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Desipramine for neuropathic pain in adults (Review)

Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T

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[Intervention Review]

Desipramine for neuropathic pain in adults

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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.

Desipramine is a tricyclic antidepressant that is occasionally used for treating neuropathic pain.

Objectives

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

Search methods

We searched CENTRAL, MEDLINE, and EMBASE from inception to 29 April 2014, and the reference lists of retrieved papers and other reviews. We also used our own hand searched database to identify older studies, and two clinical trials databases for ongoing or unpublished studies.

Selection criteria

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

Data collection and analysis

Two review authors independently extracted the 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 and considered very likely to be biased or that used outcomes of limited clinical utility, or both.

Main results

Five studies treated 177 participants with painful diabetic neuropathy (104) or postherpetic neuralgia (73). The mean or median ages in the studies were 55 to 72 years. Four studies used a cross-over, and one a parallel group design; 145 participants were randomised to receive desipramine 12.5 mg to 250 mg daily, with most taking 100 mg to 150 mg daily following titration. Comparators were placebo in three

studies (an 'active placebo' in two studies), fluoxetine, clomipramine (one study each), and amitriptyline (two studies), and treatment was for two to six 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, but data were available from three studies for our other primary outcome of Patient Global Impression of Change, reported as patient evaluation of pain relief that was 'complete' or 'a lot'. No pooling of data was possible, but third tier evidence in individual studies indicated some improvement in pain relief with desipramine compared with placebo, although this was very low quality evidence, derived mainly from group mean data and completer analyses in small, short duration studies where major bias was possible. There were too few participants in comparisons of desipramine with another active treatment to draw any conclusions.

All studies reported some information about adverse events, but reporting was inconsistent and fragmented. Participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo (very low quality evidence).

Authors' conclusions

This review found little evidence to support the use of desipramine to treat neuropathic pain. There was very low quality evidence of benefit and harm, but this came from studies that were methodologically flawed and potentially subject to major bias. Effective medicines with much greater supportive evidence are available. There may be a role for desipramine in patients who have not obtained pain relief from other treatments.

PLAIN LANGUAGE SUMMARY

Desipramine 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 (a fall, cut, or arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines like paracetamol or ibuprofen are not usually 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.

Desipramine is a tricyclic antidepressant from the same class of medicines as amitriptyline, which is widely recommended for treating neuropathic pain. Desipramine may also be useful in these painful conditions. In 2014, we performed searches to look for clinical trials where desipramine was used to treat neuropathic pain.

Five small studies, each with 24 to 54 participants, included 177 participants in total with painful diabetic neuropathy or postherpetic neuralgia. 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 desipramine (usually at a dose between 100 mg and 150 mg daily), compared with placebo, at the expense of increased adverse events. There was not enough information about other comparators to draw any conclusions.

There was too little information, which was of inadequate quality, to be sure that desipramine works as a pain medicine in painful diabetic neuropathy or postherpetic neuralgia, and no information about other types of neuropathic pain. Other medicines have been shown to be effective as treatments of first choice.

Summary of findings for the main comparison.

Desipramine compared with placebo for painful diabetic neuropathy and postherpetic neuralgia

Patient or population: adults with neuropathic pain (3 studies in painful diabetic neuropathy and postherpetic neuralgia)

Settings: community

Intervention: Desipramine 12.5 mg to 250 mg daily

Comparison: Placebo (or active placebo - benztropine)

Outcomes	Outcome with comparator (placebo)	Outcome with intervention	RR (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain	No data	No data	n/a		n/a	
At least 30% reduction in pain	No data	No data	n/a		n/a	
Proportion below 30/100 mm on VAS	No data	No data	n/a		n/a	
Patient Global Impression of Change very much improved (PGPR "complete" or "a lot")	3.8 % and 8.3% (3 events)	17% and 30% (12 events)	Not calculated	50 participants, 2 studies	Very low	Small numbers of participants in 2 studies with short duration, cross-over design, different painful neuropathy condition
Patient Global Impression of Change much or very much improved (PGPR "complete", "a lot", or "moderate")	7.7% and 8.3% (4 events)	46% in both studies (23 events)	Not calculated	50 participants, 2 studies	Very low	Small numbers of participants in 2 studies with short duration, cross-over design, different painful neuropathy condition
Adverse event withdrawals	0% to 12% (4 events)	0% to 19% (10 events)	Not calculated	76 participants, 3 studies	Very low	Small numbers of participants in 3 studies with short duration, cross-over design
Serious adverse events	None reported	None reported	n/a	177 participants, 5 studies	n/a	Small numbers of participants in 5 studies of short duration (placebo- and active-controlled)

Death	None reported	None reported	n/a	177 participants, 5 studies	n/a	Small numbers of participants in 5 studies of short duration (placebo- and active-controlled)

CI: confidence interval; PGPR: Patient global evaluation of pain relief; RR: risk ratio; VAS: visual analogue scale; n/a: not applicable

BACKGROUND

This review is based on a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a) (Appendix 1).

Desipramine is a tricyclic antidepressant (TCA) that is sometimes used to treat chronic neuropathic pain (pain due to nerve damage or changes in the central nervous system (CNS)). While its use is not specifically recommended, it is listed alongside other tricyclic antidepressants in some treatment guidelines, although this is an unlicensed indication (Attal 2010; Dworkin 2010; Finnerup 2010; Moulin 2007). It is an active metabolite of imipramine, the subject of another Cochrane review (Hearn 2014).

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 with 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 2014a).

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). The incidence of postherpetic neuralgia in the UK appears to be increasing (Hall 2013). 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 is, 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 2014a). The incidence of some forms of neuropathic pain, such as diabetic neuropathy and postsurgical chronic pain (which is often neuropathic in origin), is 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 or cognitive interventions, or both. Conventional analgesics are usually not effective. Some patients may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Derry 2014). 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 2009; Moore 2014b). An overview of treatment guidelines shows 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 2013a)) is small, generally 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNTs) usually between 4 and 10 (Moore 2013b).

Description of the intervention

Desipramine is a tricyclic antidepressant, and is an active metabolite of imipramine, which is the subject of a separate review (Hearn 2014). While these medicines are still used to treat depressive illness, they have also been used to treat neuropathic pain, although they are not licensed for use in this context in the UK or USA.

