

Nortriptyline for neuropathic pain in adults (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
Figure 1.	7
RESULTS	9
Figure 2.	10
Figure 3.	11
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	28
APPENDICES	28
WHAT'S NEW	33
CONTRIBUTIONS OF AUTHORS	33
DECLARATIONS OF INTEREST	33
SOURCES OF SUPPORT	33

[Intervention Review]

Nortriptyline 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.

Nortriptyline is a tricyclic antidepressant that is occasionally used for treating neuropathic pain, and is recommended in European, UK, and USA guidelines.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 7 January 2015, and the reference lists of retrieved papers and other reviews. We also searched two clinical trials databases for ongoing or unpublished studies.

Selection criteria

We included randomised, double-blind studies of at least two weeks' duration comparing nortriptyline 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 and clinical trial summaries.

Data collection and analysis

Two review authors independently extracted efficacy and adverse event data, and examined issues of study quality. We considered the evidence using three tiers. First tier evidence 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 evidence 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 evidence from data involving small numbers of participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both.

We planned to calculate risk ratio (RR) and numbers needed to treat for an additional beneficial outcome (NNT) and harmful outcome (NNH) using standard methods expected by The Cochrane Collaboration.

Main results

We included six studies treating 310 participants (mean or median age 49 to 64 years) with various neuropathic pain conditions. Five studies used a cross-over design, and one used a parallel-group design; 272 participants were randomised to treatment with nortriptyline, 145 to placebo, 94 to gabapentin, 56 to gabapentin plus nortriptyline, 55 to morphine, 55 to morphine plus nortriptyline, 39 to chlorimipramine, and 33 to amitriptyline. Treatment periods lasted from three to eight weeks. All studies had one or more sources of potential major bias.

No study provided first or second tier evidence for any outcome. Only one study reported our primary outcome of people with at least 50% reduction in pain. There was no indication that either nortriptyline or gabapentin was more effective in postherpetic neuralgia (very low quality evidence). Two studies reported the number of people with at least moderate pain relief, and one reported the number who were satisfied with their pain relief and had tolerable adverse effects. We considered these outcomes to be equivalent to our other primary outcome of Patient Global Impression of Change (PGIC) much or very much improved.

We could not pool data, but third tier evidence in individual studies indicated similar efficacy to other active interventions (gabapentin, morphine, chlorimipramine, and amitriptyline), and to placebo in the conditions studied (very low quality evidence). Adverse event reporting was inconsistent and fragmented. More participants reported adverse events with nortriptyline than with placebo, similar numbers with nortriptyline and other antidepressants (amitriptyline and chlorimipramine) and gabapentin, and slightly more with morphine (very low quality evidence). No study reported any serious adverse events or deaths.

Authors' conclusions

We found little evidence to support the use of nortriptyline to treat the neuropathic pain conditions included in this review. There were no studies in the treatment of trigeminal neuralgia. The studies were methodologically flawed, largely due to small size, and potentially subject to major bias. The results of this review do not support the use of nortriptyline as a first line treatment. Effective medicines with much greater supportive evidence are available, such as duloxetine and pregabalin.

PLAIN LANGUAGE SUMMARY

Nortriptyline for neuropathic pain in adults

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (for example, a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines to those used for pain from damaged tissue. Medicines such as 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.

Nortriptyline is an antidepressant from the same class of medicines as amitriptyline, which is widely recommended for treating neuropathic pain; nortriptyline may also be useful in these painful conditions.

In January 2015, we performed searches to look for clinical trials where nortriptyline was used to treat neuropathic pain in adults. We found six studies, with 310 participants with various neuropathic pain conditions. Studies were randomised and double-blind, but often with small numbers of participants. It was not possible to combine information from the different studies, but individually most studies indicated equivalent benefit from nortriptyline (usually at a dose between 50 mg and 100 mg daily) when compared with amitriptyline or chlorimipramine (other antidepressants), gabapentin (an antiepileptic), morphine (an opioid), or placebo (very low quality evidence). More people experienced adverse events with nortriptyline than with placebo, but numbers were similar for nortriptyline and other active medicines (very low quality evidence).

There was too little information of adequate quality to be sure that nortriptyline works as a pain medicine in the type of neuropathic pain studies in this review. Other medicines have been shown to be effective.

BACKGROUND

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

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is “pain caused by a lesion or disease of the somatosensory system” (Jensen 2011), based on an earlier consensus meeting (Treede 2008). Neuropathic pain is caused by injury to the nervous tissue, either peripheral or central and it can be followed by plastic changes in the central nervous system (CNS) (Moisset 2007). It tends to be chronic and may be present for months or years. The origin of neuropathic pain is complex (Baron 2010; Baron 2012; Tracey 2011; von Hehn 2012), 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 pain conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment and increased healthcare costs (Moore 2014a).

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

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

Estimates of incidence vary between individual studies for particular origins of neuropathic pain, often because of small numbers of cases. In primary care in the UK, between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain and 21 (20 to 22) for PDN (Hall 2008). However, the incidence of trigeminal neuralgia has also been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), and 12.6 per 100,000

person-years for trigeminal neuralgia and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009). One systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as PDN, can be more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000-person years (McQuay 2007).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive (or both) interventions. Conventional analgesics such as paracetamol and nonsteroidal antiinflammatory drugs are not thought to be effective, but are frequently used (Di Franco 2010; Vo 2009). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2013). Treatment is often by so-called 'unconventional analgesics', such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics (gabapentin or pregabalin; Moore 2009; Moore 2011a; Wiffen 2013).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2013b). Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

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

Description of the intervention

Nortriptyline is a tricyclic antidepressant and the main active metabolite of amitriptyline. It is not licensed in the UK or USA for treating neuropathic pain but is commonly used for chronic pain conditions, and it is commonly used for treating neuropathic pain around the world, irrespective of licensed indications. It is recommended in European, UK, and US guidelines, although not always as a first line treatment (Attal 2010; Dworkin 2008; NICE 2013). Nortriptyline is sometimes preferred to amitriptyline because it

reputedly has a lower incidence of associated adverse effects, which can increase patient compliance and can be particularly useful in older people who are more likely to experience adverse effects such as confusion and agitation, and postural hypotension.

Nortriptyline is available as 10 mg and 25 mg tablets, and as an oral solution. When used to treat neuropathic pain, an initial dose of 10 mg daily may be gradually increased to 75 mg daily. It is usually given as a single dose at night time, to reduce any sedative effects during the day. There were almost 500,000 prescriptions for nortriptyline in England in 2013, mainly for 10 mg and 25 mg tablets (PCA 2014); this compares with over 11 million prescriptions for amitriptyline in the same period. Some of these prescriptions were likely to be for the treatment of depression. The main adverse effects associated with nortriptyline are due to its anticholinergic activity, and include dry mouth, weight gain, and drowsiness.

