamol, alone or in combination with codeine or dihydrocodeine, 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

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 have no reliable indication of the likely effect.

Authors' conclusions

There is insufficient evidence to support or refute the suggestion that paracetamol alone, or in combination with codeine or dihydrocodeine, works in any neuropathic pain condition.

PLAIN LANGUAGE SUMMARY

Paracetamol (acetaminophen) alone, or in combination with codeine or dihydrocodeine, for neuropathic pain in adults

Bottom line

There is no good evidence to support or refute the suggestion that paracetamol alone, or in combination with codeine or dihydrocodeine, works in any neuropathic pain condition.

Background

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (e.g. a fall or cut, or arthritic knee). Neuropathic pain is often treated by different medicines (drugs) to those used for pain from damaged tissue, which we often think of as painkillers. Medicines that are sometimes used to treat depression or epilepsy (fits) can be very effective in some people with neuropathic pain. But sometimes paracetamol is used to treat neuropathic pain, either by itself or with the opioid painkillers codeine or dihydrocodeine.

Paracetamol has been widely available for over 50 years. There is evidence it works as a painkiller in some short-lived pains, but it does not appear to work well for long lasting pains. We do not really know how it works. Paracetamol is commonly used combined with opioid drugs.

Opioid painkillers are drugs like morphine. Morphine is derived from plants, but many opioids are also made in a laboratory rather than being extracted from plants. Codeine and dihydrocodeine are often combined with paracetamol.

Study characteristics

In July 2016, we searched for clinical trials where paracetamol alone, or in combination with codeine or dihydrocodeine, was used to treat neuropathic pain in adults. We found no studies that met our requirements for the review.

Key results

Because there were no studies that could answer the questions in a reliable way, we cannot say whether paracetamol alone, or in combination with codeine or dihydrocodeine, works for chronic neuropathic pain.

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 impact of paracetamol alone, or in combination with codeine or dihydrocodeine, in any neuropathic pain condition.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine compared with placebo for neuropathic pain						
Patient or population: adults with chronic neuropathic pain Settings: community Intervention: paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine Comparison: placebo						
Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR (95% CI)	No of studies, participants	Certainty 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 for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine
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 for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine
Lack of efficacy withdrawal	No data	No data	Not calculated	No data	Very low	No trials found for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine
Adverse event withdrawal	No data	No data	Not calculated	No data	Very low	No trials found for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine
Serious adverse events	No data	No data	Not calculated	No data	Very low	No trials found for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine

Deaths	No data	No data	Not calculated	No data	Very low	No trials found for paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine
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CI: confidence interval; PGIC: Patient Global Impression of Change; RR: risk ratio

Descriptors for levels of evidence (EPOC 2015):

High quality: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[†] is low.

Moderate quality: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[†] is moderate.

Low quality: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[†] is high.

Very low quality: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[†] is very high.

[†] Substantially different: a large enough difference that it might affect a decision

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; Moore 2012; 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 based on a definition agreed at an earlier consensus meeting (Treede 2008). Neuropathic pain is a consequence of a pathological maladaptive response of the nervous system to ‘damage’ from a wide variety of potential causes. It is characterised by pain in the absence of a noxious stimulus and may be spontaneous (continuous or paroxysmal) in its temporal characteristics or be evoked by sensory stimuli (dynamic mechanical allodynia where pain is evoked by light touch of the skin). Neuropathic pain is associated with a variety of sensory loss (numbness) and sensory gain (allodynia) clinical phenomena, the exact pattern of which vary between people and disease, perhaps reflecting different pain mechanisms operating in an individual person and, therefore, potentially predictive of response to treatment (Demant 2014; Helfert 2015; von Hehn 2012). Preclinical research hypothesises a bewildering array of possible pain mechanisms that may operate in people with neuropathic pain, which largely reflect pathophysiological responses in both the central and peripheral nervous systems, including neuronal interactions with immune cells (Baron 2012; Calvo 2012; von Hehn 2012). Overall, the treatment gains in neuropathic pain, to even the most effective of available drugs, are modest (Finnerup 2015; Moore 2013a), and a robust classification of neuropathic pain is not yet available (Finnerup 2013).

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.