Desipramine is available as tablets (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg). For treating neuropathic pain, typical starting dosages are between 10 mg and 25 mg daily, usually taken at night, increasing to 150 mg daily if necessary. Common adverse events associated with its use include dry mouth, constipation, weight gain, blurred vision, and orthostatic hypotension. It is less sedating than amitriptyline.

How the intervention might work

Desipramine is a very strong reuptake inhibitor of norepinephrine, and to a lesser extent, serotonin. It is also a metabolite of imipramine. Its mechanism of action in the treatment of neuropathic pain remains uncertain, but it is thought that norepinephrine reuptake inhibition causes activation of descending pathways in the spinal cord, which then block ascending signals to the brain. Tricyclic antidepressants are also known to inhibit sodium channels in nerve membranes, with an efficacy comparable to conventional local anaesthetics (Lenkey 2006; Sudoh 2003). This would predict a rapid onset of pain relief. TCAs are known to block sodium channels, binding at the local anaesthetic site at plasma levels found with therapeutically relevant doses.

That the mechanism differs from that in treating depression is confirmed by the observation that analgesia with antidepressants is often achieved at a lower dosage than for the onset of any antidepressant effect, and more promptly. In addition, there is no correlation between the effects of antidepressants on mood and pain, and antidepressants produce analgesia in patients with and without depression (Onghena 1992).

Why it is important to do this review

The earlier review of antidepressants for neuropathic pain is being updated with separate reviews for individual drugs due to the larger amount of data now available for some of them (Saarto

2007). The individual reviews (including amitriptyline (Moore 2012a), imipramine (Hearn 2014), and duloxetine (Lunn 2014)) will be included in an overview review of antidepressant drugs for neuropathic pain.

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy (Appendix 1). The most important change is the move from using average pain scores, or average change in pain scores, to the number of patients who have a large decrease in pain (by at least 50%) and who continue their treatment, ideally in trials of 8 to 12 weeks or longer. Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the reference guide for pain studies (AUREF 2012).

This Cochrane systematic 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) and size (ideally at least 500 participants in a comparison in which the NNT is four or above (Moore 1998)). This does set high standards and marks a departure from how reviews have been done previously.

OBJECTIVES

To assess the analgesic efficacy of desipramine for chronic neuropathic pain in adults, and to evaluate adverse events reported in the studies.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer, although the emphasis of the review was on studies of eight weeks or longer. 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

Participants were aged 18 years and above and could have one or more of a wide range of chronic neuropathic pain conditions including (but not limited to):

- cancer-related neuropathy;
- 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.

We would include studies of participants with more than one type of neuropathic pain; in such cases we would analyse results according to the primary condition. Migraine and headache studies were excluded.

Types of interventions

Oral desipramine 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 (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in the 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 the Patient Global Impression of Change (PGIC) (moderate), and very much improved on the PGIC (substantial). These outcomes concentrate on dichotomous outcomes in circumstances 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 (Summary of findings for the main comparison).

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 or consequences

5. Withdrawals due to adverse events
6. Specific adverse events, particularly somnolence and dizziness

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:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 4 of 12);
- MEDLINE (via Ovid) (1946 to 29 April 2014);
- EMBASE (via Ovid) (1974 to 29 April 2014).

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

Searching other resources

We reviewed the bibliographies of any randomised trials identified and review articles, and searched clinical trial databases (ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators or study sponsors because of the age of the studies identified and because this is not an area of active research.

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 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; decisions were made by two review authors. Two review authors then read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart shows the selection process (Moher 2009).

Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into the Cochrane Collaboration's statistical software (Review Manager 2013) 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 as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

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

We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, 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' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) 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 numbers needed to treat (NNTs) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to harm (NNH) and is calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% CI using a fixed-effect model unless significant statistical heterogeneity was

found (Assessment of heterogeneity). Continuous data were not used in the analyses.

Unit of analysis issues

The control treatment arm would be split between active treatment arms in a single study if the active treatment arms were not combined for analysis.

For cross-over studies we planned to use first period data only wherever possible. Where this was not reported we analysed the data as if the treatment periods were parallel, drawing attention to the potential bias this may introduce, and interpreting the results accordingly.

Dealing with missing data

Where possible we have used intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Missing participants were assigned zero improvement. Where this was not possible we have used the results as reported, but drawn attention to the potential bias this may introduce. 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. We would have assessed 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, though 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 for meta-analysis 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 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 all analyses to be according to individual painful conditions, because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). If there had been sufficient data we would have carried out subgroup analysis for dose of desipramine and duration of study.

Sensitivity analysis

If there had been sufficient data we would have examined details of dose escalation schedules to investigate if this could provide some basis for a sensitivity analysis.