How the intervention might work

The mechanism of action of nortriptyline in the treatment of neuropathic pain remains uncertain, although it is known to inhibit both serotonin and noradrenaline reuptake. The mechanism is likely to differ from that in depression since analgesia with antidepressants is often achieved at lower dosage than the onset of any antidepressant effect; adverse events associated with its use often wane after two or three weeks, when the benefits of the drug become apparent. In addition, there is no correlation between the effect of antidepressants on mood and pain, and antidepressants produce analgesia in people with and without depression (Onghena 1992). Nortriptyline also blocks sodium channels, which may contribute to its analgesic effects (Dick 2007).

Why it is important to do this review

Nortriptyline is a recommended first-line treatment for neuropathic pain in some guidelines (for example, Dworkin 2010). It was included in the original review of antidepressants for neuropathic pain, but few data were identified (Saarto 2007). That review is now being split into separate reviews for each drug, and this review is one of those. There may have been some new studies since the last review, but it is also important to re-review existing evidence using more stringent criteria for validity, including both the level of response obtained, and duration of study. 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. 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%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the *PaPaS Author and Referee Guidance* for pain studies of the Cochrane Pain, Palliative and Supportive Care Group (PaPaS 2012).

This Cochrane review will assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc) and size (ideally at least 500 participants in a comparison in which the NNT is 4 or above; Moore 1998). This approach sets high standards and marks a departure from how reviews were conducted previously.

OBJECTIVES

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

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 or more of treatment, although the emphasis of the review was on studies with a duration of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Our experience from previous reviews was that most studies would be older, small, and have methodological deficiencies according to present standards of evidence, and therefore we felt it appropriate to consider lower standards of evidence than those currently demanded for part of our analyses. This included reviewing data from studies of shorter duration, and studies where the outcome definition was poorly defined; all studies had to be both randomised and double-blind as a minimum. We have reported the evidence available according to the current standards, and lower levels of evidence. It is important to recognise that the lower level evidence

is likely to be subject to various positive biases, and that these lower levels of evidence cannot be used to make cross-drug comparisons of efficacy with other drugs.

Types of participants

Studies enrolled adults aged 18 years and above with 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 (PDN);
- phantom limb pain;
- postherpetic neuralgia (PHN);
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- trigeminal neuralgia;

and CRPS Type 1.

We included studies of participants with more than one type of neuropathic pain; in such cases, we analysed results according to the primary condition. We excluded studies using nortriptyline for prevention of migraine and headache as they are the subject of another Cochrane review (Chronicle 2004).

Types of interventions

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

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with most of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as:

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

These outcomes are different from those used in most earlier reviews, and 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 having no worse than mild pain (Moore 2013a; O'Brien 2010).

We have not included a 'Summary of findings' table because there was no useful information to include.

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, adverse events, and for any cause.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.
5. Specific adverse events, particularly CNS effects such as somnolence and dizziness.

Search methods for identification of studies

Electronic searches

We searched the following databases, without language restrictions.

- the Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) to 7 January 2015
- MEDLINE (via Ovid) 1946 to 7 January 2015.
- EMBASE (via Ovid) 1976 to 7 January 2015.

Appendix 2, Appendix 3, and Appendix 4 show the search strategies for CENTRAL, MEDLINE, and EMBASE, respectively.

Searching other resources

We reviewed the bibliographies of all identified RCTs and review articles, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and WHO ICTRP (apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators (except to clarify the status of ongoing studies) or study sponsors.

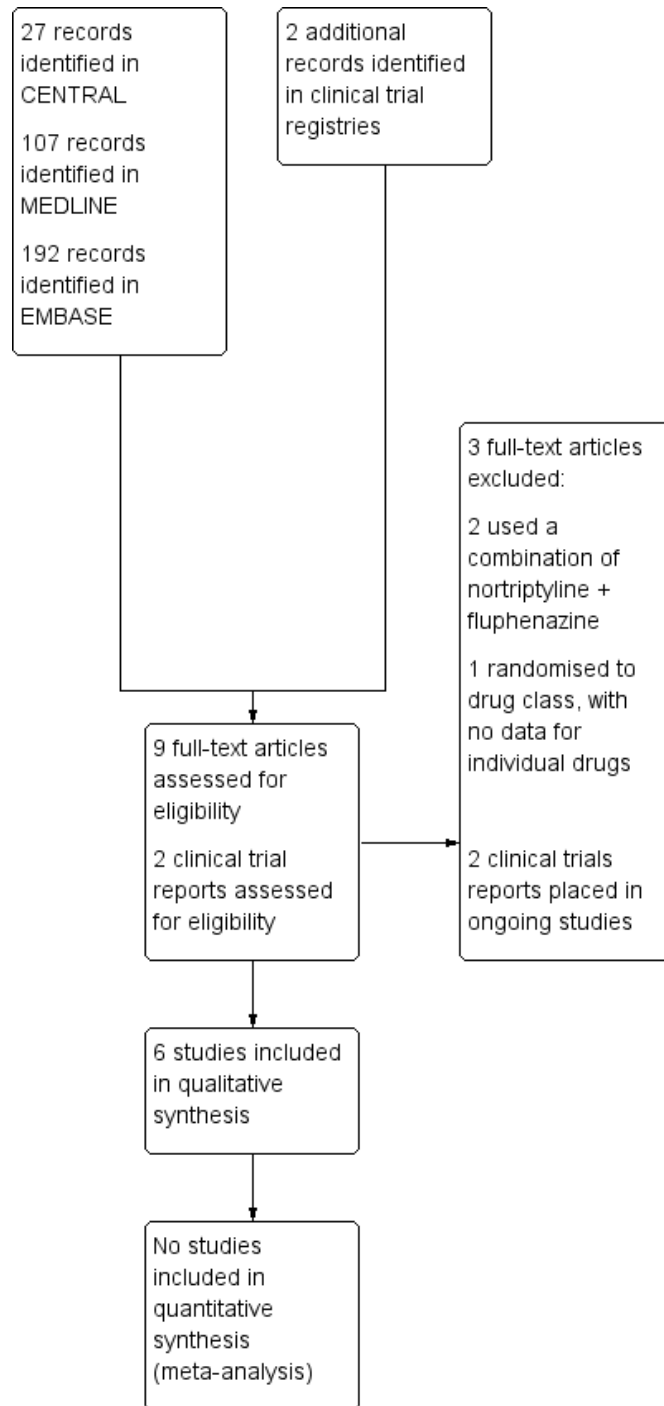
Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions. We would have performed analyses combining different neuropathic pain conditions for exploratory purposes only. In the event, there were insufficient data for any pooled analyses.

