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[Intervention Review]

Imipramine for neuropathic pain in adults

Leslie Hearn[1], Sheena Derry[2], Tudor Phillips[1], R Andrew Moore[3], Philip J Wiffen[4]

[1]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [2]Oxford, UK. [3]Plymouth, UK. [4]Thame, UK

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

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ABSTRACT

Background

Antidepressants are widely used to treat chronic neuropathic pain (pain due to nerve damage), usually in doses below those at which they exert antidepressant effects. An earlier review that included all antidepressants for neuropathic pain is being replaced by new reviews of individual drugs examining individual neuropathic pain conditions.

Imipramine is a tricyclic antidepressant that is occasionally used to treat neuropathic pain.

Objectives

To assess the analgesic efficacy of imipramine for chronic neuropathic pain in adults, and to assess the associated adverse events.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE on 18 November 2013, as well as the reference lists of retrieved papers and other reviews. We also used our own handsearched database for older studies, and two clinical trials databases.

Selection criteria

We included randomised, double-blind studies of at least two weeks' duration comparing imipramine with placebo or another active treatment in chronic neuropathic pain. Participants were adults aged 18 and over. We included only articles with full journal publication and extended trial abstracts and summaries.

Data collection and analysis

Two review authors independently extracted efficacy and adverse event data, and examined issues of study quality. We performed analysis using three tiers of evidence. First tier evidence was derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks duration, parallel design); second tier from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison; and third tier from data involving small numbers of participants which was considered very likely to be biased or used outcomes of limited clinical utility, or both.

Main results

Five studies treated 168 participants with painful diabetic neuropathy or polyneuropathy. The mean age in individual studies was between 47 and 56 years. Four studies used a cross-over, and one a parallel group design; 126 participants were randomised to receive imipramine 25 mg to 350 mg daily (most took 100 mg to 150 mg daily). Comparators were placebo (an active placebo in one study), paroxetine, mianserin, venlafaxine, and amitriptyline, and treatment was given for 2 to 12 weeks. All studies had one or more sources of potential major bias.

No study provided first or second tier evidence for any outcome. No data were available on the proportion of people with at least 50% or 30% reduction in pain or equivalent, and data were available from only one study for our other primary outcome of Patient Global Impression of Change, reported as patient evaluation of pain relief of complete or good. No pooling of data was possible, but third tier evidence in individual studies indicated some improvement in pain relief with imipramine compared with placebo, although this is was very low quality evidence, derived mainly from group mean data and completer analyses, in small, short duration studies where major bias is possible.

Four studies reported some information about adverse events, but reporting was inconsistent and fragmented, and the quality of evidence was very low. Participants taking imipramine generally experienced more adverse events, notably dry mouth, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.

Authors' conclusions

This review found little evidence to support the use of imipramine to treat neuropathic pain. There was very low quality evidence of benefit but this came from studies that were methodologically flawed and potentially subject to major bias. Effective medicines with much greater supportive evidence are available.

PLAIN LANGUAGE SUMMARY

Imipramine for neuropathic pain in adults

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages carried along healthy nerves from damaged tissue (as in a fall, a cut, or an arthritic knee). Neuropathic pain is treated with different medicines than pain from damaged tissue. Medicines like paracetamol or ibuprofen are usually not effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain.

Imipramine is from the same class of medicines as amitriptyline, which is widely recommended for treating neuropathic pain; imipramine may also be useful in these painful conditions. In 2013 we performed searches to look for clinical trials in which imipramine was used to treat neuropathic pain.

We found five studies involving 168 participants with painful diabetic neuropathy or polyneuropathy. Studies were randomised and double-blind, but all had one or more sources of potential major bias that could lead to overestimation of efficacy. It was not possible to combine information from the different studies, but individually they indicated some benefit from imipramine (usually at a dose between 100 mg and 150 mg daily) compared with placebo, at the expense of increased adverse events.

There was too little information, which was of inadequate quality, to be sure that imipramine works as a pain medicine in neuropathic pain due to diabetes or due to damage to multiple nerves. There was no information about other types of neuropathic pain. Other medicines have been shown to be effective.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Imipramine compared with placebo for painful diabetic neuropathy and polyneuropathy

Patient or population: neuropathic pain (5 studies in painful diabetic neuropathy and polyneuropathy)

Settings: community

Intervention: imipramine 25 to 350 mg daily

Comparison: placebo

Outcomes	Probable outcome with comparator (placebo)	Probable outcome with intervention	RR (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain or equivalent	No data					No data
"Moderate" benefit At least 30% reduction in pain	No data					No data
Proportion below 30/100 mm on VAS	No data					No data
Patient Global Impression of Change much or very much improved	2/40	9/40	Not calculated	40 participants 1 study	Very low	Small numbers of participants in 1 study, cross-over design
Adverse event withdrawals	3/109	3 during dose-finding open label treatment (denominator unknown) 4/109 during double blind treatment	Not calculated	109 participants 4 studies	Very low	Small numbers of studies and participants
Serious adverse events	1 "unrelated" hospitalisation for a "pronounced" urinary tract infection. Treatment group not reported		Not calculated	168 participants	Very low	Small numbers of studies and participants

			5 studies		
Death	None reported		168 participants 5 studies	Very low	Small numbers of studies and participants

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.

CI: confidence interval; RR: risk ratio.

BACKGROUND

Imipramine is a tricyclic antidepressant that is sometimes used to treat chronic neuropathic pain (pain due to nerve damage or changes in the central nervous system (CNS)). Its use is not specifically recommended, but it is listed alongside other tricyclic antidepressants in some treatment guidelines, although this is an unlicensed indication (Attal 2010; Finnerup 2010; Moulin 2007).

Description of the condition

The 2011 International Association for the Study of Pain (IASP) definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the CNS (Moisset 2007). It is complex (Apkarian 2011; Tracey 2011), and neuropathic pain features can be found in patients with joint pain (Soni 2013). Many people with neuropathic pain conditions are significantly disabled by moderate or severe pain for many years.

Chronic painful conditions comprise 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, employment, and increased health costs (Moore 2013a).

In primary care in the UK the incidences, per 100,000 person years observation, have been reported as 28 (95% confidence interval (CI) 27 to 30) for postherpetic neuralgia, 27 (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 painful diabetic neuropathy (Hall 2008). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with *prevalence* rates up to 400 per 100,000 person years (McQuay 2007) illustrating how common the condition was as well as its chronicity. The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). Some forms of neuropathic pain, such as diabetic neuropathy and post surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008).

Neuropathic pain is known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical and/or cognitive interventions. Conventional analgesics are usually not effective. Some patients may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Khaliq 2007). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is more usually by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009a; Moore 2011a). An overview of treatment guidelines identified general similarities based on the evidence available, but guidelines are not always consistent with one another (O'Connor 2009). The proportion of patients who achieve worthwhile pain relief (typically at least 50% pain intensity reduction (Moore 2013b)) is small, generally 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNTs) usually between 4 and 10 (Moore 2013c).