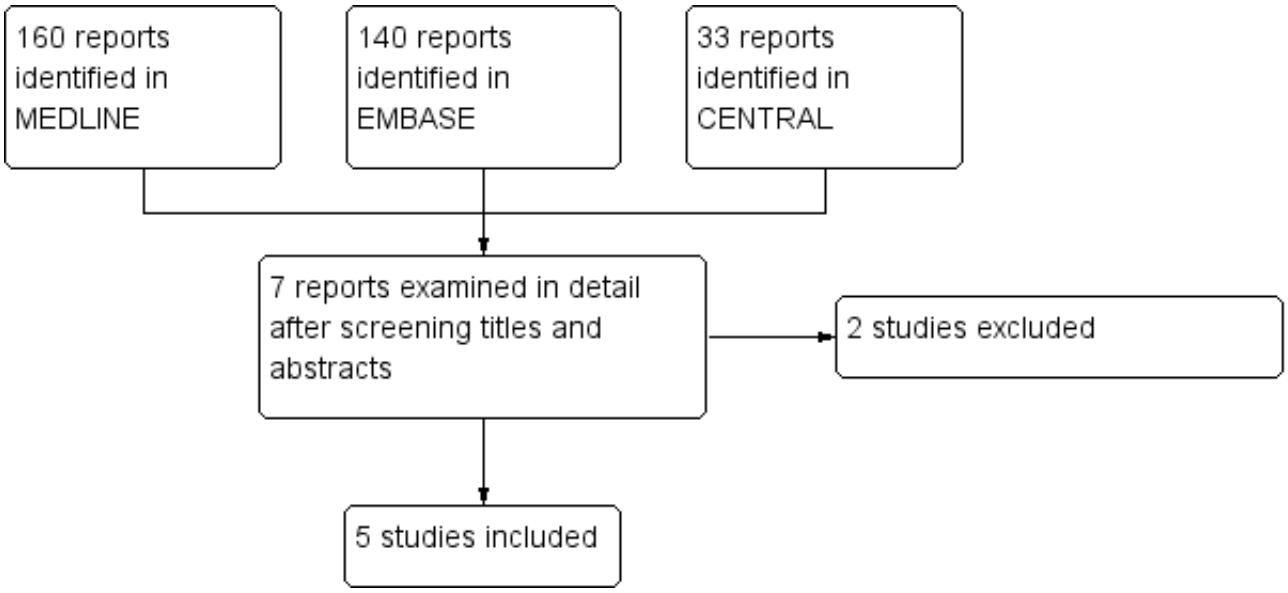
RESULTS

Description of studies

Results of the search

Searches of bibliographic databases found 33 titles in CENTRAL, 160 in MEDLINE, and 140 in EMBASE, which we examined for inclusion. After screening titles and abstracts, we obtained full copies and examined seven reports in detail. We included five studies and excluded two (Figure 1). Searches of trial databases and study or review reference lists did not identify any additional studies.

Figure 1. Study flow diagram.



Included studies

Five studies treated 177 participants, of whom 145 were randomised to desipramine (Kishore-Kumar 1990; Max 1991; Max 1992; Rowbotham 2005; Sindrup 1990); in the cross-over studies, however, it was not clear that all randomised participants received all treatments, and most studies did not report results for all randomised participants (that is, completer analyses reported). In four studies, there was a desipramine dose-finding phase (Kishore-Kumar 1990; Max 1991; Max 1992; Rowbotham 2005): in the first of these, 3 out of 32 participants withdrew because of adverse effects. Participants took oral desipramine for between two and six weeks. Daily doses were between 12.5 mg and 250 mg daily (mostly 100 mg to 200 mg). The licensed maximum dose is 300 mg. In one study, poor metabolisers were treated with lower doses (Sindrup 1990).

Study participants were aged between 20 and 84 years (study means or medians from 55 to 72 years), with an approximately five to four ratio of men to women (94 men; 76 women; 7 not stated (Sindrup 1990)). Participants had experienced pain associated with postherpetic neuralgia (Kishore-Kumar 1990; Rowbotham 2005) (73 participants) or diabetic neuropathy (Max 1991; Max 1992; Sindrup 1990) (104 participants) for at least three months. Common grounds for exclusion from studies were severe depression, severe pain of other cause, and medical contra-indication.

In three studies, desipramine was compared to placebo (Sindrup 1990) or active placebo (benztropine) (Kishore-Kumar 1990; Max 1991). The active placebo was chosen to mimic dry mouth, which is associated with TCAs, and help maintain blinding.

In three studies, other analgesics were compared to desipramine: clomipramine (Sindrup 1990); amitriptyline (Max 1992; Rowbotham 2005); fluoxetine (Rowbotham 2005).

One study used a parallel-group design (Rowbotham 2005), while the other four used a cross-over design (Kishore-Kumar 1990; Max 1991; Max 1992; Sindrup 1990). One study had washout periods between cross-over periods (Sindrup 1990).

Stable medication for diabetes was maintained.

Excluded studies

We excluded two studies after reading the full papers. Coquoz 1991 used participants who were healthy volunteers, while Raja 2002 randomised participants to drug classes, not to individual drugs, and results for individual drugs were not reported separately.

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 came from small study size.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

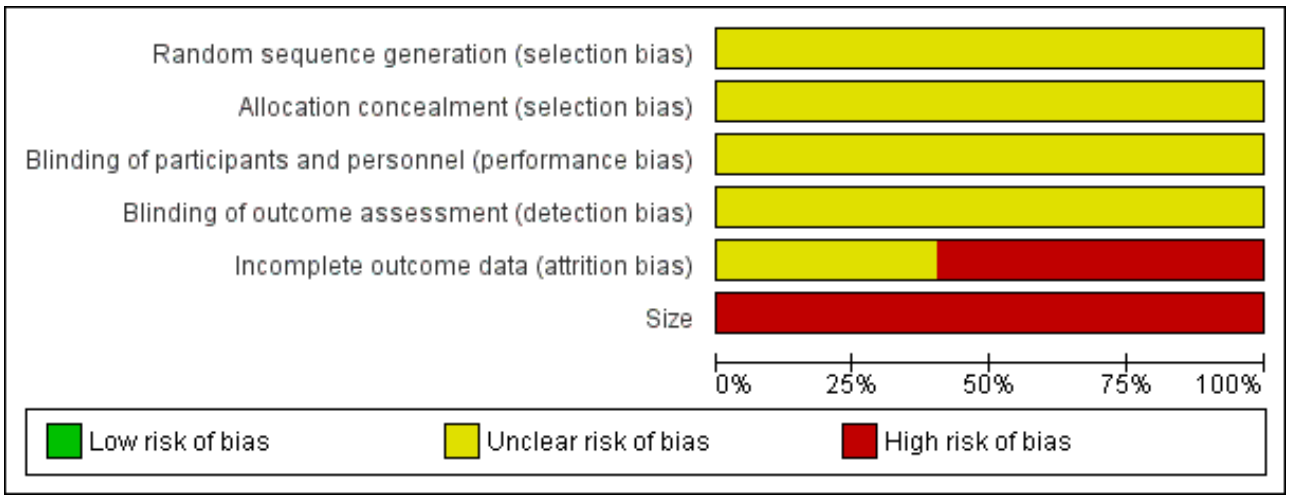
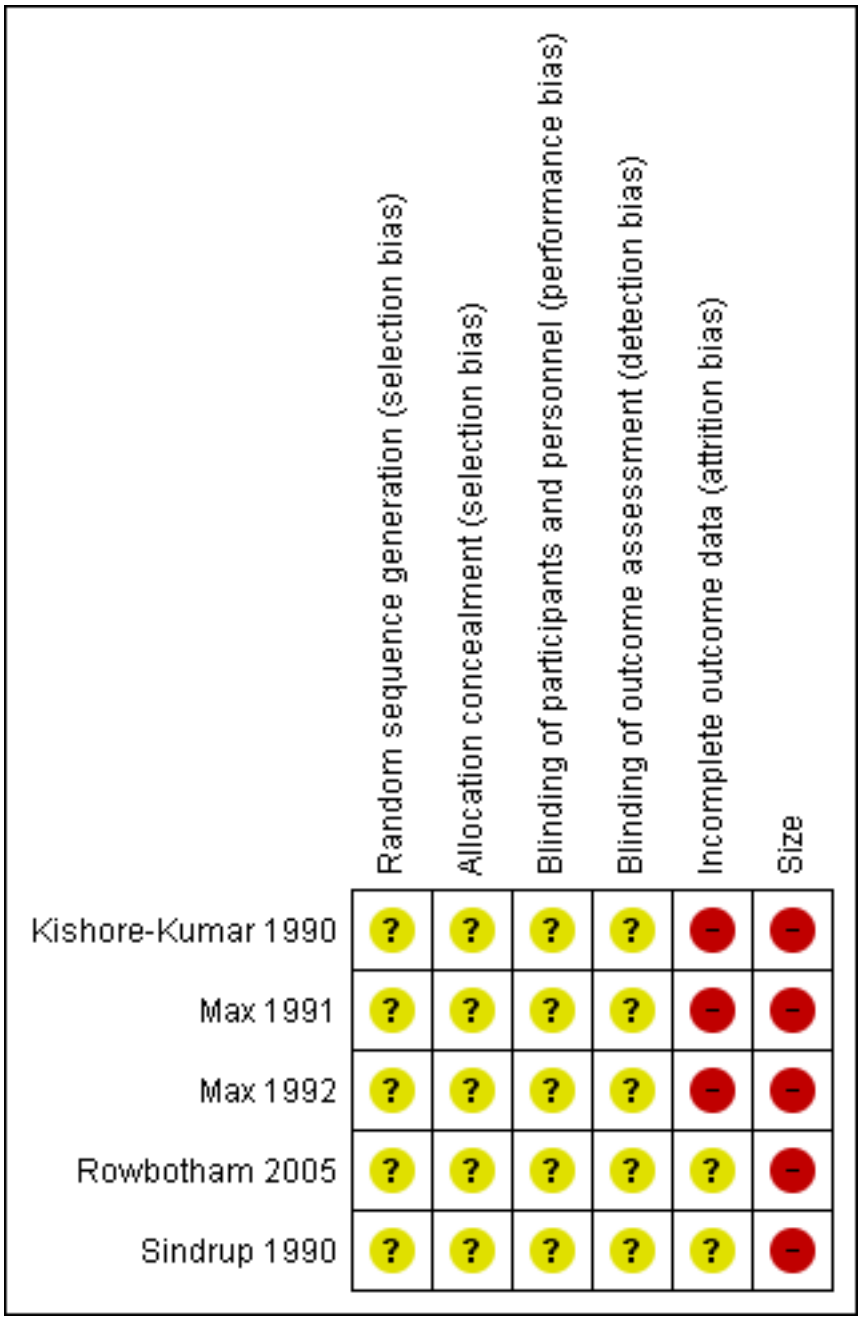