Selection of studies

Two review authors independently determined eligibility by first reading the title and abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors then independently read these studies to determine inclusion and reached agreement by discussion. We did not anonymise the studies before assessment. [Figure 1](#) shows the PRISMA flow chart.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager (RevMan 2014) and other analysis tools. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (for example, parallel-group or cross-over, placebo or active control, titration schedule), 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, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996).

Two review authors independently assessed the risk of bias for each study, using the criteria outlined in the 'Risk of bias' tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group. We resolved any disagreements 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 such as random number table or 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 (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' 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 or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We planned to pool dichotomous data to calculate risk ratio (RR) with 95% CIs using a fixed-effect model unless we found significant statistical heterogeneity (see [Assessment of heterogeneity](#)), and 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 to harm (NNH) and is calculated in the same manner. We did not plan to use continuous data in analyses. In the event, there were insufficient data and we were able only to present results descriptively.

Unit of analysis issues

For cross-over studies, we planned to use first period data only, wherever possible, but only one of the studies reported any results in this way. Most of the cross-over studies reported only for participants completing more than one phase of treatment, so in the absence of any pooled analysis, we have used results as reported in the individual studies, but have drawn attention to the potential bias this may introduce.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. We assigned missing participants zero improvement wherever possible.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L'Abbé 1987) and using the I^2 statistic, but pooling of data was not possible.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility and of value to people with neuropathic pain (Moore 2010b; Moore 2013a). The review did not depend on what authors of the original studies chose to report or not, although clearly difficulties arose in studies that did not report any dichotomous results. We planned to extract and use continuous data, which probably poorly reflect efficacy and utility, only where useful for illustrative purposes.

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). We were unable to do this because of a lack of data.

Data synthesis

We planned to use a fixed-effect model for meta-analysis unless there was significant clinical heterogeneity and it was still considered appropriate to combine studies, in which case we would have used a random-effects model. However, there were insufficient data for any pooled analysis.

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

- The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation method other than BOCF for dropouts, reported an ITT analysis, lasted eight or more weeks, had a parallel-group design, and had at least 200 participants (preferably at least 400) in the comparison (Moore 2010a; Moore 2012b). We planned to report these top-tier results first.
- The second tier used data from at least 200 participants, but where one or more of the above conditions was 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 related to data from fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were 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 for the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). We also planned to examine details of dose escalation schedules to investigate if this could explain any observed heterogeneity, but there were insufficient data for any one condition for any combined efficacy analysis.

Sensitivity analysis

There were insufficient data to carry out sensitivity analyses for dose of nortriptyline and duration of study.

RESULTS

Description of studies

Results of the search

Searches of bibliographic databases found 27 titles in CENTRAL, 107 in MEDLINE, and 192 in EMBASE, which we examined for inclusion. After screening titles and abstracts, we obtained full copies and examined nine reports in detail. We included six studies (see [Characteristics of included studies](#) table), and excluded three (see [Characteristics of excluded studies](#) table). Searches of trial databases identified two additional studies that are ongoing (ACTRN12612001304820; ISRCTN04803491), details of which are in the [Characteristics of ongoing studies](#) table. We found no additional studies in the reference lists of studies or reviews. See [Figure 1](#).

Included studies

Six studies treated 310 participants, of whom 272 were randomised to nortriptyline, although not all randomised participants received each treatment in the cross-over studies (Chandra 2006; Gilron 2009; Hammack 2002; Khoromi 2007; Panerai 1990; Watson 1998). One study used a parallel group design (Chandra 2006) and five used a cross-over design. Treatment periods were between three and eight weeks, and all but one of the cross-over studies (Panerai 1990) had a washout period between treatments lasting between 4 and 14 days.

All the studies started with a low dose of nortriptyline, usually 25 mg daily, and titrated up to the maximum tolerated dose (target usually 100 mg daily) over one to four weeks. One study used a starting dose of 20 mg daily for participants aged under 65 years and 10 mg daily for those aged 65 years or more, titrating up by 10 mg increments over three weeks (Watson 1998).

The mean or median age of study participants, where reported, was between 49 and 64 years, and there were approximately equal numbers of men and women; Hammack 2002 and Watson 1998 did not report these demographics. Participants were experiencing pain due to PHN (Chandra 2006; Gilron 2009; Watson 1998), PDN (Gilron 2009), cis-platinum-induced neuropathy (Hammack 2002), lumbar radiculopathy (Khoromi 2007), and central pain following limb amputation (with phantom or stump pain), PHN, or post-traumatic nerve lesions (Panerai 1990). Four of the studies required participants to be experiencing at least moderate pain before enrolment. Hammack 2002 and Panerai 1990 did not specify this as an inclusion criterion, although the mean baseline pain intensity in Hammack 2002 was 59/100 and 60/100 (no standard deviation (SD) reported) in the two treatment arms. In Panerai 1990 the mean was 49 (SD 17), 46 (SD 17) and 37 (SD 13) in the three treatment arms, indicating that a small number of participants may have experienced only mild pain (less than 30/100) at baseline.

Three studies compared nortriptyline with placebo (Hammack 2002; Khoromi 2007; Panerai 1990), and five studies used an active comparator, which was titrated to the maximum tolerated dose.

- Gabapentin (Chandra 2006)
- Gabapentin or gabapentin plus nortriptyline (Gilron 2009)
- Morphine or morphine plus nortriptyline (Khoromi 2007)

- Chlorimipramine (clomipramine) (Panerai 1990)
- Amitriptyline (Watson 1998)

Most studies required that treatment with antidepressants, antiepileptics, and opioids was stopped before starting the study, but some specifically permitted continued, stable use of non-steroidal anti-inflammatory drugs (Hammack 2002), non-study medication for sciatica (Khoromi 2007), and “analgesics” (Watson 1998).

Excluded studies

We excluded three studies after reading the full papers. Gómez-Pérez 1985 and Gómez-Pérez 1986 combined nortriptyline with fluphenazine, with no nortriptyline only treatment arm, while Raja 2002 randomised participants to drug classes, not to individual drugs, and did not report results for individual drugs separately.

Risk of bias in included studies

Comments on potential biases in individual studies are in the ‘Risk of bias’ section of the Characteristics of included studies table. Figure 2 and Figure 3 show the findings; we did not carry out any sensitivity analyses. 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.