Many people with neuropathic pain conditions are significantly disabled with moderate or severe pain for many years. Chronic pain conditions comprised five 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).

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 are increasing, particularly PDN and postsurgical chronic pain (which is often neuropathic in origin) (Hall 2008). The prevalence of PHN is likely to fall if vaccination against the herpes virus becomes widespread.

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 (95% CI 26 to 29) for trigeminal neuralgia, 0.8 (95% CI 0.6 to 1.1) for phantom limb pain, and 21 (95% CI 20 to 22) for PDN (Hall 2008). Other studies have estimated an incidence of 4 in 100,000 per year for trigeminal neuralgia (Katusic 1991; Rappaport 1994), and 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 (NSAID) are not thought to be effective, but without evidence to support or refute that view. 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 2013a). Treatment is often by so-called ‘unconventional analgesics’ (pain modulators) such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2014b; Moore 2015; Sultan 2008), or antiepileptic drugs (gabapentin or pregabalin; Moore 2009; Moore 2014c; Wiffen 2013).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013b) 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 2013a). 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 2013a).

The current National Institute for Health and Care Excellence (NICE) guidance for the pharmacological management of neuropathic pain suggests offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (except for trigeminal neuralgia), with switching if the first, sec-

ond, or third drugs tried are not effective or not tolerated (NICE 2013). This concurs with other recent guidance (Finnerup 2015).

Description of the intervention

Paracetamol (acetaminophen) is available in a very large number of formats and products with different names, including Panadol and Tylenol. Paracetamol plus codeine often comes with the generic name co-codamol, and paracetamol plus dihydrocodeine as co-dydramol. A listing of brand names by country is available but the list is too long to be given here (Drugs.com 2016). Paracetamol use is measured in thousands of tonnes, and questions have been asked about the benefits and risk of such extensive use (Moore 2016).

Paracetamol was first identified as the active metabolite of two older antipyretic drugs, acetanilide and phenacetin, in the late nineteenth century (Axelrod 2003). Since then it has become one of the most popular antipyretic and analgesic drugs worldwide, and is often also used in combination with other drugs. It became available in the UK on prescription in 1956, and without prescription (over-the-counter) in 1963 (PIC 2015). Nonprescription medications are less expensive, more accessible, and have favourable safety profiles relative to many prescription treatments.

Despite a low incidence of adverse effects, paracetamol has a recognised potential for hepatotoxicity and is thought to be responsible for approximately half of all cases of liver failure in the UK (Hawton 2001), and about 40% in the US (Norris 2008). One study evaluating all cases of acute liver failure leading to registration for transplantation (ALFT) across seven European countries for a three-year period showed that paracetamol overdose was responsible for one sixth of cases of ALFT, though this varied considerably between each country (Gulmez 2015). Acute paracetamol hepatotoxicity at therapeutic doses has been judged to be extremely unlikely, despite reports of so-called 'therapeutic misadventure' (Prescott 2000). However, it has been observed that non-overdose ALFT is more likely to follow therapeutic-dose paracetamol exposure than similar NSAID exposure (Gulmez 2013). Legislative changes have been introduced in the UK to restrict pack sizes and the maximum number of tablets permitted in nonprescription sales (CSM 1997) on the basis of evidence that poisoning is lower in countries that restrict availability (Gunnell 1997; Hawton 2001). The contribution of these changes, which were inconvenient and costly (particularly to people with chronic pain), to any observed reductions in incidence of liver failure or death, remains uncertain (Bateman 2014a; Bateman 2014b; Hawkins 2007; Hawton 2013). There have been concerns over the safety of paracetamol in people with compromised hepatic function (people with severe alcoholism, cirrhosis, or hepatitis), but these have not been substantiated (Dart 2000; PIC 2015).

The use of paracetamol during pregnancy has been questioned following reports that it is linked to behavioural problems and hyperkinetic disorders in children whose mothers took it during

pregnancy (Liew 2014), and suggestions that it can interfere with sex hormones (Mazaud-Guittor 2013).

In an analysis of single dose studies in migraine, there was no evidence that adverse events were more common with paracetamol 1000 mg than with placebo, and no serious adverse events occurred with paracetamol alone (Derry 2013b).