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were randomised. No studies adequately described how allocation to treatment groups was concealed.

Blinding

All studies were double blind. Only one study (Sindrup 1990) adequately described the methods used to ensure that participants and interacting investigators were unable to differentiate between active and control groups; another referred to use of placebo capsules to maintain the same dosing regime (Rowbotham 2005).

Incomplete outcome data

All four cross-over studies (Kishore-Kumar 1990; Max 1991; Max 1992; Sindrup 1990) performed efficacy analyses only on those participants who completed all treatment phases of the study (completer analyses), and did not report results for the first phase only. The parallel group study performed an intention-to-treat (ITT) analysis (imputation not reported) (Rowbotham 2005).

Proportions of withdrawals with desipramine varied: 5/26 (Kishore-Kumar 1990); 2/24 (Max 1991); 7/54 (Max 1992); 2/15 (Rowbotham 2005); 3/26 (Sindrup 1990). Therefore, some 13% of participants randomised to desipramine dropped out.

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 their methods but these were usually not our preferred (primary) outcomes. Pain was not reported separately in Sindrup 1990.

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 54 (although only 38 provided data) (Max 1992) so the risk of bias is high for this item.

Effects of interventions

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

Efficacy

There was 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.

Details of data from individual studies are shown in Appendix 5.

Third tier evidence

None of the studies reported our primary outcome of participants with at least 30% or at least 50% reduction in pain intensity. Four studies used a six-point scale to assess the Patient Global evaluation of Pain Relief (PGPR) (complete, a lot, moderate, slight, none, worse). We considered that PGPR complete or a lot was equivalent to our primary outcome of PGIC very much improved, and PGPR complete, a lot, or moderate was equivalent to PGIC much or very much improved.

Kishore-Kumar 1990 reported that PGPR was complete or a lot for 8/19 (ITT 8/26) taking desipramine (1/19 with placebo; ITT 1/26) and at least moderate for 12/19 with desipramine (2/19 with placebo). Participants' weekly rating of pain intensity was significantly lower with desipramine than with placebo by the end of the study. Some pain components were also reduced compared with placebo (steady: 9/19 compared with 1/19; brief: 4/8 compared with 0/8; mechanical allodynia: 7/18 compared with 1/18).

Max 1991 reported similar findings that PGPR was complete or a lot for 4/20 (ITT 4/24) taking desipramine (2/20 with placebo; ITT 2/24) and at least moderate for 11/20 with desipramine (2/20 with placebo). Participants' weekly rating of pain intensity was significantly lower with desipramine than with placebo by the end of the study. Some pain components were also reduced compared with placebo: pain described as "steady, burning pain" was significantly reduced).

Max 1992 found that PGPR was similar for desipramine and amitriptyline (placebo not used): complete or a lot for 15/38 (ITT 15/54) and 18/38 (ITT 18/54) participants respectively, and at least moderate for 23/38 and 28/38 respectively. Participants' weekly rating of pain intensity was not significantly different.

Rowbotham 2005 reported that Visual Analogue Scale (VAS) readings fell by 47% with desipramine, compared with 38% and 35% falls with amitriptyline and fluoxetine respectively. PGPR was at least moderate for 12/15 with desipramine, 9/17 with amitriptyline, and 5/15 with fluoxetine (ITT analysis).

In Sindrup 1990, pain was not reported separately but as part of a set of neuropathy symptoms. Both observers and participants reported a significant reduction in symptom scores with desipramine compared to placebo; there was a non-significant fall in the individual pain item score with desipramine.

Adverse events

Details of adverse events reported in individual studies are in Appendix 6. All studies reported some information about adverse events, but reporting was inconsistent and fragmented.