Description of the intervention

Imipramine is a tricyclic antidepressant (TCA) that is most commonly used to treat depressive illness in adults and nocturnal enuresis in children. It is partially converted in the body to an active metabolite, desipramine, another TCA. Imipramine is not licensed in the UK for treating neuropathic pain but is used for this condition. It is also used around the world for neuropathic pain, irrespective of licensing.

Imipramine is available as tablets (10 mg and 25 mg) and as an oral liquid. For treating neuropathic pain, typical starting dosages are between 10 mg and 25 mg daily, usually taken at night, increasing to 75 mg daily if necessary. The main adverse effects are due to its anticholinergic activity and include dry mouth, weight gain, and drowsiness (although it is less sedating than amitriptyline).

How the intervention might work

The mechanism of action of imipramine in the treatment of neuropathic pain remains uncertain, although it is known to be a strong reuptake inhibitor of serotonin and, to a lesser extent, norepinephrine (Watson 2013). Its active metabolite, desipramine, is conversely a very strong reuptake inhibitor of norepinephrine and, to a lesser extent, serotonin. The mechanism is likely to differ from that in depression since analgesia with TCAs is often achieved at lower doses than are needed for antidepressant effects. An alternative mechanism is likely to involve its action, and that of desipramine (as with many other analgesics) in blocking sodium channels in nerve membranes. TCAs are known to block sodium channels, binding at the local anaesthetic site at blood levels found at therapeutically relevant doses.

Why it is important to do this review

The earlier review of antidepressants for neuropathic pain (Saarto 2007) is being replaced by separate reviews for individual drugs due to the large amount of data now available for some of them. These separate reviews will use more stringent criteria of validity, which include the level of response obtained, duration of the study, and method of imputation of missing data (Moore 2012b). The individual reviews will be included in an overview of antidepressant drugs for neuropathic pain. Appendix 1 gives details of recent changes to the thinking about chronic pain and evidence.

This Cochrane review assesses evidence in ways that make both statistical and clinical sense, and uses developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed 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 four or above (Moore 1998)). This sets high standards and marks a departure from how reviews have been done previously.

OBJECTIVES

To assess the analgesic efficacy of imipramine for chronic neuropathic pain in adults and to assess the associated adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Studies included adult participants aged 18 years and over. Participants could have one or more of a wide range of chronic neuropathic pain conditions including (but not limited to):

- cancer-related neuropathy;
- central neuropathic pain;
- complex regional pain syndrome (CRPS) Type II;
- human immunodeficiency virus (HIV) neuropathy;
- painful diabetic neuropathy;
- phantom limb pain;
- postherpetic neuralgia;
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- trigeminal neuralgia;

and

- CRPS Type I.

If studies included participants with more than one type of neuropathic pain we planned to analyse results according to the primary condition. Migraine and headache studies were excluded as they are the subject of another Cochrane review (Chronicle 2004).

Types of interventions

Oral imipramine, at any dose, administered for the relief of neuropathic pain and compared to placebo or any active comparator.

Types of outcome measures

Studies used a variety of outcome measures, with the majority using subjective scales (categorical scale, numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes concentrate 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%, and with pain not worse than mild (O'Brien 2010).

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

Primary outcomes

1. Patient-reported pain relief of 30% or greater.
2. Patient-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.
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/consequences.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence, dizziness, and weight gain.

These outcomes were not eligibility criteria for this review, but outcomes of interest within the included studies.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (in *The Cochrane Library*, 2013, Issue 11 of 12).
- MEDLINE (via Ovid), January 2009 to 18 November 2013.
- EMBASE (via Ovid), January 2009 to 18 November 2013.

The search strategies for CENTRAL, MEDLINE, and EMBASE are in Appendix 2, Appendix 3, and Appendix 4, respectively. There were no language restrictions.

Searching other resources

We searched our own hand-searched database for older studies and two clinical trials databases (ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/)), together with the reference

lists of included studies and relevant review articles. We did not contact investigators or study sponsors.

Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions. Analyses combining different neuropathic pain conditions would be done for exploratory purposes only.

Selection of studies

We determined eligibility by reading the title and abstract of each study identified by the search. We eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies; decisions were made by two review authors. Two review authors read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment.

Data extraction and management

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

Assessment of risk of bias in included studies

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

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

1. We assessed the following for each study: Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, for example random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, 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 (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, 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 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 (< 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' analysis); 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 per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We planned to calculate NNTs as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat for an additional harmful outcome (NNH) and is calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). Continuous data were not used in analyses.

Unit of analysis issues

We accepted randomisation to individual participants only.

For cross-over studies, we planned to use only the first period, if this was available. Where only combined data for both periods were reported, we treated the study as if it was a parallel study, drawing attention to the potential bias that this confers, and interpreting the results accordingly.

Dealing with missing data

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. Missing participants would be assigned zero improvement.

Where only mean data were reported, using a completer analysis or with uncertain imputation methods, we have reported the results and drawn attention to potential biases. These data were not used in any analyses.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and assess statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010c). The review did not depend on what authors of the original studies chose to report or not, although clearly difficulties

arose in studies failing to report any dichotomous results. We have extracted and reported continuous data, which probably poorly reflect efficacy and utility, where useful, for illustrative purposes only.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect 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, or use a random-effects model if there was significant clinical heterogeneity and it was considered appropriate to combine studies.

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

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

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

We did not plan any sensitivity analysis because the evidence base was known to be too small to allow reliable analysis. We would have examined details of dose escalation schedules if we had felt it could provide some basis for a sensitivity analysis.

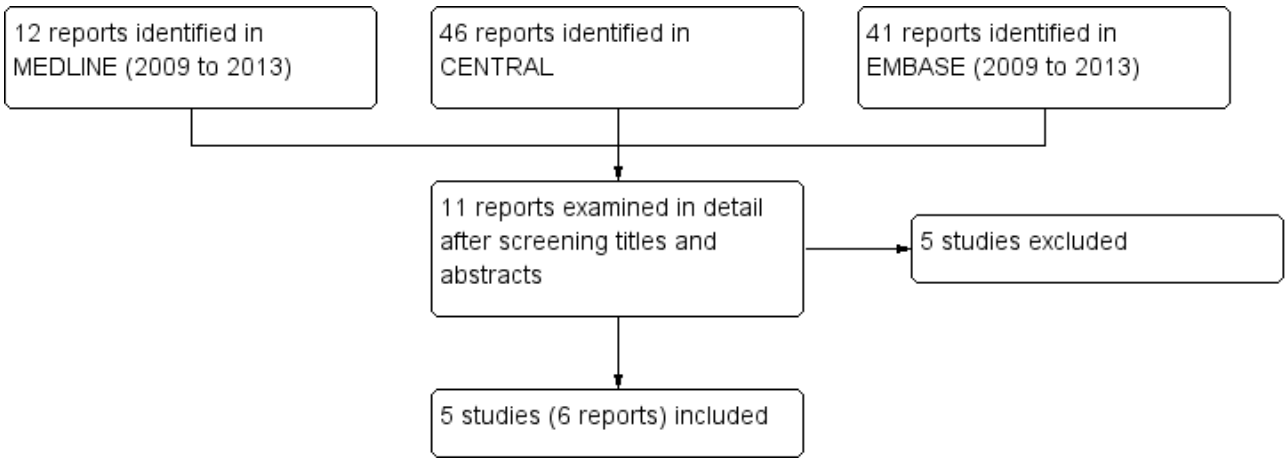
RESULTS

Description of studies

Results of the search

Searches found fewer than 100 titles that we examined for inclusion. After screening titles and abstracts, we obtained full copies and examined 11 reports in detail. We included five studies (six reports; one study was published both in English and in Danish (Kvinesdal 1984)) and excluded five studies (Figure 1). We did not identify any new studies that were not in the earlier review (Saarto 2007), but we excluded one study that was in the earlier version because it enrolled fewer than 10 participants per treatment arm (Sindrup 1989).