Oral paracetamol has long been used as a first-line analgesic for a variety of acute and chronic conditions. It has modest efficacy in acute pain and migraine (Derry 2013b; Toms 2008), although some randomised trials, systematic reviews, and meta-analyses have suggested that there is no good evidence for a clinically relevant benefit of paracetamol (as monotherapy) in many chronic pain conditions such as osteoarthritis and back pain (Machado 2015; Moore 2014d; Williams 2014). There are few or no data for a range of other common painful conditions, including dysmenorrhoea and neck pain. Moreover, accumulating evidence from observational studies indicates a considerable degree of paracetamol toxicity, especially at the upper end of standard analgesic doses (Roberts 2016).

Oral paracetamol in fixed-dose combination with codeine or dihydrocodeine are frequently used in treating people with neuropathic pain (Hall 2013). There is good evidence showing that paracetamol plus codeine combinations are effective in acute pain (Toms 2009), but limited evidence for cancer pain (Straube 2014). Dihydrocodeine was not effective in acute postoperative pain (Moore 2000), and there is very little evidence on its efficacy in other pain conditions. Codeine is not effective in acute postoperative pain (Derry 2010). There is current uncertainty about the efficacy of opioids in chronic noncancer pain because of the influence of imputation methods where there are high levels of participant withdrawals in trials, and also in clinical practice. Reviews of oxycodone and buprenorphine for neuropathic pain have found no evidence of efficacy (Gaskell 2014; Wiffen 2015).

How the intervention might work

Paracetamol

The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of NSAIDs; yet, despite years of use and research, the mechanisms of action of paracetamol are not fully understood. NSAIDs act by inhibiting the activity of cyclo-oxygenase (COX), now recognised to consist of two isoforms (COX-1 and COX-2), which catalyses the production of prostaglandins responsible for pain and inflammation. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but is now being considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis', wherein the efficacy

of paracetamol is attributed to its specific inhibition of a third COX isoform enzyme, COX-3 (Borring 2000; Chandrasekharan 2002), now has little credibility, and a central mode of action of paracetamol is thought to be likely (Graham 2005). Paracetamol metabolism is subject to genetic variation (Zhao 2011).

There is some experimental research in rats to suggest that paracetamol may have an effect in neuropathic pain via cannabinoid receptors (Curros-Criado 2009; Dani 2007). One single case report suggested intravenous paracetamol was effective for phantom limb pain (Gulcu 2007).

Codeine and dihydrocodeine

Codeine and dihydrocodeine are opioids.

The analgesic effects of codeine are attributed to its metabolism in the liver to the active compounds morphine and morphine-6-glucuronide. Normally between 5% and 10% is converted to morphine, and a dose of codeine phosphate of about 30 mg is considered equivalent to morphine 3 mg. However, the capacity to metabolise codeine to its active metabolites varies between people, with up to 10% of white people, 2% of Asian people, and 1% of Arabic people being 'poor metabolisers'. In these people, codeine is a relatively ineffective analgesic. The enzyme CYP2D6 is a member of the cytochrome P450 mixed-function oxidase system enzymes, and one of the most important enzymes involved in the metabolism of xenobiotics in the body. Due to genetic variability in the CYP2D6 enzyme, up to 40% of people in some societies are 'ultra-metabolisers' and are able to convert more of the codeine to morphine, putting them at increased risk of toxicity from standard doses (Sistonen 2007). Various medications interfere with the enzymes that catalyse the metabolism of codeine, increasing or decreasing the extent of conversion and hence the analgesic effect. For example, the selective serotonin reuptake inhibitors fluoxetine and paroxetine reduce conversion, while rifampicin and dexamethasone increase it. The US and Canada issued warnings about the potentially life-threatening adverse effects in infants of breastfeeding mothers taking codeine, in 2007 (US) and 2008 (Canada), and this has led to reductions in codeine use in the postpartum period (Smolina 2015).

Dihydrocodeine is a synthetic opioid analgesic developed in the early 1900s. Its structure and pharmacokinetics are similar to that of codeine (Rowell 1983), and it has been infrequently used for the treatment of postoperative pain or as an antitussive. Dihydrocodeine analgesia seems not to be linked to metabolism through CYP2D6 activity, because the parent compound has analgesic effects, there are multiple metabolic pathways, and there is a limited role of dihydromorphine (Leppert 2016).