Participants experiencing any adverse event

One study reported the number of participants who experienced one or more adverse events for all those who were treated (ITT) (Max 1992). Two studies reported this number for completers (Kishore-Kumar 1990; Max 1991). Two studies reported on mean or median adverse event scores (based on the intensity of the event) for completers only (Rowbotham 2005; Sindrup 1990).

Kishore-Kumar 1990 reported that all completers had experienced at least one adverse event with desipramine (19/19), while 15/19 had done so with placebo. The most common events with desipramine were dry mouth, constipation, dizziness, sedation, micturition difficulty, insomnia, and sweating. The most common with placebo were dry mouth, dizziness, and constipation, but these were experienced at lower levels than with desipramine.

Max 1991 reported that nearly all completers had experienced at least one adverse event with desipramine (18/20), while nearly as many had done so with placebo (15/19). The most common (over 10%) events with desipramine were dry mouth, sedation, insomnia, constipation, orthostatic symptoms, palpitations, and increased sweating. The most common with placebo were dry mouth, sedation, constipation, and insomnia. Insomnia, constipation, and dry mouth were slightly more frequent with desipramine.

Max 1992 reported similar numbers of participants with one or more adverse events with both desipramine (29/54) and amitriptyline (31/54). The most common (over 10%) events with desipramine were dry mouth, tiredness, constipation, insomnia, increased sweating, headache, lightheadedness. Figures were similar for amitriptyline.

Rowbotham 2005 reported that completers' scores (presumably means) on a symptom checklist increased by more than 1 (for a range of 0 to 3) for adverse events as follows.
Desipramine and amitriptyline: dry mouth, constipation, bitter taste; fluoxetine: sleepiness and lightheadedness.

Sindrup 1990 reported medians of completers' total scores for 14 side effects, with observers assigning values to each symptom (5-point scale from 0 to 2.0). For desipramine and clomipramine the medians of the total scores were 4.5 and 4.0 respectively. They reported a median of 0.02 for placebo scores but this must be erroneous.

Participants experiencing any serious adverse event

No serious adverse events were reported during desipramine treatment, though one participant was hospitalised for nausea and weakness with hyponatraemia during fluoxetine treatment (Rowbotham 2005).

There were no deaths.

Withdrawals

All five studies reported on withdrawals. Details of withdrawals reported in individual studies are in Appendix 6.

Withdrawals due to adverse events

All five studies reported on withdrawals due to adverse events.

In four studies (Kishore-Kumar 1990; Max 1991; Max 1992; Sindrup 1990) 17/130 participants withdrew during desipramine treatment, 4/76 during placebo treatment (Kishore-Kumar 1990; Max 1991; Sindrup 1990), 7/54 during amitriptyline treatment (Max 1992), and 3/26 during clomipramine treatment (Sindrup 1990).

There was a variety of reasons for these withdrawals: three were due to rash, two to fever, two to bundle branch block, five to possible symptoms of low blood pressure, and one each to tiredness, insomnia, palpitations, tremor, jitteriness, chest pain, and "seizure".

The four placebo withdrawals were due to combinations of vertigo, nausea, rash, unsteadiness, mental fogginess, and chest pain. All occurred with the 'active' placebo treatment.

Rowbotham 2005 reported nine withdrawals but gave reasons for only five of these. There were 2/15 with desipramine and 2/17 with amitriptyline: adverse events were cited for three of these but the drug involved was not specified. There were 5/15 withdrawals with fluoxetine, adverse events being cited for two of these and no reason given for the others.

Withdrawals due to lack of efficacy

There were no withdrawals due to lack of efficacy with desipramine, one with placebo (Max 1991), and one with clomipramine (Sindrup 1990).

Withdrawals for other reasons

Kishore-Kumar 1990 reported 2/26 withdrawals for "intercurrent illness", and Max 1992 reported two "voluntary" withdrawals.

As noted above, Rowbotham 2005 gave reasons for only 5/9 withdrawals. Three from the fluoxetine arm remain unexplained, as did one from either the desipramine or amitriptyline arms.

DISCUSSION

Summary of main results

We found five studies enrolling 177 participants with chronic neuropathic pain, 59% of whom had painful diabetic neuropathy and 41% of whom had postherpetic neuralgia.

None of the studies reported our primary outcomes of at least 30% or at least 50% pain relief, but three reported outcomes we considered equivalent to our other primary outcomes of PGIC much or very much improved, and PGIC very much improved. 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 desipramine compared with placebo, although this was derived mainly from group mean data and completer analyses (see Appendix 1), in small, short duration studies where major bias is possible. Participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo. See Summary of findings for the main comparison.

Comparison with alternative treatments indicate more effective and safer medicines are available (Lunn 2014; Moore 2009; Moore 2014b).

Overall completeness and applicability of evidence

Desipramine was tested only in painful diabetic neuropathy and postherpetic neuralgia, so results cannot be reliably extrapolated to other neuropathic conditions.

Since desipramine is a TCA, depression among participants may conceivably affect the results. Three studies excluded people with severe depression (Kishore-Kumar 1990; Max 1991; Max 1992). One reported on the incidence of depression in participants and its progress during the trial (Rowbotham 2005); the small numbers involved do not lend themselves to any conclusion about the effect of depression on pain relief. Sindrup 1990 do not mention depression. Three studies showed a rapid onset of pain relief (Kishore-Kumar 1990; Max 1991; Max 1992), consistent with prompt action on sodium channels, and a different mechanism of action than that of its antidepressant effect. Rowbotham 2005 do not describe the speed of onset; Sindrup 1990 only tested for two weeks and, while there is evidence of pain relief, changes were not significant.

Short-term studies (less than six weeks) may not accurately predict longer-term efficacy in chronic conditions: four studies were of six weeks' duration, while one was of only two weeks duration. Furthermore, caution is required in interpreting adverse event data from short duration studies for real world clinical practice, particularly where so few participants have been studied.

Quality of the evidence

Reporting quality in the studies was generally poor by current standards. While 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 54 participants in any treatment arm). Four of the five were of short duration (six weeks), used cross-over design without separate reporting of first period data, and reported only on participants who completed more than one phase of treatment. One was of very short duration (two weeks).

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. None of the studies reported asking 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. Three studies did this (Kishore-Kumar 1990; Max 1991; Max 1992), giving proportions reporting particular

symptoms, but not reporting the time course of adverse events. Rowbotham 2005 used a checklist but only reported qualitatively. Sindrup 1990 seems to have used a checklist but reported only median scores (and those incorrectly).