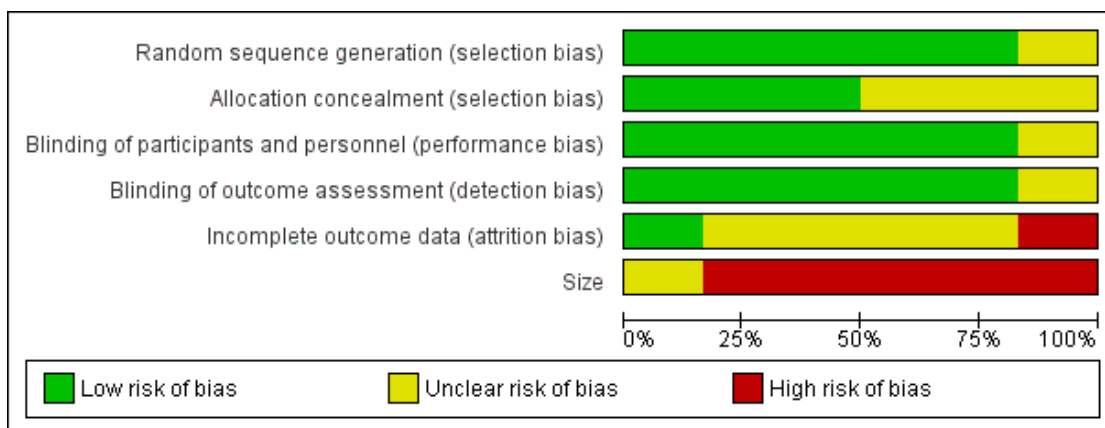


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Size
Chandra 2006	+	+	+	+	?	-
Gilron 2009	+	+	+	+	?	?
Hammack 2002	+	?	?	?	?	-
Khoromi 2007	+	?	+	+	?	-
Panerai 1990	?	?	+	+	-	-
Watson 1998	+	+	+	+	+	-

Allocation

All studies were randomised, and five adequately described the method of sequence generation (Chandra 2006; Gilron 2009; Hammack 2002; Khoromi 2007; Watson 1998). Three studies adequately described the method of concealing treatment allocation (Chandra 2006; Gilron 2009; Watson 1998).

Blinding

All studies were double blind and only one did not adequately describe the method used to ensure that participants and interacting investigators were unable to differentiate between active and control groups (Hammack 2002).

Incomplete outcome data

Only one of the studies adequately accounted for all participants and reported on use of imputation for missing data (Watson 1998).

Selective reporting

All studies reported the outcomes specified in their methods but these were often not our preferred outcomes.

Other potential sources of bias

None of the studies analysed sufficient numbers of participants to minimise the bias associated with small studies (Nüesch 2010).

Effects of interventions

There was no first or second tier evidence of efficacy. We downgraded evidence primarily because of the short duration of most studies, small numbers of participants in comparisons, reporting results only for participants who completed cross-over studies (completer analyses), and a lack of desirable primary outcomes.

Appendix 5 and Appendix 6 provide the details from individual studies for efficacy data and adverse events and withdrawals data respectively.

Third tier evidence

Chandra 2006 reported that 14/34 participants experienced our preferred outcome of at least 50% reduction in pain intensity (using 100 mm VAS) with nortriptyline, and 13/36 with gabapentin. Numbers were somewhat lower in both groups using a Likert scale. The study also reported a responder outcome of 'good or excellent', defined as participants with "no worse than mild pain and disability, tolerable side effects, who slept well and were satisfied

with treatment". This was experienced by 16/36 participants with nortriptyline and 16/34 with gabapentin.

Gilron 2009 reported at least moderate pain relief in 38/50 participants with nortriptyline, 30/46 with gabapentin, and 42/50 with nortriptyline plus gabapentin. We considered this outcome to be equivalent to our preferred outcome of PGIC much or very much improved.

Hammack 2002 reported mean data for pain and paraesthesiae, with no statistically significant difference between nortriptyline and placebo, and "at best, a small minority perhaps receiving a clinically significant benefit from nortriptyline". For the first treatment period only, 8/26 (30%) of participants taking nortriptyline and 8/25 (33%) taking placebo experienced a reduction in pain intensity of at least 10/100, using 100 mm VAS (a difference the authors considered was clinically significant).

Khoromi 2007 used a 6-point scale to assess pain relief, reporting that at least moderate relief was experienced by 12/30 participants with nortriptyline, 13/31 with morphine, 18/27 with nortriptyline plus morphine, and 11/30 with placebo. We considered this outcome to be equivalent to our preferred outcome of PGIC much or very much improved.

Panerai 1990 used a 100 mm VAS to assess pain intensity, and reported only mean data: chlorimipramine and nortriptyline were both superior to placebo, and chlorimipramine was slightly better than nortriptyline.

Watson 1998 reported a responder outcome, defined as "participants who were satisfied with their pain relief and had tolerable side effects". This was experienced by 15/33 participants with nortriptyline and 17/33 with amitriptyline. We considered this outcome to be equivalent to our preferred outcome of PGIC much or very much improved. The authors also reported that 4/33 participants had mild or no pain with nortriptyline and severe pain with amitriptyline, while 5/33 had mild or no pain with amitriptyline and severe pain with nortriptyline.

Adverse events

All studies reported some information about adverse events, but reporting was inconsistent and fragmented. There were insufficient data comparing nortriptyline with the same comparator for any pooled analysis, even when we combined pain conditions.

Participants experiencing any adverse event

Chandra 2006 reported that 21/36 participants experienced at least one adverse event with nortriptyline, but there were no data for gabapentin. Dry mouth, constipation, and postural hypotension were more frequent with nortriptyline than gabapentin, while

sleepiness was equally common, and fatigue, giddiness, urticaria, urinary retention, and cough were infrequent in both groups.

[Gilron 2009](#) reported a higher incidence of adverse events during titration than while at the maximum tolerated dose (in part presumably because some participants withdrew due to intolerable adverse events during titration). Dry mouth was more frequent with nortriptyline than gabapentin during both phases. Fatigue remained higher with nortriptyline, and high blood sugar (home monitoring) with gabapentin, at maximum dose. Results for the combination of nortriptyline plus gabapentin were similar to those for nortriptyline alone.

In [Hammack 2002](#), more participants reported adverse events while taking nortriptyline than placebo, but 8/51 (15%) participants had missing data. Dry mouth, dizziness, and constipation were more frequent with nortriptyline than placebo. Physicians reported more dry mouth and constipation with nortriptyline. Most events were of mild or moderate intensity.