Figure 1. Flow diagram.



Included studies

Five studies treated 168 participants, of whom 126 were randomised to imipramine (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003; Turkington 1980); in the cross-over studies, however, it was not clear whether all randomised participants received all treatments, and most studies did not report results for all randomised participants. Two studies included an imipramine dose-finding phase (Sindrup 1990; Sindrup 1992): in the first of these, 3 of 32 participants withdrew because of adverse events. Participants took oral imipramine for between 2 and 12 weeks. Daily doses were between 25 mg and 350 mg (mostly 100 mg to 150 mg). The licensed maximum dose is commonly 200 mg, except in hospitalised patients. Poor metabolisers were excluded or treated with the lowest doses.

Study participants were aged between 20 and 75 years (study mean ages from 47 to 56 years) and there were approximately

equal numbers of men and women, except in Sindrup 2003 (23 men, 9 women). Participants had experienced pain associated with diabetic neuropathy or painful polyneuropathy for at least six months. Common grounds for exclusion from studies were anaemia, renal or cardiac dysfunction, hypothyroidism, and amputation.

Imipramine was compared with placebo (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003) or active placebo (diazepam (19 participants in parallel arm) Turkington 1980).

In four studies, another analgesic was compared with imipramine: paroxetine (22 participants, Sindrup 1990), mianserin (22 participants, Sindrup 1992), venlafaxine (40 participants, Sindrup 2003), and amitriptyline (20 participants, Turkington 1980).

One study used a parallel group design (Turkington 1980), and the other four used a cross-over design (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003).

Two studies had washout periods before or between cross-over periods (Sindrup 1992; Sindrup 2003), and two gave imipramine in a dose-finding phase (Sindrup 1990; Sindrup 1992). Stable medication for diabetes was maintained.

No included studies involved any other type of neuropathic pain.

Excluded studies

We excluded five studies after reading the full papers. Sindrup 1989 had fewer than 10 participants, Kvinesdal 1985, Rasmussen 2004, and Wysenbeek 1985 were not RCTs, and Minotti 1998 described imipramine as an "add-on" to diclofenac treatment.

Risk of bias in included studies

Comments on potential biases in individual studies are reported in the Risk of bias section of the Characteristics of included studies table. The findings are displayed in Figure 2 and Figure 3; no sensitivity analysis was undertaken. The greatest risk of bias was associated with small study size.

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

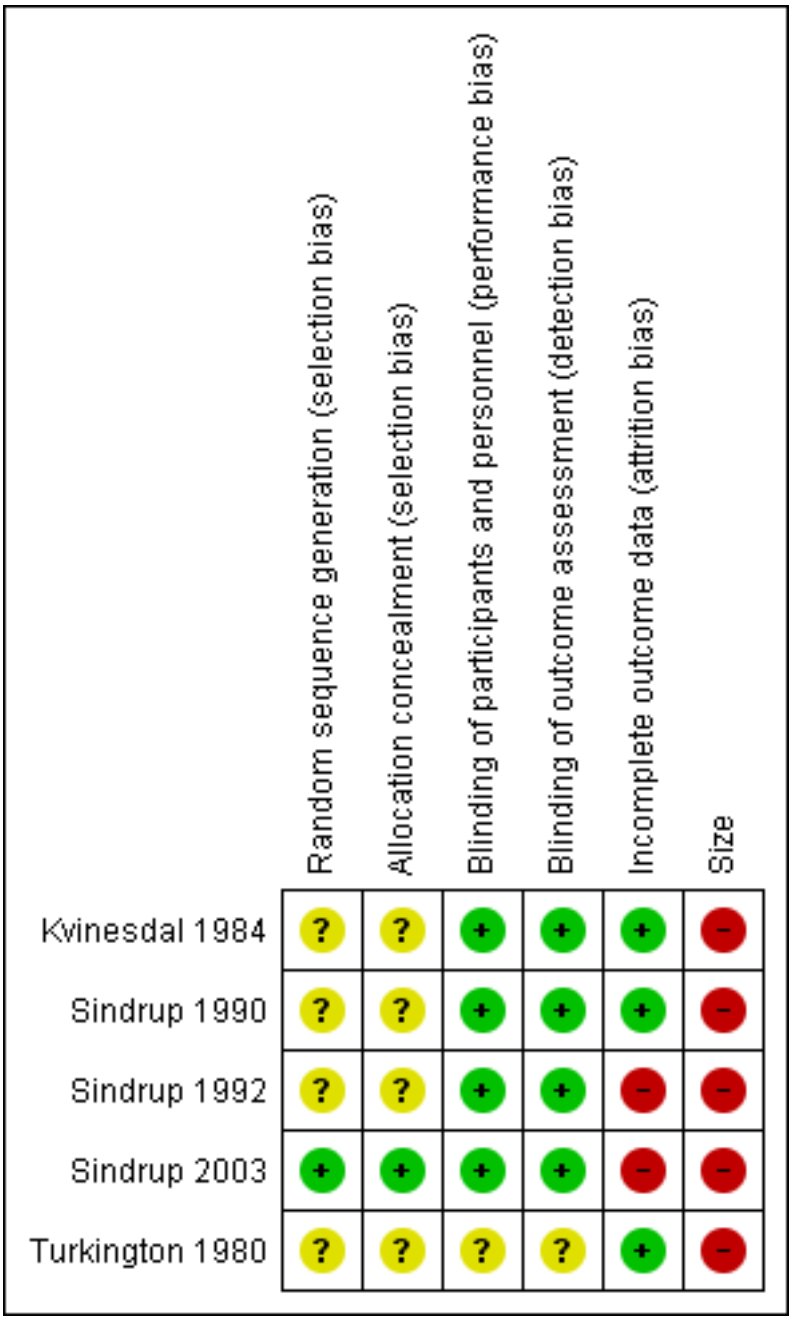
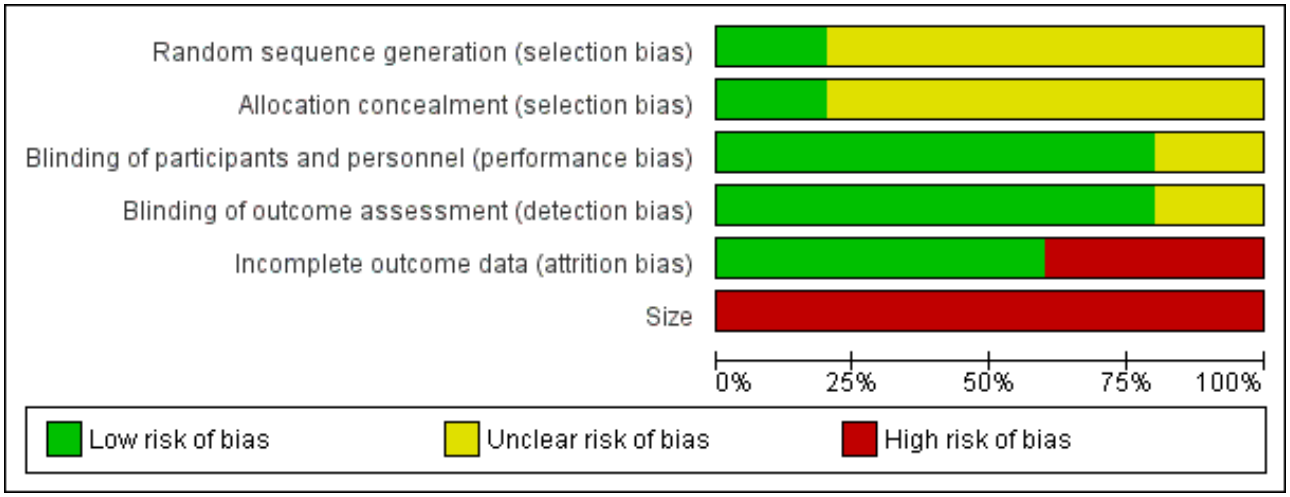