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). None of the studies lasted more than six weeks, which may lead to an overestimate of efficacy.
- The degree of exaggeration of treatment effects in cross-over trials compared to parallel-group designs, as has been seen in some circumstances (Khan 1996), is unclear but 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. The majority of data in this review were from cross-over studies.
- 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 indicated results for an ITT analysis (adding missing participants back into the denominator) for one primary outcome, to give a more conservative estimate.
- The absence of publication bias (unpublished trials showing no benefit of desipramine 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.

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 and UK do not specifically recommend use of desipramine (Attal 2010; NICE 2013). In USA, Dworkin 2010 recommend desipramine as an alternative to nortriptyline as a first-line TCA treatment for neuropathic pain.

AUTHORS' CONCLUSIONS

Implications for practice

This review found little evidence to support the use of desipramine to treat neuropathic pain. There was very low quality evidence of some effect from studies that were methodologically flawed and potentially subject to major bias. There are more effective and safer medicines available. There may be a role for use of desipramine in patients who have not obtained pain relief from other treatments.

Implications for research

Larger, better-designed studies would provide more definitive conclusions on the efficacy of desipramine, 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 evidence available.

Reasonable levels of evidence exist for the benefit of other antiepileptic and antidepressant drugs in the treatment of chronic neuropathic pain. There is a need to develop new treatments for neuropathic pain conditions, given that at present we have limited efficacy for a limited number of drugs, and some people remain inadequately treated.

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CHARACTERISTICS OF STUDIES

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

Kishore-Kumar 1990

Methods	Randomised, double-blind, placebo-controlled, cross-over study After clinical assessment, 2 x 6 weeks of desipramine or placebo. Dose titrated to maximum tolerated over 4 weeks, then stable for 2 weeks. No washout between treatment periods
Participants	Postherpetic neuralgia for at least 3 months; normal cognition and communication ability Exclusions: other severe pain; severe depression; medical contra-indication N = 26 (19 completed) M 17; F 9 Median age 62 years (range 38 - 79)
Interventions	Desipramine 12.5 mg - 250 mg daily Benztropine (active placebo) 0.5 mg - 1.0 mg daily
Outcomes	Patient Global evaluation of Pain Relief (PGPR): 6-point categorical scale, from complete to worse at end of treatment period PI: 4-point scale for steady, brief, allodynia (mechanical, heat, cold), before and after treatment Daily PI diary, using 13 descriptors. Converted into numerical scores and weekly means calculated
Notes	Oxford Quality Score: R = 1; DB = 1; W = 1. Total = 3/5

Kishore-Kumar 1990 *(Continued)*

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	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	High risk	Completer analysis reported
Size	High risk	< 50 participants per treatment arm (≤ 26)

Max 1991

Methods	Randomised, double-blind, placebo-controlled, cross-over study After clinical assessment, 2 x 6 weeks of desipramine or placebo. Dose titrated to maximum tolerated over 4 weeks, then stable for 2 weeks. No washout between treatment periods
Participants	Painful diabetic neuropathy for at least 3 months; normal cognition and communication ability Exclusions: other etiology for neuropathy; other severe pain; severe depression; medical contra-indication N = 24 (20 completed) M 15; F 9 Median age 62 years (range 21 - 71)
Interventions	Desipramine 12.5 mg - 250 mg daily Benztropine (active placebo) 0.5 mg - 1.0 mg daily
Outcomes	PGPR at end of treatment period: 6-point categorical scale, from complete to worse Comparison of PI before and after treatment: 4-point scale for steady burning, steady aching, brief, allodynia (mechanical, warm), cold hyperalgesia Daily PI diary, using 13 descriptors. Converted into numerical scores and weekly means calculated
Notes	Oxford Quality Score: R = 1; DB = 1; W = 1. Total = 3/5

Risk of bias

Max 1991 *(Continued)*

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	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	High risk	Completer analysis reported
Size	High risk	< 50 participants per treatment arm (≤ 24)

Max 1992

Methods	Randomised, double-blind, cross-over study After clinical assessment, 2 x 6 weeks of desipramine or amitriptyline. Dose titrated to maximum tolerated over 4 weeks, then stable for 2 weeks. No washout between treatment periods
Participants	Painful diabetic neuropathy for at least 3 months; stable glycaemic control Exclusions: other more severe pain; severe depression; postural hypotension; vascular disease; nephropathy; medical contra-indication N = 54 (38 completed) M 33; F 21 Median age 58 years (range 20 - 84)
Interventions	Desipramine 12.5 mg - 150 mg daily Amitriptyline 12.5 mg - 150 mg daily
Outcomes	PGPR at end of treatment period: 6-point categorical scale, from complete to worse Daily PI diary, using 13 descriptors. Converted into numerical scores and weekly means calculated
Notes	Oxford Quality Score: R = 1; DB = 1; W = 0. Total = 2/5

Risk of bias

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

Max 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
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	High risk	Completer analysis reported. Claims ITT analysis "similar". Withdrawals > 10% (but evenly distributed between groups)
Size	High risk	< 50 participants evaluated per treatment arm (54 randomised, but only 38 completers)

Rowbotham 2005

Methods	Randomised, double-blind, parallel group study Titration to maximum tolerated dose over 3 weeks, then stable dose for further 3 weeks
Participants	Postherpetic neuralgia for >3 months; normal cognition and communication ability; never had adequate trial of antidepressant Exclusions: previous withdrawal due to antidepressant adverse event; other more severe pain; medical contra-indication N = 47 (38 completed) M 20; F 27 Mean age 72 years (range 40 - 84)
Interventions	Desipramine 25 mg - 150 mg daily Amitriptyline 25 mg - 150 mg daily Fluoxetine 10 mg - 60 mg daily
Outcomes	PI: Visual Analogue Scale of pain intensity obtained weekly PR: 6-point scale, from 0 = worse to 5 = complete relief
Notes	Oxford Quality Score: R = 1; DB = 1; W = 1. Total = 3/5

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

Rowbotham 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details of blinding not reported Probably satisfactory as it is stated that placebo capsules were used to maintain the dose of 2 capsules twice daily
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details of blinding not reported, probably satisfactory
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not reported. ITT analysis is similar to completer analysis
Size	High risk	< 50 participants per treatment arm (≤ 47)