Why it is important to do this review

Paracetamol, alone or in fixed dose combination with codeine or dihydrocodeine, was one of the most commonly used first-line

treatments for neuropathic pain conditions such as PHN (27% of patients), PDN (17%), neuropathic low back pain (37%), or even phantom limb pain (13%) (Hall 2013). We found no previous review of paracetamol or paracetamol in combination with opioids for treating neuropathic pain. Paracetamol combined with an opioid is considered a reasonable treatment for breakthrough pain occurring with neuropathic pain treatment in one Canadian guideline (Moulin 2014), but it is not suggested as a treatment in other guidelines (NICE 2013) or reviews (Finnerup 2015).

The standards used to assess evidence in chronic pain trials have changed 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. Pain intensity reduction of 50% or more correlates with improvements in comorbid symptoms, function, and quality of life generally (Moore 2013a), and in people with neuropathic pain (Hoffman 2010). These standards are set out in the *PaPaS Author and Referee Guidance* for pain studies of the Cochrane Pain, Palliative and Supportive Care Group (PaPaS 2012).

This Cochrane review assessed evidence using methods that make both statistical and clinical sense, using developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed must have met a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc.), and size. Ideally at least 500 participants are needed in a comparison in which the NNT is 4 or above to measure the magnitude of a treatment effect adequately (Moore 1998). This approach sets high standards for the demonstration of efficacy and marks a departure from how reviews were conducted previously.

OBJECTIVES

To assess the analgesic efficacy and adverse events of paracetamol with or without codeine or dihydrocodeine for chronic neuropathic pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs) 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, except for online clinical trial results summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We excluded short abstracts (usually meeting reports). We excluded studies that were nonrandomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies included 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. 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.

We planned to analyse included studies of participants with more than one type of neuropathic pain according to the primary condition.

Types of interventions

Oral paracetamol with or without codeine or dihydrocodeine, at any dose, 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 or visual analogue scale) 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 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).

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 patient, 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 CRSO) on 7 July 2016;
2. MEDLINE (via Ovid) from 1946 to 7 July 2016;
3. Embase (via Ovid) from 1974 to 7 July 2016;
4. Oxford Pain Relief Database (Jadad 1996a).

The search strategies for CENTRAL, MEDLINE, and Embase are in Appendix 3, Appendix 4, and Appendix 5, respectively.

Searching other resources

We reviewed the bibliographies of any RCTs identified and review articles, and searched clinical trial databases (ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)) to identify additional published or unpublished data (to 7 June 2016). We did not plan to contact investigators or study sponsors.

Data collection and analysis

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

We planned to perform analyses separately for paracetamol alone, paracetamol plus codeine, and paracetamol plus dihydrocodeine according to daily dose of drug used.

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 we obtained full copies of the remaining studies for further consideration. Two review authors (RAM and SD) read studies independently and reached agreement by discussion. We did not anonymise the studies before assessment. We have provided a PRISMA flow chart.

Data extraction and management

Two review authors (RAM, SD) planned to extract data independently using a standard form and check for agreement before entry into Review Manager 5 (RevMan 2014), or any other analysis tool. We resolved disagreements by discussion, involving a third review author (PW), if necessary. 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 1996b), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors (SD, RAM) planned to independently assess 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 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 planned to exclude studies at a high risk of bias that used a nonrandom 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 the method was not clearly stated). We planned to exclude studies that did not conceal allocation and were therefore at a high risk of bias (open list).

3. Blinding of participants and personnel (checking for possible performance bias), and 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, used 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 planned 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 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, or both); unclear risk of bias (used 'last observation carried forward' (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 the number needed to treat for an additional beneficial outcome (NNT) as the reciprocal of the absolute risk reduction (ARR; McQuay 1998). For unwanted effects, the number needed to treat 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 Data synthesis). We would not use continuous data in analyses.

Unit of analysis issues

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. We did not anticipate that any cross-over studies would be included, as they are usually of short duration.