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All studies were randomised. Only Sindrup 2003 adequately described how allocation to treatment groups was concealed; the others did not report this.

Blinding

All studies were double blind. Four studies (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003) adequately described the methods used to ensure that participants and interacting investigators were unable to differentiate between active and control groups; Turkington 1980 did not discuss this.

Incomplete outcome data

Turkington 1980 reported no withdrawals or losses to follow-up. The remaining studies (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003) performed efficacy analyses only on those participants who completed the study (completer analyses). Proportions of withdrawals were relatively high: 3/15 (Kvinesdal 1984), 10/29 (Sindrup 1990), 4/22 (Sindrup 1992), 8/40 (Sindrup 2003).

Missing participants can sometimes be added back in (analysed as non-responders) for dichotomous outcomes, but this is not possible when mean data are reported.

Selective reporting

All studies reported the outcomes specified in the methods but these were not usually our preferred (primary) outcomes. Pain was not reported separately in Kvinesdal 1984, Sindrup 1990, Sindrup 1992.

Other potential sources of bias

None of the studies randomised sufficient numbers of participants to minimise the bias associated with small studies (Nüesch 2010). The greatest number randomised was 32 (Sindrup 2003) so the risk of bias is high.

Effects of interventions

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

Efficacy

We found no first or second tier evidence of efficacy. Evidence was downgraded primarily because of the short duration of the studies, small numbers of participants in comparisons, reporting of completer analyses in cross-over studies, and lack of desirable primary outcomes.

Four studies reported at least one pain-related outcome indicating some improvement with imipramine compared with placebo. Three studies (Kvinesdal 1984; Sindrup 1990; Sindrup 1992) reported improvement on a set of neuropathy symptoms, which included pain, but only one (Sindrup 1990) reported the pain item separately (as group median scores). Details of data from individual studies are shown in Appendix 5.

Third tier evidence

Kvinesdal 1984 assessed six symptoms (pain, dysaesthesia, paraesthesia, numbness, nightly aggravation, and sleep disturbances) which were combined to give a neuropathy symptom score; pain was not reported separately. The authors reported that 8/12 participants who completed both phases of the cross-over (ITT 8/15) assessed their condition as "improved" (undefined) with imipramine 100 mg daily, compared with 1/12 (ITT 1/15) with placebo.

In Sindrup 1990, pain was not reported separately but only as part of a set of neuropathy symptoms.

Participants' median VAS scores for pain shown on a graph indicated about an 80% reduction in pain rating at the end of the treatment period from baseline or placebo for those who completed all phases of the cross-over. Participants with at least 50% reduction, compared with placebo, in combined VAS scores for five symptoms (pain, paraesthesia, dysaesthesia, nightly aggravation, and sleep disturbances) with imipramine 25 mg to 350 mg daily, numbered 12/19 for completers (ITT 12/29). For at least 30% reduction, the number was 14/19 for completers (ITT 14/29).

Sindrup 1992 also reported a combined set of neuropathy symptoms (pain, paraesthesiae, dysaesthesiae, numbness, nightly

exacerbation, and sleep disturbance) assessed by both participants and observers. Participants reporting at least 50% reduction in symptoms with imipramine 25 mg to 350 mg (median 150 mg) daily totaled 3/18 for those who completed all phases of the cross-over (ITT 3/22), with 9/18 completers (ITT 9/22) reporting at least 30% reduction, both figures relative to placebo. The relevant figures for mianserin were 3/18 and 5/18, respectively.

Sindrup 2003 reported participants' ratings for several types of pain (pain paroxysms, constant pain, touch-evoked pain, pressure-evoked pain). These were reduced by 29%, 29%, 4%, and 20%, respectively, for completers with imipramine up to 150 mg daily. An overall reduction of 23% from baseline is quoted.

Participants' global evaluation of pain relief (complete, good, moderate, slight, none, worse) was complete or good for 9/29 with imipramine in those who completed all phases of the cross-over (ITT 9/40), 7/30 with venlafaxine (ITT 7/40), and 2/29 with placebo (ITT 2/40). For an evaluation of complete, good, or moderate, the numbers were 14/29 with imipramine (ITT 14/40), 8/30 with venlafaxine (ITT 8/40), and 2/29 with placebo (ITT 2/40). A subgroup analysis indicated that the subgroup of participants with diabetic neuropathy were more likely to obtain clinically relevant pain relief.

The study authors report an NNT of 2.7 for > 50% pain relief, but do not report the raw data on which this calculation was based, or any confidence intervals. We believe it may be based on a completer analysis of participants giving complete, good, or moderate global evaluations of pain relief, which we would consider to be closer to ≥ 30% pain relief.

Turkington 1980 reported complete (100%) pain relief with imipramine 100 mg daily (20/20 completers and ITT) and no relief with placebo (0/20 completers and ITT).

Adverse events

Details of adverse events reported in individual studies are in Appendix 6. Four studies (Kvinesdal 1984; Sindrup 1990; Sindrup 1992; Sindrup 2003) reported some information about adverse events, but reporting was inconsistent and fragmented; the remaining study (Turkington 1980) did not mention adverse events.