Of the 28/55 participants completing all four treatment phases in [Khoromi 2007](#), 19 experienced at least one adverse event with nortriptyline, 26 with morphine, 25 with the combination of nortriptyline plus morphine, and 14 with placebo. Dry mouth, constipation, and dizziness were the most frequent adverse events; dry mouth was more common with nortriptyline, and constipation and dizziness with morphine. Results for the combination of nortriptyline plus morphine were similar to those for morphine alone.

Of the 24/39 participants completing all four treatment phases in [Panerai 1990](#), 23 experienced at least one adverse event with nortriptyline, 22 with chlorimipramine, and 10 with placebo. The adverse events were described as usually of mild to moderate *severity*, although it is likely that the authors mean mild to moderate *intensity*, and there were no events that were “not usually seen with antidepressants”.

[Watson 1998](#) reported that 26/33 participants experienced at least one adverse event with nortriptyline and 21/33 with amitriptyline. Dry mouth, constipation, and drowsiness were the most frequent, with constipation slightly more common with nortriptyline.

Participants experiencing any serious adverse event

None of the studies reported any serious adverse events (see [Panerai 1990](#), Participants experiencing any adverse event).

Deaths

None of the studies reported any deaths.

Withdrawals

There were insufficient data comparing nortriptyline with the same comparator for any pooled analysis, even when pain conditions were combined.

Withdrawals due to adverse events

There were small numbers of withdrawals due to adverse events in all studies and most treatment arms.

Withdrawals due to lack of efficacy

There were few withdrawals due to lack of efficacy from any active treatment arm. They were more frequent in the placebo arms.

DISCUSSION

Summary of main results

We found six studies enrolling 310 participants with various types of chronic neuropathic pain. Only one study reported our primary outcome of at least 50% reduction in pain intensity, but three reported outcomes we considered equivalent to our other primary outcome of PGIC much or 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 similar efficacy to other active interventions (gabapentin, morphine, chlorimipramine and amitriptyline), and to placebo, although this was derived mainly from completer analyses (see [Appendix 1](#)), in small, short duration studies where major bias is possible. More participants reported adverse events with nortriptyline than with placebo, similar numbers with nortriptyline and other antidepressants (amitriptyline and chlorimipramine) and gabapentin, and slightly more with morphine, although reporting was inconsistent and fragmented.

Overall completeness and applicability of evidence

Nortriptyline was tested in small numbers of participants with six different neuropathic pain conditions. It was not possible to determine efficacy in any one condition.

Short-term studies (less than six weeks) may not accurately predict longer term efficacy in chronic conditions: four studies were of three to five weeks' duration, while only one was of six, and one of eight 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 56 participants randomised to any treatment arm, not all of whom provided results. Five of the six studies were of six weeks' duration or less and used a cross-over design. Only one of these reported any data for the first treatment period separately, and there were concerns or uncertainty about the completeness of reporting in all of them due to reporting only on participants who completed more than one phase of treatment or lack of information about any imputation methods used.

Adverse event reporting was inconsistent. For example, [Chandra 2006](#) reported numbers of participants with any adverse event for nortriptyline but not for gabapentin, [Khoromi 2007](#) and [Panerai 1990](#) reported adverse events only for participants who completed all four treatment phases, and [Khoromi 2007](#) reported on specific events only if the incidence was at least 5%. [Hammack 2002](#) reported physician-reported toxicities and patient-reported symptoms, but approximately 15% of participant reports were missing, and the reports used different denominators and adverse event terms.

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 include the following.

- 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](#)). The majority of data in this review were from cross-over studies.
- Withdrawals meant that any results were more likely to be per protocol for completers than for a true ITT analysis. Four of the five cross-over studies reported results only for those who completed at least two treatment periods, which is likely to overestimate efficacy.
- The absence of publication bias (unpublished trials showing no benefit of nortriptyline 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 recommend use of a tricyclic antidepressant (amitriptyline, chlomipramine (PDN only), nortriptyline, desipramine, imipramine) for PDN, PHN, and central pain, but not trigeminal neuralgia ([Attal 2010](#)). Nortriptyline is not usually recommended as a first line treatment

([Attal 2010](#); [NICE 2013](#)), though it is specifically recommended as a first line treatment in other guidelines ([Dworkin 2010](#)). The results of this review do not support the use of nortriptyline as a first line treatment. Effective medicines with much greater supportive evidence are available, such as duloxetine, pregabalin, and gabapentin ([Lunn 2014](#); [Moore 2009](#); [Moore 2014b](#)).

There appears to be general agreement that tricyclic antidepressants have approximately equivalent efficacy, and if treatment of an individual fails with one it is worthwhile trying another. This is supported by results from [Watson 1998](#) in this review that demonstrated some participants benefited with amitriptyline but nortriptyline, and vice versa, and by [Raja 2002](#), in which participants were randomised to nortriptyline but could switch to desipramine if required; 13 (22%) of participants did so.

AUTHORS' CONCLUSIONS

Implications for practice

This review found little evidence to support the use of nortriptyline to treat neuropathic pain. There was some evidence of some effect but this came from studies that were methodologically flawed and potentially subject to major bias. Because of its low cost and wide availability, nortriptyline may be worth trying if a different tricyclic antidepressant has failed, but there are other medicines available with better evidence for efficacy and harm.

Implications for research

Reasonable levels of evidence exist for the benefit of other antiepileptic and antidepressant drugs in the treatment of chronic neuropathic pain.

It is likely that nortriptyline will remain an option to treat neuropathic pain where other tricyclic antidepressants have been ineffective, or have intolerable adverse events. Larger, better-designed studies would provide more definitive conclusions on the efficacy of nortriptyline and support its continued use in neuropathic pain, but it is unlikely that these will be carried out, given the age of the drug and the alternatives available.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chandra 2006

Methods	Randomised, double-blind, active-controlled, parallel-group study Duration: 1-week run-in followed by 8-week treatment period Muscle relaxants, anticonvulsants, topical analgesics, antiviral agents discontinued \geq 1 week before screening
Participants	Postherpetic neuralgia. Pain > 8 weeks after healing of rash, and PI \geq 40/100 on VAS at baseline with average pain score \geq 4/10 Exclusion: previous treatment with study drugs or neurolytics or surgical treatment for postherpetic neuralgia N = 76 (70 for ITT) M 34, F 42 Mean age 54 years
Interventions	Nortriptyline n = 38 Gabapentin n = 38 Nortriptyline started at 25 mg x 2 daily, and gabapentin at 300 mg x 3 daily. Titrated up at 2 and 4 weeks to maximum tolerated dose and acceptable pain relief Rescue medication: non-opioid analgesics as required
Outcomes	PI: \geq 50% reduction from baseline using 100 mm VAS and 11-point Likert scale Clinical response, evaluating pain, tolerability, disability, satisfaction: 4-point VRS (excellent, good, improved but unsatisfactory, unchanged) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random number table"
Allocation concealment (selection bias)	Low risk	Probably adequate: "sealed envelopes opened by investigator only at time of enrolment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules"