Sindrup 1990

Methods	Randomised, double-blind, placebo-controlled, cross-over study 3 x 2 weeks of desipramine, clomipramine or placebo. Washout between treatment periods: 1 week for extensive metabolisers of sparteine (EM); 3 weeks for poor metabolisers (PM)
Participants	Painful diabetic neuropathy N = 26 (19 completers) Mean age 55 years (29 to 78) (completers) M 9, F 10 (completers)
Interventions	Desipramine 200 mg daily (EM) or 50 mg daily (PM) Clomipramine 75 mg daily (EM) or 50 mg daily (PM) Placebo
Outcomes	Neuropathy symptom scale: 6 item (pain, paraesthesia, dysaesthesia, numbness, nightly deterioration, sleep disturbance); 0 to 2, maximum score 12 • performed daily by participants (one did not do this consistently - not included) and at end of treatment period by physician • pain item also reported separately Greater than 25% reduction in neuropathy score from baseline (participant daily self-rating)
Notes	Oxford Quality Score: R = 1; DB = 2; W = 1. 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)	Unclear risk	"Placebo tablets were of identical size and colour"

Sindrup 1990 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Placebo tablets were of identical size and colour"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completer analysis
Size	High risk	< 50 participants per treatment arm (≤ 26)

DB: double blind; F: female; ITT: intention-to-treat; M: male; N: number of participants in study; PGPR: Patient Global evaluation of Pain Relief; PI: pain intensity; PR: pain relief; R: randomised; W: withdrawals

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

Study	Reason for exclusion
Coquoz 1991	Participants were healthy volunteers
Raja 2002	Participants randomised to drug class, not individual drug, and results for individual drugs not reported separately

APPENDICES

Appendix 1. Methodological considerations for chronic pain

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

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010c), arthritis (Moore 2010b), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The 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 2010b); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009; Moore 2010b; Straube 2008; Sultan 2008). A Cochrane systematic review of pregabalin in neuropathic pain demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Finally, presently unpublished individual patient analyses 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).

Appendix 2. Search strategy for CENTRAL (The Cochrane LIbrary)

#1 MeSH descriptor Pain explode all trees (32778)

#2 MeSH descriptor Peripheral Nervous System Diseases explode all trees (2993)
#3 MeSH descriptor Somatosensory Disorders explode all trees (718)
#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 (16907)
#5 ((neur* or nerv*) and (compress* or damag*)):it,ab,kw (2029)
#6 (1 or 2 or 3 or 4 or 5) (46034)
#7 MeSH descriptor Desipramine, this term only (382)
#8 (desipramine or Norpramin or Pertofrane):it,ab,kw (635)
#9 7 or 8 (635)
#10 6 and 9 (36)
#11 Limit 10 to CENTRAL (33)

Appendix 3. Search strategy for MEDLINE (via Ovid)

1. exp PAIN/ (302655)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (113897)
3. exp SOMATOSENSORY DISORDERS/ (15847)
4. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (37625)
5. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (47198)
6. 1 or 2 or 3 or 4 or 5 (444403)
7. Desipramine/ (5411)
8. (desipramine or Norpramin or Pertofrane).mp. (7445)
9. 7 or 8 (7445)
10. randomized controlled trial.pt. (370572)
11. randomized.ab. (269403)
12. placebo.ab. (145013)
13. drug therapy.fs. (1688999)
14. randomly.ab. (191615)
15. trial.ab. (279322)
16. groups.ab. (1232736)
17. 10 or 11 or 12 or 13 or 14 or 15 or 16 (3135037)
18. 6 and 9 and 17 (160)

Appendix 4. Search strategy for EMBASE (via Ovid)

1. exp neuralgia/ (71974)
2. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (78492)
3. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (66848)
4. 1 or 2 or 3 (176956)
5. desipramine/ (20432)
6. (desipramine or Norpramin or Pertofrane).mp. (21023)
7. 5 or 6 (21023)crossover-procedure/ (38616)
8. double-blind procedure/ (115238)
9. randomized controlled trial/ (342543)
10. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1188683)
11. 8 or 9 or 10 or 11 (1265261)
12. 4 and 7 and 12 (140)

Appendix 5. Summary of outcomes in individual studies: efficacy

Study	Treatment	Pain outcome	Other efficacy outcome

(Continued)

	(taken at night, unless stated)		
Kishore-Kumar 1990	18:00 single dose Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Active placebo (benztropine) 0.5 mg daily , increasing to 1 mg daily	Participants' global evaluation of pain relief (6 items: worse to complete): **moderate or better** Desipramine 12/19; Placebo 2/19 **a lot or complete** Desipramine 8/19; Placebo 1/19 Weekly participant rating of pain intensity: desipramine superior to placebo by end of week 6 (p<0.001) (also by end of week 3: p<0.05) (inclusion of drop-outs did not change conclusion)	Reduction in pain components (desipramine:placebo) Steady 9/19:1/19 Brief 4/8:0/8 Mechanical allodynia 7/18:1/18
Max 1991	18:00 single dose Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Active placebo (benztropine) 0.5 mg daily , increasing to 1 mg daily	Participants' global evaluation of pain relief (6 items: worse to complete): moderate or better Desipramine 11/20; Placebo 2/20 a lot or complete Desipramine 4/20; Placebo 2/20 Weekly participant rating of pain intensity: Desipramine superior to placebo by end of week 6 (p<0.01) (also by start of week 5: p<0.05) (inclusion of one drop-out who completed at least part of both phases did not change conclusion)	Reduction in pain components: Steady burning significantly reduced with desipramine (P<0.05) "Trend" towards reduction with steady aching and brief pains
Max 1992	21:00 single dose Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Amitriptyline 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated	Participants' global evaluation of pain relief (6 items: worse to complete): moderate or better Desipramine 23/38; Amitriptyline 28/38 a lot or complete Desipramine 15/38; Amitriptyline 18/38 ITT analysis results "similar" Weekly mean of participant rating of pain intensity: no significant difference between desipramine and amitriptyline	

(Continued)