Participants experiencing any adverse event

No study adequately reported the number of participants who experienced one or more adverse events for all those who were treated (ITT).

Kvinesdal 1984 reported that "side effects were generally few". Dry mouth was reported by 9/12 completers with imipramine and 1/12 with placebo, and impaired micturition was reported in two participants with imipramine, and dizziness in two participants, probably with imipramine.

Sindrup 1990 asked participants to score the intensity of a range of adverse events using a VAS. Mean ratings for dry mouth, sweating, dizziness and fatigue were higher for imipramine than for placebo, but only dry mouth was notably higher. Frequencies of adverse events were not given except that 4/18 participants showed withdrawal symptoms (nausea, tremor, vomiting) after cessation of imipramine treatment.

Sindrup 1992 asked participants to score the intensity of a number of adverse events on a scale of 0 to 2.0. The most common events were dry mouth, orthostatic dizziness, and fatigue. The total adverse events score was not significantly different between imipramine and mianserin, but scores for both active drugs were significantly higher than for placebo, with the total adverse event score for imipramine approximately four times that for placebo. Almost half (10/22) of participants experienced one or more adverse events during treatment with placebo.

Sindrup 2003 reported that of 29 participants completing all three treatment phases with valid results, 20 experienced an adverse event (of any intensity) with imipramine, 20 with venlafaxine, and 14 with placebo. At least one additional adverse event leading to withdrawal was reported with imipramine, four with venlafaxine, and two with placebo.

There was a tendency for more adverse events with active treatment, particularly dry mouth with imipramine and tiredness with venlafaxine. Specific adverse events that were more common with imipramine than with placebo were as follows (in completers): dry mouth (12, 3); nausea (5, 1); sweating (5, 0); dizziness (3, 1); and blurred vision (1, 0).

Turkington 1980 did not report any adverse events.

Participants experiencing any serious adverse event

No study reported serious adverse events as such, although Sindrup 2003 reported that one participant had to drop out due to hospitalisation for a "pronounced" urinary tract infection (report does not state during which phase).

Withdrawals

Details of withdrawals reported in individual studies are provided in Appendix 6. Turkington 1980 did not report any withdrawals, so withdrawals are discussed only for participants in the other four studies.

Withdrawals due to adverse events

The remaining four studies reported withdrawals due to adverse events.

Seven participants withdrew during treatment with imipramine, three during a dose-finding phase (nausea, fatigue, dry mouth), and four (of 109) during a treatment phase. All four cited dizziness, in combination with, variously, orthostatic hypotension (1), tiredness (3), and vomiting (2).

Three (of 109) dropped out during placebo treatment (gastritis, nausea/diarrhoea, vomiting), and four withdrew during venlafaxine treatment.

Withdrawals due to lack of efficacy

There was only one withdrawal due to lack of efficacy reported during imipramine treatment (Sindrup 2003) and none during placebo treatment.

Withdrawals for other reasons

Three studies (69 participants) reported eight withdrawals for other reasons (Kvinesdal 1984; Sindrup 1990; Sindrup 1992).

During imipramine treatment, three participants withdrew for lack of compliance, two for personal reasons, and two because they

needed analgesia for other pain. One from each of placebo and mianserin treatment groups withdrew for personal problems.

Two participants were lost to follow-up in Sindrup 2003 (treatment group was not specified).

DISCUSSION

Summary of main results

The review found five studies enrolling 168 participants with chronic neuropathic pain, 90% of whom had painful diabetic neuropathy and 10% had polyneuropathy of non-diabetic origin. We did not identify any new studies but excluded one study that was included in an earlier review, because it enrolled fewer than 10 participants per treatment arm (Sindrup 1989).

No first or second tier evidence was available. No pooling of data was possible, but third tier evidence in individual studies indicated some improvement in pain relief with imipramine compared with placebo, although this was very low grade evidence, derived mainly from group mean data and completer analyses (see Appendix 1) in small, short duration studies in which major bias is possible. Four studies reported some information about adverse events, but reporting was inconsistent and fragmented. Participants taking imipramine generally experienced more adverse events, notably dry mouth, and a higher rate of withdrawal due to adverse events, compared with participants taking placebo. See Summary of findings for the main comparison.

More effective and safer medicines are available (Lunn 2014; Moore 2009a; Moore 2011a).

Overall completeness and applicability of evidence

Imipramine was tested only in painful neuropathy (primarily diabetic neuropathy), so results cannot be reliably extrapolated to other neuropathic conditions. Participants recruited into studies varied according to prevalence of depression and it is unclear whether this affected results. It is notable that Turkington 1980 reported a remarkable effect on pain with imipramine given for three months to participants with depression; mean depression scores were more than halved in this group but unchanged in the placebo group. However, Kvinesdal 1984 and Sindrup 1990 observed that none of their participants had any signs or symptoms of depression before or during treatment, but also experienced an effect on pain, albeit less marked. The other studies did not mention depression but perhaps this should have been measured at baseline, given the anti-depressant action of imipramine. One study referred to the rapid onset of pain relief (Sindrup 1990), suggesting an immediate action on sodium channels, and a mechanism of action different from that of its antidepressant effect.

Short-term studies (less than six weeks) may not accurately predict longer term efficacy in chronic conditions, and only one of the included studies lasted longer than five weeks. Furthermore, caution is required in interpreting adverse event data from short duration studies for real-world clinical practice, particularly when so few participants have been studied.

Quality of the evidence

Reporting quality in the studies was generally poor by current standards. Although all the studies were randomised and double-blind, none provided data that met predefined criteria for first or second tier analysis. All the studies were small (with a maximum of 40 participants in any treatment arm), and four of the five were of short duration (five weeks or less), used cross-over design without separate reporting of first period data, and reported only on participants who completed more than one phase of treatment.

Differential rates of adverse events between placebo and treatment arms can suggest unblinding, but in these studies adverse events were assessed inconsistently, making comparisons difficult. Turkington 1980 used an active placebo to help maintain blinding but reported no adverse events or withdrawals. None of the studies reported whether they asked participants to guess their allocation at the end of the trial to check for unblinding. The methods used to collect adverse events could usefully include symptom checklists for self-completion at baseline and at assessment points; these can even be graded for severity.

Potential biases in the review process

The review was restricted to randomised double-blind studies, thus limiting the potential for bias. Other possible sources of bias that could have affected the review included the following:

- Duration - NNT estimates of efficacy in chronic pain studies tend to increase (get worse) with increasing duration (Moore 2010b). All studies except one were five weeks or shorter, which may overestimate efficacy.
- Only one study reported an outcome equivalent to IMMPACT-defined moderate or substantial improvement. It is likely that lesser benefits, such as 'any benefit' or 'any improvement', are potentially related to inferior outcomes, although this remains to be clarified.
- The degree of exaggeration of treatment effects in cross-over trials compared with parallel group designs, as has been seen in some circumstances (Khan 1996), is unclear but unlikely to be the source of major bias (Elbourne 2002). Withdrawals meant that any results were more likely to be per protocol for completers than for a true ITT analysis. Most of the data in this review were from cross-over studies.
- The absence of publication bias (unpublished trials showing no benefit of imipramine over placebo) can never be proven. We carried out a broad search for studies and feel it is unlikely that significant amounts of data remain unknown to us.
- All four cross-over studies reported results only for those who completed at least two treatment periods, which is likely to overestimate efficacy. Where possible, we have added missing participants back into the denominator to provide an ITT analysis and thus a more conservative estimate.