Chandra 2006 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	“identical capsules”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported
Size	High risk	< 50 participants per treatment arm

Gilron 2009

Methods	Randomised, double-blind, active-controlled, cross-over study Duration: 3 x 6 weeks, with 6-day washout between treatments	
Participants	Painful diabetic neuropathy or postherpetic neuralgia. Pain \geq moderate for 6 months N = 56 (47 completed 2 phases, 45 completed all 3 phases) M 34, F 22 Median age 64 years Initial mean pain score 5.4/10	
Interventions	Nortriptyline 100 mg daily (maximum) Gabapentin 3600 mg daily (maximum) Gabapentin plus nortriptyline 3600 mg/100 mg daily (maximum) Titration to target dose or limit of tolerability over first 4 weeks of each treatment phase, stable dose for 1 week, then tapered dose for 1 week	
Outcomes	PR: \geq moderate PI: mean data reported Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“trial pharmacist prepared a concealed allocation schedule by computer randomisation”
Allocation concealment (selection bias)	Low risk	“trial pharmacist prepared a concealed allocation schedule”. Allocation by “consecutive numbers”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy technique

Gilron 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy technique
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported
Size	Unclear risk	Maximum of 50 participants analysed per treatment arm for efficacy, 54 for adverse events

Hammack 2002

Methods	Randomised, double-blind, placebo-controlled, cross-over study Duration: 2 x 4 weeks, plus 1-week washout between treatment periods Antidepressants, opioids, antiepileptics or other adjuvant analgesics discontinued \geq 1 week before start of study. Nonsteroidal anti-inflammatory drugs allowed
Participants	Cis-platinum-induced peripheral neuropathy and painful paraesthesiae for \geq 1 month, life expectancy \geq 4 months N = 51 Sex not reported Mean age 59 years
Interventions	Nortriptyline 100 mg daily (maximum) Placebo Initial dose 25 mg daily, increased at weekly intervals to target of 100 mg daily (39/51 tolerated 70 mg to 100 mg)
Outcomes	PI: 100 mm VAS and 5-point VRS (mean data reported) Treatment preference Quality of life: 100 mm VAS and effect on activities of daily living Satisfaction at end of treatment period: 5-point VRS Adverse events Withdrawals
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)	Low risk	Did not use simple random sampling. "Treatment assignment was calculated using a dynamic allocation procedure which balances the marginal distributions of the stratification factors between the two treatment-sequence groups (Pocock and Simon,

Hammack 2002 (Continued)

		1975)"
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Probably OK for efficacy: used 'last observation carried forward', 'baseline observation carried forward', and completer analysis and reported "identical" results. For adverse events a high number of participants did not provide data
Size	High risk	Maximum 51 participants analysed per treatment arm for efficacy, < 50 for adverse events

Khoromi 2007

Methods	Randomised, double-blind (double-dummy), placebo- and active-controlled, cross-over study Duration: 4 x 5 weeks with 10-day taper and 4-day placebo washout between treatment phases
Participants	Lumbar radiculopathy, ≥ 3 months with average PI $\geq 4/10$ N = 55 (28 completed all treatment phases) M 25, F 30 Mean age 53 years (range 19 to 65)
Interventions	Nortriptyline 20 mg to 100 mg daily Morphine (MS Contin) 15 mg to 90 mg daily Nortriptyline 20 mg to 100 mg + morphine 15 mg to 90 mg daily Placebo (benztropine 0.25 mg to 1.0 mg daily) Medication titrated at weekly intervals over 3 weeks to maximum tolerated dose
Outcomes	PR: 6-point VRS Leg pain: scale 0 to 10 Additional assessments for depression, disability, and quality of life Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Khoromi 2007 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"by random numbers", used Latin Square
Allocation concealment (selection bias)	Unclear risk	Possibly remote allocation
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	Unclear risk	Full completer analysis for adverse events, paired completer analysis for efficacy
Size	High risk	< 50 participants per treatment arm (as analysed)

Panerai 1990

Methods	Randomised, double-blind, placebo- and active-controlled cross-over study Duration: 3 x 3 weeks, with no washout between treatment periods
Participants	Central pain \geq 6 months following limb amputation, phantom/stump pain, postherpetic neuralgia, or post-traumatic nerve lesions N = 39 (24 completed) M 14, F 10 (completers) Mean age 49 years
Interventions	Nortriptyline film 25 mg Chlorimipramine film 25 mg Placebo film Initial dose 1 film daily (evening), increasing up to 2 films twice daily on subsequent days, then stable for next 2 weeks All previous treatment stopped \geq 1 week before start of study (placebo washout period)
Outcomes	PI: 100 mm VAS (mean data reported) Additional assessment for depression Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 1, W = 1. Total = 4/5

Panerai 1990 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Details of method of blinding not specifically reported, but all medication given as "film"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details of method of blinding not specifically reported, but all medication given as "film"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Drop-out patients were substituted and not considered in the analysis except when the cause of withdrawal was the lack of compliance"
Size	High risk	< 50 participants per treatment arm

Watson 1998

Methods	Randomised, double-blind, active-controlled, cross-over study Duration: 2 x 5 weeks with 2 week washout between treatment periods
Participants	Postherpetic neuralgia, 3 months with PI ≥ moderate N = 33 Demographics not reported
Interventions	Nortriptyline Amitriptyline Initial dose 10 mg if aged ≥ 65 years, 20 mg if under 65 years. Dose increased by 10 mg every 3 to 5 days, over 3 weeks, until adequate PR and tolerable side effects achieved Antidepressants and neuroleptics withdrawn ≥ 3 weeks; analgesics continued unchanged
Outcomes	PI: 10 cm VAS and 5-point VRS Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 2. Total = 5/5

Risk of bias

Watson 1998 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized by telephone at another site by computer"
Allocation concealment (selection bias)	Low risk	"sequence concealed in sequential, numbered, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical blue gelatin capsules", "no difference in patient or physician guesses as to treatment received"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical blue gelatin capsules", "no difference in patient or physician guesses as to treatment received"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	High risk	< 50 participants per treatment arm