Rowbotham 2005	Two doses per day (times not given) Desipramine 25-150 mg daily, titrated to maximum tolerable Amitriptyline 25-150 mg daily, titrated to maximum tolerable Fluoxetine 10-60 mg daily, titrated to maximum tolerable	Weekly results from Visual Analogue Scale of pain intensity: baseline to end Desipramine 50 to 29mm (47% decrease) Amitriptyline 59 to 39mm (38%) decrease) Fluoxetine 53 to 36mm (35% decrease) 6 item pain relief scale (worse to complete): at least moderate relief Desipramine 12/15 Amitriptyline 9/17 Fluoxetine 5/15 Relief category scale (0-5: 3 = moderate relief) Desipramine 3.1 Amitriptyline 2.7 Fluoxetine 2.1	
Sindrup 1990	20:00 single dose Desipramine 200 mg daily (EM); 50 mg daily (PM) Clomipramine 75 mg daily (EM); 50 mg daily (PM) Placebo	Pain not assessed separately but as one of set of neuropathy symptoms Neuropathy symptom scale (6 item, 0 to 2): pain, paraesthesia, dysaesthesia, numbness, nightly deterioration, sleep disturbance) Performed daily by participants and at end of treatment period by physician Scores significantly better than placebo with both observer and self-rating: desipramine 0.05<P<0.10 Median reduction with observer scores >25% reduction in score compared with placebo: Desipramine 10/25 Clomipramine 14/25	Single items: desipramine not significantly lower than placebo for pain Median [sic but probably mean] 1.02 versus 1.50 (0-2 scale) (P>0.30)

EM: extensive metaboliser; PM: poor metaboliser

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

Study	Treatment (taken at night, unless stated)	Adverse events	Withdrawals
Kishore-Kumar 1990	18:00 single dose	Any AE: Desipramine 19/19 completers Placebo 15/19 completers	Due to AEs: Desipramine 5/26 (syncope, palpitations/left bundle branch block, jitteriness/atypical chest pain, fever, vertigo)

(Continued)

	Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Active placebo (benztropine) 0.5 mg daily , increasing to 1 mg daily	Most common with desipramine: dry mouth, constipation, dizziness, sedation, micturition difficulty, insomnia, sweating Most common with placebo: dry mouth, dizziness, constipation	Placebo 3/26 (vertigo/nausea, skin rash, unsteadiness/mental fogginess) Intercurrent illness: 2
Max 1991	18:00 single dose Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Active placebo (benztropine) 0.5 mg daily , increasing to 1 mg daily	Any AE: Desipramine 18/20 completers Placebo 17/20 completers Most common with desipramine: dry mouth, sedation, insomnia, constipation, orthostatic symptoms, palpitations, sweating Most common with placebo: dry mouth, sedation, constipation, insomnia	Due to AEs: Desipramine 2/24 (seizure, insomnia) Placebo 1/24 (chest pain) Lack of efficacy: Desipramine 0/24 Placebo 1/24
Max 1992	21:00 single dose Desipramine 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated Amitriptyline 12.5 mg daily initially, increasing to 250 mg daily or maximum tolerated	Any AE: Desipramine 29/54 Amitriptyline 31/54 Most common with desipramine: dry mouth, tiredness, constipation, insomnia, sweating, headache, lightheadedness, orthostatic symptoms, palpitations Most common with amitriptyline: dry mouth, tiredness, headache, palpitations, sweating, constipation, lightheadedness, orthostatic symptoms	Due to AEs: Desipramine 7/54 (rash (3), orthostatic hypotension, fever, tremor, bundle branch block) Amitriptyline 7/54 (confusion (2), orthostatic hypotension, fatigue, malaise, rash, hypomania) Two other withdrawals were described as "voluntary"
Rowbotham 2005	Two doses per day (times not given) Desipramine 25-150 mg daily, titrated to maximum tolerable Amitriptyline 25-150 mg daily, titrated to maximum tolerable Fluoxetine 10-60 mg daily, titrated to maximum tolerable	Ratings were obtained weekly for a 28-item side effects checklist Scores increased for adverse events as follows: Desipramine: dry mouth, constipation, bitter taste Amitriptyline: dry mouth, constipation, bitter taste Fluoxetine: sleepiness, lightheadedness	For all causes*: Desipramine 2/15 Amitriptyline 2/17 Fluoxetine 5/15 *reasons given for only five withdrawals Due to AEs: Desipramine and amitriptyline combined: 2 sedation/cognitive impairment; 1 symptomatic orthostasis Fluoxetine: 1 recurrence of atrial fibrillation; 1 hospitalised for nausea and weakness with hyponatraemia Non-completers had less pain relief, lower maximum tolerated dose, and higher adverse event symptom score

(Continued)

Sindrup 1990	20:00 single dose Desipramine 200 mg daily (EM); 50 mg daily (PM) Clomipramine 75 mg daily (EM); 50 mg daily (PM) Placebo	A list of side effects was scored: median of total score was significantly higher for desipramine (4.5) and clomipramine (4.0) than placebo (0.02*) *clearly, this figure cannot be correct: if only 6 participants (out of 19 completers) report adverse events, the median value must be zero. By contrast the lowest possible value for the mean would be 0.2. Most common adverse events: dry mouth, sweating, orthostatic dizziness, fatigue 6 participants reported one or more of these during placebo	Due to AEs: Desipramine 3/26 (nausea, tiredness, dizziness) Clomipramine 3/26 (nausea, tiredness, dizziness, confusion) Lack of efficacy: Desipramine 0/26 Clomipramine 1/26

AE: adverse event; EM: extensive metaboliser; PM: poor metaboliser

WHAT'S NEW

Date	Event	Description
4 October 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2014
Review first published: Issue 9, 2014

Date	Event	Description
1 October 2014	Review declared as stable	This review will be assessed for further updating in 2019 as it is unlikely that new evidence will be published.

CONTRIBUTIONS OF AUTHORS

LH, SD and RAM wrote the protocol. LH and SD carried out searches, assessed studies for inclusion, and extracted data. PW acted as arbitrator. All authors were involved in writing the review. RAM will be responsible for updating the review.

DECLARATIONS OF INTEREST

LH has no known conflicts of interest.

TP, SD, PW, and RAM have no conflicts relating to this review or any similar product.

For transparency, TP, SD, PW, and RAM have received research support from charities, government, and industry sources at various times, but none relate to this review. SD, PW and RAM are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

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Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol specified any route of administration of desipramine, but since formulations are available for oral administration only, this was specified in the full review.

NOTES

A restricted search in September 2019 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. We will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Amitriptyline [therapeutic use]; Analgesics [*therapeutic use]; Antidepressive Agents, Tricyclic [*therapeutic use]; Chronic Pain [*drug therapy]; Clomipramine [therapeutic use]; Desipramine [*therapeutic use]; Diabetic Neuropathies [*drug therapy]; Fluoxetine [therapeutic use]; Neuralgia, Postherpetic [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Humans; Middle Aged