Agreements and disagreements with other studies or reviews

This new review does not change the results of the previous Cochrane review (Saarto 2007).

Guidelines to treat neuropathic pain in Europe, UK, and USA do not specifically recommend use of imipramine (Attal 2010; NICE 2013; Dworkin 2010).

AUTHORS' CONCLUSIONS

Implications for practice

This review found little evidence to support the use of imipramine to treat neuropathic pain. There was very low quality evidence of some benefit in the proportion of people with Patient Global Impression of Change much or very much improved and with at least 50% or at least 30% reductions in neuropathy symptom scores, but this came from studies that were methodologically flawed and potentially subject to major bias. There may be a role in patients who have not obtained pain relief from other treatments.

Implications for research

There are reasonable levels of evidence for the benefit of other anti-epileptic and antidepressant drugs in the treatment of chronic neuropathic pain.

Larger, better-designed studies would provide more definitive conclusions on the efficacy of imipramine, but it is unlikely that these will be carried out, given the age of the drug and the alternatives available, or that they could be justified on the basis of the available evidence.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Kvinesdal 1984

Methods	Randomised, double-blind, placebo-controlled, cross-over study After clinical assessment, 2 x 5 weeks of imipramine or placebo. No washout between treatment periods
Participants	Insulin-dependent diabetes with painful diabetic neuropathy for at least 2 years Mean neuropathy symptom score at start 7.3 (6 item scale; max score 12; physician-assessed) Diabetes stable during study (blood glucose levels, insulin requirements) Exclusions: participants with foot problems, limping, amputations, renal or cardiac dysfunction, anaemia, taking drugs interacting with TCAs N = 15 (12 completed)

Kvinesdal 1984 *(Continued)*

	Age 30 to 75 years (mean = 54) (completers)
	M = 5; F = 7 (completers)
Interventions	Imipramine 50 mg daily in week 1; 100 mg daily in weeks 2 to 5 (as undivided dose)
	Placebo
	No participants had taken TCAs before
Outcomes	Pain not assessed separately but as one of set of neuropathy symptoms
	Patient assessment of global improvement at end of treatment period
	Mean neuropathy symptom score at end of each phase (6 item scale; max score 12; physician-assessed)
	Physician assessment of global improvement
Notes	Oxford Quality Score: R1; DB2; W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets same size and colour; same number given at same time daily
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Tablets same size and colour; same number given at same time daily
Incomplete outcome data (attrition bias) All outcomes	Low risk	No imputation. Completer analysis reported but non-completers can be added back in High risk for all continuous data (completer analysis)
Size	High risk	Only 15 participants

Sindrup 1990

Methods	Randomised, double-blind, placebo-controlled, cross-over study
	10-day dose-finding period for imipramine; 1 week of placebo for baseline observations (not reported); 3 x 2 weeks of imipramine, placebo, and paroxetine (pl-im-pa, pa-pl-im, im-pa-pl, pa-im-pl; four of six possible combinations)
	Washout between treatments only for poor sparteine metabolisers (causing persistence of imipramine metabolite desipramine in blood). Others had pauses of 2 to 4 weeks if needed for their convenience
Participants	Insulin-dependent diabetes with diabetic neuropathy symptoms for at least 1 year, including one or more types of pain

Sindrup 1990 *(Continued)*

	Exclusions: renal or cardiac dysfunction, pernicious anaemia or reduced B12 or folic acid, untreated hypothyroidism, recent weight loss or major change in metabolic control N = 29 (19 completers) Age 28 to 75 years (mean = 47) (completers) M = 9; F = 10 (completers)
Interventions	Dose-finding based on plasma drug concentrations following 50 mg or 75 mg imipramine daily for 10 days (two elderly poor sparteine metabolisers were given 25 mg imipramine daily for treatment period) 1 week on placebo "for baseline studies" Imipramine doses 50 mg to 350 mg daily (except poor metabolisers) Paroxetine 40 mg daily (all participants) Placebo
Outcomes	Pain not assessed separately but as one of set of neuropathy symptoms Median neuropathy symptom score at end of each phase (6 item scale: max score 12; physician-assessed) 50% or greater reduction in combined score vs. placebo Pain single item median scores reported separately Median VAS of neuropathy symptoms (5-item 100mm each: max score 500; participant-completed during treatment) 50% or greater reduction in combined score vs placebo
Notes	Oxford Quality Score: R1; DB2; W1. Total = 4/5 Baseline evaluation not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablets same size and colour; same number were given at same time daily
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo tablets same size and colour; same number were given at same time daily
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis reported for dichotomous data: non-completers can be added back in High risk for all continuous data (completer analysis)

Sindrup 1990 *(Continued)*

Size	High risk	Only 26 participants

Sindrup 1992

Methods	Randomised, double-blind, placebo-controlled, cross-over study Imipramine titrated pre-study to find dose for optimal blood level 1 week of baseline observations; 3 x 2 weeks of imipramine, mianserin and placebo (all six possible combinations) Washout period between treatments of at least 1 week for extensive metabolisers, 3 weeks for poor metabolisers
Participants	Diabetes with painful diabetic neuropathy for at least 1 year Exclusions: renal or cardiac dysfunction, anaemia, hypothyroidism, ankle/arm SBP index < 0.9 N = 22 (18 completed; 17 analysed for imipramine) Age 31 to 69 years (mean = 56) (probably completers) M = 9; F = 9 (completers) Insulin-dependent diabetes: 12 (completers)
Interventions	Imipramine titrated to optimal blood level using a 10-day pre-study with fixed dose of 50 or 75 mg/d 1 week baseline observations Imipramine 25 mg to 350 mg daily (median 150 mg) Mianserin 60 mg daily Placebo
Outcomes	Participant assessment of symptoms daily on 6-item neuropathy scale (5-point, 0 to 2; maximum 12) Median of last 10 days used for analysis Marginally significant reduction in combined score with imipramine (P = 0.079) (not mianserin) compared with placebo Physician assessment of symptoms on same scale at end of each period (5-point, 0 to 2; maximum 12) Medians reported. Pain item score (and nightly deterioration) reported (no figures given) Change from baseline given in graph
Notes	Oxford Quality Score: R1; DB2; W1. Total = 4/5 Baseline measurements not given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported

Sindrup 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy technique
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double dummy technique
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported
Size	High risk	Only 22 participants