DB: double blind; F: female; ITT: intention to treat; M: male; N: number of participants in study; n: number of participants in treatment arm; PI: pain intensity; PR: pain relief; R: randomised; VAS: visual analogue scale; VRS: verbal rating scale; W: withdrawals.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Gómez-Pérez 1985	Nortriptyline combined with fluphenazine, no nortriptyline only treatment arm
Gómez-Pérez 1986	Nortriptyline combined with fluphenazine, no nortriptyline only treatment arm
Raja 2002	Participants randomised to drug class, not individual drug, and results for individual drugs not reported separately

Characteristics of ongoing studies [ordered by study ID]

ACTRN12612001304820

Trial name or title	High versus low dose nortriptyline for pain control and sleep in the presence of radicular back pain
Methods	Randomised, triple-blind, parallel group, dose comparison study Block randomisation; set out in a table and given in order of presentation. Sealed opaque envelopes Duration: 3 months Medication given as a single daily dose Data collection by telephone questionnaire
Participants	Radicular back pain: leg-dominant pain that is worse below the gluteal fold Target sample size: 100 Male and female Age 18 to 70 years
Interventions	Nortriptyline 50 mg daily Nortriptyline 10 mg daily
Outcomes	PI: VAS at 0, 2, 6, 12 weeks Sleep: Medical Outcome Study Sleep Scale at 0, 2, 6, 12 weeks
Starting date	24 December 2012
Contact information	Dr Carl Chisholm Wellington Hospital, Riddiford Street, Newtown Wellington 6021, New Zealand Email: carlchisholm@gmail.com
Notes	

ISRCTN04803491

Trial name or title	A double-blind, randomised controlled trial of nortriptyline, morphine, and their combination for neuropathic pain
Methods	Randomised, double-blind (double-dummy), cross-over study Duration: 3 x 6 weeks (dose titrated over 24 days to maximum tolerated, maintenance for 7 days, then 11-day taper-washout) Maximum dose 100 mg for both drugs
Participants	Neuropathic pain, aged 18 to 89 years, male and female
Interventions	Nortriptyline Morphine Nortriptyline + morphine
Outcomes	Daily PI during treatment with maximum tolerated dose (days 25 to 31) Global PR Adverse events

ISRCTN04803491 (Continued)

Starting date	1 November 2009
Contact information	Dr Ian Gilron Email: gilroni@queensu.ca
Notes	Email on 13 May 2014: recruitment nearing completion

PI: pain intensity; PR: pain relief; VAS: visual analogue scale

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Methodological considerations for chronic pain

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

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.

2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010d); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion of 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 2010d; Moore 2013b; Moore 2014c; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.

4. 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 2010b; Moore 2014a).

5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. Search strategy for CENTRAL (via CRO)

1. (nortriptyline or Allegron or Aventyl or Noritren or Norpress or Nortrilen or Pamelor or Sensoval):TI,AB,KY (616)
2. MESH DESCRIPTOR pain EXPLODE ALL TREES (29786)
3. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES (2534)
4. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (699)
5. ((pain* or discomfort*) and (central or complex or nerv* or neuralg* or neuropath*)):TI,AB,KY (8558)
6. ((neur* or nerv*) and (compress* or damag*)):TI,AB,KY (1765)
7. #2 OR #3 OR #4 OR #5 OR #6 (37461)
8. #1 AND #7 (27)

Appendix 3. Search strategy for MEDLINE (via Ovid)

1. exp PAIN/ (306193)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (115068)
3. exp SOMATOSENSORY DISORDERS/ (16091)
4. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (38237)
5. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (47759)
6. 1 or 2 or 3 or 4 or 5 (449361)
7. Nortriptyline/ (2043)
8. (nortriptyline or Allegron or Aventyl or Noritren or Norpress or Nortrilen or Pamelor or Sensoval).mp. (2781)
9. 7 or 8 (2781)
10. randomized controlled trial.pt. (376175)
11. controlled clinical trial.pt. (88531)
12. randomized.ab. (274544)
13. placebo.ab. (146796)
14. drug therapy.fs. (1708719)
15. randomly.ab. (194627)
16. trial.ab. (284610)
17. groups.ab. (1250317)
18. or/10-17 (3208598)
19. 6 and 9 and 18 (107)

Appendix 4. Search strategy for EMBASE (via Ovid)

1. exp neuralgia/ (72992)
2. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (79896)
3. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (67830)
4. 1 or 2 or 3 (179618)
5. Nortriptyline/ (13089)
6. (nortriptyline or Allegron or Aventyl or Noritren or Norpress or Nortrilen or Pamelor or Sensoval).mp. (13326)
7. 5 or 6 (13326)
8. crossover-procedure/ (39290)
9. double-blind procedure/ (116416)
10. randomized controlled trial/ (346881) (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1210076)
11. 8 or 9 or 10 or 11 (1287159)
12. 4 and 7 and 12 (192)

Appendix 5. Summary of outcomes in individual studies: efficacy

Study	Treatment	Pain outcome	Other efficacy outcome
Chandra 2006	Nortriptyline initially 25 mg x 2 daily, n = 38 Gabapentin initially 300 mg x 3 daily, n = 38 Drugs titrated at 2 and 4 weeks to maximum tolerated dose and accept-	PI: ≥ 50% reduction from baseline (VAS): Nortriptyline 14/36 Gabapentin 13/34 PI: ≥ 50% reduction from baseline (Likert): Nortriptyline 9/36	Responder: Good/excellent (≤ mild pain, low level side effects, slept well, satisfied) Nortriptyline 16/36 Gabapentin 16/34 Responder: Excellent (no pain, tolerable side effects, no disability, sat-

(Continued)

	able PR	Gabapentin 7/34	ified) Nortriptyline 4/36 Gabapentin 8/34
Gilron 2009	Nortriptyline 100 mg daily (target) Gabapentin 3600 mg daily (target) Gabapentin plus nortriptyline 3600 mg/100 mg daily (target) N = 56 Titration to target doses or limit of tolerability over 24 days, then stable dose for 1 week, and tapered dose for 1 week (6 weeks in total); 6-day washout and cross-over to next treatment	PR: ≥ moderate: Nortriptyline 38/50 Gabapentin 30/46 Combination 42/50	Mean daily PI significantly lower with combination than either drug alone
Hammack 2002	Nortriptyline 100 mg daily (target) Placebo N = 51 Initial dose 25 mg daily, increased at weekly intervals to target of 100 mg daily 39/51 tolerated 70 mg to 100 mg	No change in median values for PI (categorical scale) at end of first treatment period for either group Minimal changes (<10/100) for PI using VAS	Quality of life (100 mm VAS), effect on activities of daily living, sleep (hours) : no change at end of first period Patient preference: Nortriptyline 41% Placebo 16% No preference 44%
Khoromi 2007	Nortriptyline 20 to 100 mg daily Morphine (MS Contin) 15 to 90 mg daily Nortriptyline + morphine Placebo (benztropine 0.25 to 1.0 mg daily) N = 55 Medication titrated at weekly intervals over 5 weeks to maximum tolerated dose	Global pain relief (6-point scale) ≥ moderate: Nortriptyline 12/30 Morphine 13/31 Combination 18/27 Placebo 11/30	No difference between treatments for mean leg pain
Panerai 1990	Nortriptyline film 25 mg Chlorimipramine film 25 mg Placebo film N = 39 Initial dose 1 film daily (eve), increasing up to 2 films twice daily on subsequent days, then stable for next 2 weeks	Mean PI (VAS): Chlorimipramine “more active” than nortriptyline, both superior to placebo at 14 and 21 days	Physician global evaluation of efficacy at 21 days (4-point scale): Nortriptyline and chlorimipramine more effective than placebo, chlorimipramine superior to nortriptyline