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 postbaseline assessment. We planned to assign missing participants as zero improvement wherever possible.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions. We planned to assess statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. If the I^2 value was greater than 50%, we planned to 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 people with neuropathic pain (Hoffman 2010; Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). The review did not depend on what the authors of the original studies chose to report or not. We would have extracted and used continuous data, which probably will reflect efficacy and utility poorly, if 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 required to make any result clinically irrelevant (usually taken to mean a NNT of 10 or higher in this condition; Moore 2008).

Data synthesis

We planned to use a fixed-effect model for meta-analysis. We would use a random-effects model for meta-analysis if there was significant clinical heterogeneity and it was considered appropriate to combine studies.

Quality of evidence

We planned to use 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, Higgins 2011). At least two review authors planned to independently rate the quality of evidence for each outcome. We planned to assess 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 use 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 there were no data reported for an outcome, we planned to report the level of evidence as very low quality (Guyatt 2013b). We would also consider any other factors while making GRADE assessments.

'Summary of findings' table

We planned to include a 'Summary of findings' table as set out in the Pain, Palliative and Supportive Care Group (PaPaS) author guide (PaPaS 2012), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 4.6.6 (Higgins 2011). The table would have included outcomes equivalent to moderate benefit (at least 30% pain intensity reduction or PGIC much or very much improved, or both) and substantial benefit (at least 50% pain intensity reduction or PGIC very much improved, or both), withdrawals due to lack of efficacy, withdrawals due to adverse events, serious adverse events, and death (a particular serious adverse event).

For the 'Summary of findings' table we used the following descriptors for levels of evidence (EPOC 2015).

- **High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[†] is low.
- **Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[†] is moderate.
- **Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[†] is high.
- **Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[†] is very high.

[†] Substantially different: a large enough difference that it might affect a decision.

Subgroup analysis and investigation of heterogeneity

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

Possible issues for subgroup analysis might be dose, formulation, and route of administration. A minimum of two studies and 200 participants were required for any subgroup analysis.

Sensitivity analysis

We planned no sensitivity analysis because the evidence base is known to be too small to allow reliable analysis.