Sindrup 2003

Methods	Randomised, double-blind, placebo-controlled, cross-over study 3 x 4 weeks of imipramine, venlafaxine and placebo (all 6 possible combinations) Washout period between treatments of at least 1 week
Participants	Painful polyneuropathy for at least 6 months, with baseline pain at least 4/10 Exclusions: cardiac dysfunction, recent myocardial infarction, pregnancy, poor sparteine metabolisers, "severe" terminal illness N = 32 (completing at least 2 treatment phases) Age 31 to 69 years (mean = 56) M = 23; F = 9 (completers)
Interventions	Other medications for neuropathic pain were tapered off over 1 week; no treatment for 1 further week for baseline observations Imipramine 50 mg daily in week 1, 100 mg daily in week 2, 150 mg daily in weeks 3, 4 Venlafaxine 75 mg daily in week 1, 150 mg daily in week 2, 225 mg in weeks 3, 4 Placebo Doses divided; rescue medication (paracetamol) allowed
Outcomes	Participants' daily separate ratings of 4 pain aspects (constant, paroxysmal, touch-evoked, pressure-evoked) on 0-10 scales were summed. Week 4 value used for statistical analysis Participants' ratings of specific pain phenomena (0-10 scales) Number of paracetamol tablets used per week (in week 4) Participants' global evaluation of pain relief (complete, good, moderate, slight, none, worse) Evaluation of diabetic participants given separately
Notes	Oxford Quality Score: R2; DB2; W1. Total = 5/5

Sindrup 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Coded drug packs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy technique
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double dummy technique
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported
Size	High risk	Only 40 participants

Turkington 1980

Methods	Randomised, double-blind, active-controlled, parallel study Pre-study, all participants treated with phenytoin 200 mg x3 on first day then 100 mg x3 daily for 2 weeks. Then treated with carbamazepine 200 mg x3 daily for 1 week. After each treatment subjective evaluation of pain was made Study treatment with imipramine, amitriptyline or diazepam for 12 weeks
Participants	Insulin-dependent diabetes with leg pain secondary to diabetic neuropathy All considered to have substantial degrees of depression Exclusion: amputations N = 59 Age 20 to 59 years M = 27; F = 32
Interventions	Pre-study: phenytoin 2 weeks; carbamazepine 1 week Imipramine 100 mg daily, n = 20 Amitriptyline 100 mg daily, n = 19 Diazepam 5 mg x3 daily, n = 20
Outcomes	Subjective pain assessment Depression scores
Notes	Oxford Quality Score: R1; DB1; W1. Total = 3/5

Turkington 1980 *(Continued)*

	Baseline pain not reported although all said to have pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported ("tablets dispensed under coded conditions")
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No imputation
Size	High risk	< 50 participants per treatment arm

DB: double-blind; N: number of participants in study; n: number of participants in treatment arm; R: randomised; SBP: systolic blood pressure; TCA: tricyclic antidepressant; W: withdrawals.

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

Study	Reason for exclusion
Kvinesdal 1985	Not an original report of an RCT
Minotti 1998	Add-on to diclofenac treatment
Rasmussen 2004	Not an RCT
Sindrup 1989	N < 10
Wysenbeek 1985	Not an RCT

APPENDICES

Appendix 1. Methodological considerations for chronic pain

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

inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010b; Moore 2010e), arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010), and generally in chronic pain (Moore 2014); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009b; Moore 2010c; Moore 2014; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009a). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Finally, individual patient analyses and other evidence indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010d; Moore 2013a).

Appendix 2. Search strategy for CENTRAL

1. MeSH descriptor Pain explode all trees
2. MeSH descriptor Peripheral Nervous System Diseases explode all trees
3. MeSH descriptor Somatosensory Disorders explode all trees
4. ((pain* or discomfort*) and (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):it,ab,kw
5. ((neur* or nerv*) and (compress* or damag*)):it,ab,kw
6. (1 or 2 or 3 or 4 or 5)
7. MeSH descriptor Imipramine, this term only
8. (imipramine or melipramine or Tofranil or Pryleugan or Janimine or Norchlorimipramine or Imizin):it,ab,kw
9. 7 or 8
10. 6 and 9
11. Limit 10 to CENTRAL

Appendix 3. Search strategy for MEDLINE via Ovid

1. exp PAIN/
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/
3. exp SOMATOSENSORY DISORDERS/
4. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
5. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
6. or/1-5
7. Imipramine/
8. (imipramine or melipramine or Tofranil or Pryleugan or Janimine or Norchlorimipramine or Imizin).mp.
9. 7 or 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. or/10-17

19.6 and 9 and 18

Appendix 4. Search strategy for EMBASE via Ovid

1. Imipramine/
2. (imipramine or melipramine or Tofranil or Pryleugan or Janimine or Norchlorimipramine or Imizin).mp.
3. 1 or 2
4. exp neuralgia/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
7. 4 or 5 or 6
8. crossover-procedure/
9. double-blind procedure/
10. randomized controlled trial/
11. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw.
12. or/8-11
13. 3 and 7 and 12

Appendix 5. Summary of outcomes in individual studies: efficacy

Study	Treatment (taken at night, unless stated)	Pain outcome	Other efficacy outcome
Kvinesdal 1984	20:00 single dose Imipramine 50 mg/day week 1, then 100 mg/day weeks 2 to 5 Placebo	Pain not assessed separately but as one of set of neuropathy symptoms Participant assessment of global improvement at end of treatment period: **imipramine** 8/12 (completers); 8/15 (ITT) **placebo** 1/12 (completers); 1/15 (ITT) (significance not reported) For observing physicians, global improvements were: imipramine 7/15; placebo 0/15 (significant: P < 0.02) Physician-assessed mean neuropathy symptom scores at end of each phase were: imipramine 2.9/12; placebo 5.5/12 (marginally significant: P < 0.10)	
Sindrup 1990	20:00 single dose 50 mg/day or 75 mg/day imipramine for 10 days (excl 2 elderly poor sparteine metabolisers not included) 1 week on placebo "for baseline studies" Imipramine 50 to 350 mg/day (except poor metabolisers 25 mg/day) 2 weeks	Pain not assessed separately but as one of set of neuropathy symptoms Neuropathy symptom scores and VAS figures were given for participants. The following figures were calculated by LH: ≥ 50% reduction in combined score for **imipramine vs placebo**: 14/19 (completers); 14/26 (ITT) ≥ 30% reduction in combined score for **imipramine vs placebo**: 17/19 (completers); 17/26 (ITT) ≥ 50% reduction in VAS for **imipramine vs placebo**: 12/19 (completers); 12/26 (ITT) ≥ 30% reduction in VAS for **imipramine vs placebo**: 14/19 (completers); 14/26 (ITT)	Single item scores for other neuropathy symptoms: (placebo:imipramine) paraesthesia 1.48:0.49 dysaesthesia 0.75:0.03

(Continued)