(Continued)

<p>Watson 1998</p>	<p>Nortriptyline Amitriptyline N = 33</p> <p>Initial dose 10 mg if aged \geq 65 years, 20 mg if under 65 years. Dose increased every 3 to 5 days, over 3 weeks, by 10 mg until adequate PR and tolerable side effects achieved</p>	<p>Responder (satisfaction with pain relief and tolerable of side effects): Nortriptyline 15/33 Amitriptyline 17/33</p> <p>Note that 9 participants had mild or no pain with one drug and moderate or severe pain with the other Nortriptyline 4/33 Amitriptyline 5/33</p>	
<p>PI: pain intensity; PR: pain relief; VAS: visual analogue scale</p>			

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

Study	Treatment (taken at night, unless stated)	Adverse events	Withdrawals
<p>Chandra 2006</p>	<p>Nortriptyline initially 25 mg x 2 daily, n = 38 Gabapentin initially 300 mg x 3 daily, n = 38</p> <p>Drugs titrated at 2 and 4 weeks to maximum tolerated dose and acceptable PR</p>	<p>Any AE: Nortriptyline 21/36 Gabapentin - not reported</p> <p>Sleepiness Nortriptyline 6/36 Gabapentin 4/34</p> <p>Giddiness Nortriptyline 0/36 Gabapentin 1/34</p> <p>Dry mouth Nortriptyline 18/36 Gabapentin 0/34</p> <p>Postural hypotension Nortriptyline 12/36 Gabapentin 0/3 No SAE reported</p>	<p>All cause: Nortriptyline 3/38 Gabapentin 5/38</p> <p>AE: Nortriptyline 1/38 Gabapentin 0/38</p> <p>LoE: Nortriptyline 1/38 Gabapentin 0/38</p>
<p>Gilron 2009</p>	<p>Nortriptyline 100 mg daily (target) Gabapentin 3600 mg daily (target) Gabapentin plus nortriptyline 3600 mg/100 mg daily (target) N = 56</p> <p>Titration to target doses or limit of tolerability over 24 days, then stable dose for 1 week, and tapered dose</p>	<p>No data for participants with any AE At maximum tolerated dose:</p> <p>Dry mouth Nortriptyline 29/50 Gabapentin 8/46 Combination 30/50</p> <p>Fatigue Nortriptyline 6/50 Gabapentin 2/46</p>	<p>All cause: Nortriptyline 2/52 Gabapentin 8/54 Combination 1/52</p> <p>AE: Nortriptyline 1/52 Gabapentin 7/54 Combination 1/52</p>

(Continued)

	for 1 week (6 weeks in total); 6-day washout and cross-over to next treatment	Combination 4/50 Dizziness Nortriptyline 2/50 Gabapentin 4/46 Combination 4/50 No SAE	LoE: Nortriptyline 1/52 Gabapentin 0/54 Combination 0/52
Hammack 2002	Nortriptyline 100 mg daily (target) Placebo N = 51 Initial dose 25 mg daily, increased at weekly intervals to target of 100 mg daily 39/51 tolerated 70 mg to 100 mg	No data for participants with any AE Patient-reported symptoms: dry mouth, dizziness, and constipation were more frequent with nortriptyline than placebo, but approximately 15% had missing data No SAE reported	AE: Nortriptyline 2/51 Placebo 4/51 No further information
Khoromi 2007	Nortriptyline 20 to 100 mg daily Morphine (MS Contin) 15 to 90 mg daily Nortriptyline + morphine Placebo (benztropine 0.25 to 1.0 mg daily) N = 55 Medication titrated at weekly intervals over 5 weeks to maximum tolerated dose	Any AE (completers): Nortriptyline 19/28 Morphine 26/28 Combination 25/28 Placebo 14/28 No SAE reported	AE: Nortriptyline 2 Morphine 5 Combination 4 Placebo 1 LoE: Nortriptyline 0 Morphine 0 Combination 0 Placebo 3 Other: Nortriptyline 1 Morphine 4 Combination 2 Placebo 5: Denominator unclear
Panerai 1990	Nortriptyline film 25 mg Chlorimipramine film 25 mg Placebo film N = 39 Initial dose 1 film daily (evening), increasing up to 2 films twice daily on subsequent days, then stable for next 2 weeks	Any AE: Nortriptyline 23/24 Chlorimipramine 22/24 Placebo 10/24 Usually of mild or moderate intensity, none unexpected for antidepressants No SAE reported	All cause: 15/39 AE: Nortriptyline 2/39 Chlorimipramine 0/39 Placebo 1/39 LoE: Nortriptyline 5/39 Chlorimipramine 1/39 Placebo 6/39
Watson 1998	Nortriptyline Amitriptyline N = 33 Initial dose 10 mg if aged ≥ 65 years, 20 mg if under 65 years. Dose in-	Any AE: Nortriptyline 26/33 Amitriptyline 21/33 Dry mouth Nortriptyline 24/33	Participants "left the study": Nortriptyline 1 due to LoE and AEs Amitriptyline 1 due to AEs

(Continued)

	creased every 3 to 5 days, over 3 weeks, by 10 mg until adequate PR and tolerable side effects achieved	Amitriptyline 21/33 Constipation Nortriptyline 13/33 Amitriptyline 9/33 Drowsiness Nortriptyline 5/33 Amitriptyline 3/33 No SAE reported	
AE: adverse event; LoE: lack of efficacy; SAE: serious adverse event			

WHAT'S NEW

Last assessed as up-to-date: 7 January 2015.

Date	Event	Description
8 January 2015	Review declared as stable	This review will be assessed for further updating in 2020.

CONTRIBUTIONS OF AUTHORS

PW, RAM, and SD wrote the protocol. RAM 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

The review authors have no known conflicts of interest.

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