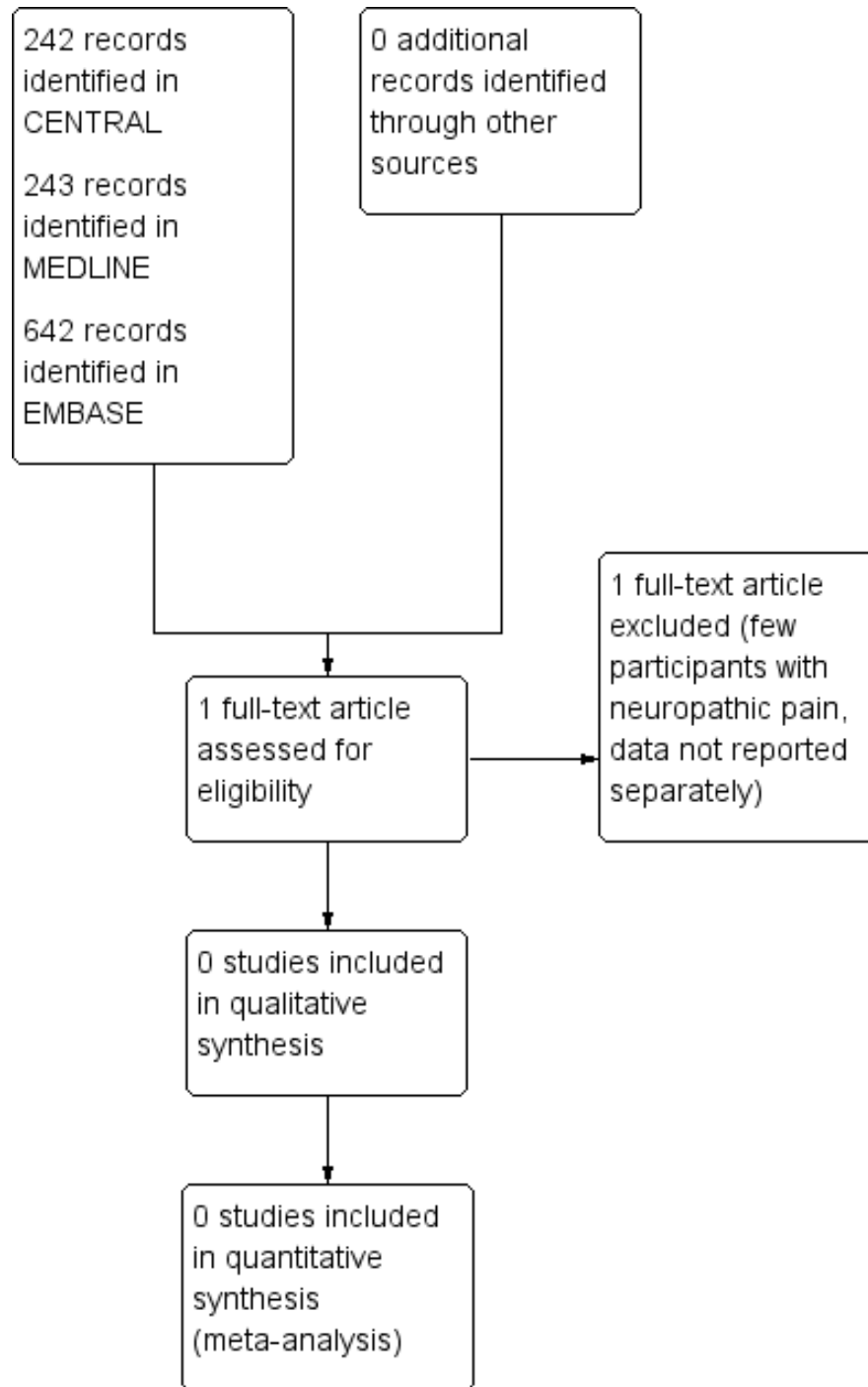
RESULTS

Description of studies

Results of the search

The searches of CENTRAL, MEDLINE, and Embase identified 1127 records; 1126 of these clearly did not satisfy the inclusion criteria. We read the full text of the one remaining record for possible inclusion and excluded it ([Palangio 2000](#)). Searches of clinical trials databases did not identify any relevant ongoing or unpublished studies (see [Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

No studies satisfied our inclusion criteria.

Excluded studies

We excluded one study (Palangio 2000). This was a randomised, double-blind comparison of paracetamol plus codeine with ibuprofen plus hydrocodone over four weeks in 469 participants with chronic pain. Of these, three participants had diabetic neuropathy, five had PHN, and 21 had other neurological chronic pain; most participants had chronic musculoskeletal pain. Results for these actual and possible neuropathic pain conditions were not presented separately.

Risk of bias in included studies

We did not assess risk of bias as there were no included studies.

Effects of interventions

See: [Summary of findings for the main comparison Paracetamol alone, paracetamol plus codeine, or paracetamol plus dihydrocodeine compared with placebo for neuropathic pain](#)

We found no studies satisfying our inclusion criteria. We have only very low quality evidence and are very uncertain about estimates of benefit and harm.

DISCUSSION

Summary of main results

We found no RCTs assessing the beneficial or harmful effects of paracetamol alone, or in combination with codeine or dihydrocodeine, in the treatment of any type of neuropathic pain; only very low quality evidence was available. This is despite paracetamol, alone or in fixed dose combination with codeine or dihydrocodeine, being one of the most commonly used first-line treatments for neuropathic pain conditions such as PHN, PDN, neuropathic low back pain, or phantom limb pain (Hall 2013). The absence of evidence for efficacy probably explains why these treatments do not feature in neuropathic pain guidelines.

Overall completeness and applicability of evidence

There is no evidence from randomised, double-blind, comparative studies to support or refute the use of paracetamol alone, or combined with codeine or dihydrocodeine, for the treatment of neuropathic pain. One excluded study had only a trivial number of participants with neuropathic pain and did not report on them separately (Palangio 2000).

During our searches, we found no large body of evidence with other study designs, such as open comparative studies, or observational studies, other than one case report of one patient given intravenous paracetamol (Gulcu 2007).

There are only small amounts of evidence for combinations of paracetamol with other opioids. For paracetamol combinations with tramadol, we identified a single randomised, double-blind, placebo-controlled study of modest size (160 participants) (Freeman 2007), an open randomised study (Ko 2010), and a cohort study (Danilov 2007), all in the treatment of PDN. We also found a single observational study of paracetamol plus oxycodone (Gatti 2009). While our searches were not designed to find all studies with paracetamol combined with opioids, the absence of a significant body of evidence is confirmed by other reviews (Finnerup 2015).