	Paroxetine 40 mg/day (all participants) 2 weeks Placebo 2 weeks	Medians were provided as follows: Neuropathy scores: imipramine 1.97 placebo 5.75 VAS of neuropathy symptoms, max score 500 (completers): imipramine 37 placebo 140 Both observer and participant scores were significantly different for imipramine vs placebo (P < 0.00005 and P = 0.0002) Medians for single items were provided. For pain, imipramine 0.49 placebo 1.47 ("significant") (Note: baseline figures not given separately but median VAS scores for pain shown on graph indicate about 80% drop in pain rating at end of treatment period from baseline or placebo)	nightly aggravation 1.49:0.04 sleep disturbance 0.75:0.02 All "significant"
Sindrup 1992	Time of dose not given 50 or 75mg/day imipramine for 10 days 1 week baseline observations Imipramine 25 to 350 mg/day 2 weeks Mianserin 60 mg/day 2 weeks Placebo 2 weeks	Pain not assessed separately but as one of set of neuropathy symptoms Participant assessment on 6-item neuropathy scale daily Median of last 10 days: **imipramine** 4.0 (marginal significance compared with placebo) **placebo** 5.0 mianserin 5.5 Observer rating on 6-item neuropathy scale at end of treatment period. Significantly lower scores with imipramine than with placebo (itself significantly lower than baseline) Significant reduction in pain item score	
Sindrup 2003	Doses at breakfast and dinner 1 week baseline observations Imipramine 50 mg/day in week 1, 100 mg/day in week 2, 150 mg/day in weeks 3, 4 Venlafaxine 75 mg/day in week 1, 150 mg/day in week 2, 225 mg/day in weeks 3, 4 Placebo 5 weeks	Participants' global evaluation of pain relief (complete, good, moderate, slight, none, worse): Complete/good: **imipramine** 9/29; **venlafaxine** 7/30; **placebo** 2/29 Complete/good/moderate: **imipramine** 14/29; **venlafaxine** 8/30; **placebo** 2/29. Completer analysis only; data not available for ITT Participants' daily separate ratings of 4 pain aspects (constant, paroxysmal, touch-evoked, pressure-evoked) were summed: week 4 value for imipramine 77% of baseline/placebo Authors report NNT of 2.7 for > 50% pain relief, but do not give the raw data on which this calculation was based, or any confidence intervals	Mean (SD) number of paracetamol tablets used in week 4: imipramine 8 (15) placebo 13 (17) Diabetic participants (n = 15) more likely to gain clinically relevant pain relief than non-diabetic

(Continued)

			participants (n = 17)
Turkington 1980	Imipramine 100 mg/day Amitriptyline 100 mg/day Diazepam 5 mg x3/day	Complete relief with imipramine and amitriptyline; no relief with placebo	Depression scores halved with imipramine and amitriptyline; not affected with placebo

ITT: intention to treat; LH: Lesley Hearn; NNT: number needed to treat to benefit; VAS: visual analogue scale.

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

Study	Treatment (taken at night, unless stated)	Adverse events	Withdrawals
Kvinesdal 1984	20:00 undivided dose Imipramine 50 mg/day week 1; 100 mg/day weeks 2 to 5 Placebo	Imipramine: 2 dizziness (1 with orthostatic hypotension); 9 dry mouth; 2 impaired micturition Placebo: 1 dry mouth	3 imipramine: 1 dizziness; 2 "compliance problems"
Sindrup 1990	20:00 single dose 50 mg/day or 75 mg/day imipramine for 10 days (excl 2 elderly poor sparteine metabolisers not included) 1 week on placebo "for baseline studies" Imipramine 50 to 350 mg/day (except poor metabolisers 25 mg/day) 2 weeks Paroxetine 40 mg/day (all participants) 2 weeks Placebo 2 weeks	Participants asked to score intensity of symptoms with each treatment for dry mouth, sweating, visual disturbances, tinnitus, palpitations, dizziness, headache, fatigue, micturition difficulties, nausea, diarrhoea Rating for dry mouth sig higher for imipramine than placebo Rating for dry mouth, palpitation, dizziness sig higher for imipramine than paroxetine 4 showed withdrawal symptoms (nausea, tremor, vomiting) after cessation of imipramine	3 imipramine dose-finding phase 4 imipramine (2 tiredness, dizziness, vomiting; 2 "personal reasons") 1 "compliance problems" 2 needed analgesics to treat other pain
Sindrup 1992	Time of dose not given 50 or 75mg/day imipramine for 10 days 1 week baseline observations Imipramine 25 to 350 mg/day 2 weeks Mianserin 60 mg/day 2 weeks Placebo 2 weeks	10 reported ≥ 1 adverse events during placebo Most common during imipramine or mianserin were dry mouth, orthostatic dizziness, fatigue. No further breakdown given except that total adverse event score with imipramine approximately 4x placebo total	1 imipramine (dizziness and tiredness) 1 placebo (gastritis) 1 placebo and 1 mianserin (personal problems)

(Continued)

Sindrup 2003	Doses at breakfast and dinner 1 week baseline observations Imipramine 50 mg/day in week 1, 100 mg/day in week 2, 150 mg/day in weeks 3, 4 Venlafaxine 75 mg/day in week 1, 150 mg/day in week 2, 225 mg/day in weeks 3, 4 Placebo 5 weeks	14 placebo (P); 20 venlafaxine (V); 20 imipramine (I) Specific (in order P:V:I) Tiredness 3:9:3 Dizziness 1:2:3 Dry mouth 3:4:12 Gastric upset 3:3:0 Nausea 1:6:5 Constipation 2:1:0 Sweating 0:2:5 Palpitation 1:0:1 Disturbed micturition 0:2:0 Impotence 1:1:0 Blurred vision 0:1:1 Headache 3:2:3	2 placebo (1 nausea/diarrhoea; 1 vomiting) 4 venlafaxine (all nausea with 1 dizziness, 1 tiredness, 1 vomiting) 1 imipramine (lack of pain relief) (Also 2 lost to follow-up)
Turkington 1980	Imipramine 100 mg/day Amitriptyline 100 mg/day Diazepam 5 mg x3/day	No data	None mentioned

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 10, 2013
Review first published: Issue 5, 2014

Date	Event	Description
19 May 2014	Review declared as stable	This review will be assessed for updating in 2019.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to writing the protocol.

LH and SD searched for studies, selected studies for inclusion, and carried out data extraction. LH and SD carried out analyses. All review authors were involved in writing the review.

DECLARATIONS OF INTEREST

LH and TP have no known conflicts of interest. SD, PW, and RAM have received research support from charities, government and industry at various times, but none related to this review. In the last five years RAM and PW have consulted for, and RAM has received lecture fees from, various pharmaceutical companies related to analgesics and other healthcare interventions.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol included treatment of fibromyalgia. After publication of the protocol a decision was taken by the Review Group to carry out separate reviews of pharmacological treatments for neuropathic pains and for fibromyalgia, and so fibromyalgia was dropped from the title and methods.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Antidepressive Agents, Tricyclic [*therapeutic use]; Diabetic Neuropathies [*drug therapy]; Imipramine [*therapeutic use]; Neuralgia [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans; Middle Aged