The main importance is the stark contrast between widespread use of paracetamol, with or without codeine or dihydrocodeine, in neuropathic pain, and absence of evidence of efficacy. This is especially important at a time when the efficacy of paracetamol in other chronic pain conditions is being challenged. Paracetamol alone is no better than placebo for low back pain (Saragiotto 2016), spinal pain, or osteoarthritis (Machado 2015), and its use has been challenged in cancer pain (Mercadante 2013). The assumed safety of paracetamol is also being challenged (Roberts 2016).

Quality of the evidence

We found no RCTs.

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 paracetamol alone or in combination with codeine or dihydrocodeine in neuropathic pain.

Agreements and disagreements with other studies or reviews

We identified no other relevant reviews. A wide-ranging review of drug therapies for neuropathic pain also found no relevant trials (Finnerup 2015), as did a Cochrane Review on combination pharmacotherapy (Chaparro 2012).

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

There is insufficient evidence to support or refute the suggestion that paracetamol, alone or in combination with codeine or dihydrocodeine, has any efficacy in any neuropathic pain condition.

For clinicians

There is insufficient evidence to support or refute the suggestion that paracetamol, alone or in combination with codeine or dihydrocodeine, has any efficacy in any neuropathic pain condition.

For policy makers

There is insufficient evidence to support or refute the suggestion that paracetamol, alone or in combination with codeine or dihydrocodeine, has any efficacy in any neuropathic pain condition. It should be noted that there is evidence of lack of effect of paracetamol alone in other chronic pain conditions. In the absence of any supporting evidence, these drugs should probably not be recommended, except at the discretion of a pain specialist.

For funders

There is insufficient evidence to support or refute the suggestion that paracetamol, alone or in combination with codeine or dihydrocodeine, has any efficacy in any neuropathic pain condition. It

should be noted that there is evidence of lack of effect of paracetamol alone in other chronic pain conditions.

Implications for research

Large, robust randomised trials with patient-centred outcomes would be required to produce evidence to support or refute efficacy of paracetamol, alone or in combination with codeine or dihydrocodeine, in neuropathic pain. The necessary design of such trials is well established, but, for opioids in neuropathic pain, the outcomes should be those of at least 30% and at least 50% pain intensity reduction 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 last observation carried forward (LOCF) analysis should not be used. This is because, in chronic pain, opioids frequently produce withdrawal rates of 50% or more, meaning that LOCF analysis can overstate treatment efficacy to a large extent.

Given the knowledge that paracetamol is proven to be without effect or has no evidence to support efficacy in any chronic pain condition, the value of such trials would be questionable.

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The protocol followed the agreed template for neuropathic pain, which was developed in collaboration with the Cochrane Musculoskeletal Group and Cochrane Neuromuscular Diseases Group. The editorial process was managed by the Cochrane Pain, Palliative and Supportive Care Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Palangio 2000	Few participants with neuropathic pain participants; results not supported separately

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 7 July 2016.

Date	Event	Description
23 January 2017	Amended	Minor typo corrected in PLS.

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol, though this was based on a template that had previously been the subject of input from many sources, and which has been subject to extensive peer review.

SD and RAM searched for and selected studies for inclusion.

All review authors were involved in writing the full review.

PW will be responsible for any updates required.

DECLARATIONS OF INTEREST

PW: none known.

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

SD: none known.

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

TP: none known; TP is a specialist pain physician and manages patients with neuropathic 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 (2014) about the design of network meta-analyses, and RB on understanding 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

We have removed the planned analysis by tiers of evidence as this is largely replaced by GRADE, updated the criteria for assigning a quality level to a body of evidence in line with the latest standards, and extended the description of the GRADE assessment for exceptional circumstances to explain possible decisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*therapeutic use]; Analgesics, Non-Narcotic [*therapeutic use]; Analgesics, Opioid [*therapeutic use]; Chronic Pain [*drug therapy]; Codeine [*analogs & derivatives; *therapeutic use]; Neuralgia [*drug therapy]

MeSH check words

Adult; Humans