Amitriptyline for neuropathic pain and fibromyalgia in adults (Review)

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ

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[Intervention Review]

Amitriptyline for neuropathic pain and fibromyalgia in adults

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ABSTRACT

Background

Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and is recommended in many guidelines. These types of pain can be treated with antidepressant drugs in doses below those at which the drugs act as antidepressants.

Objectives

To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia.To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE to September 2012, together with reference lists of retrieved papers, previous systematic reviews, and other reviews; we also used our own handsearched database for older studies.

Selection criteria

We included randomised, double-blind studies of at least four weeks' duration comparing amitriptyline with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. 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 last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants in the comparison. The second tier used data that failed to meet this standard and were therefore subject to potential bias.

Main results

Twenty-one studies (1437 participants) were included; they individually involved between 15 and 235 participants, only four involved over 100 participants, and the median study size was 44 participants. The median duration was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common.

There was no top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia.

Second-tier evidence indicated no evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain, and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals; 8/153 (5%) withdrew because of lack of efficacy with amitriptyline and 14/119 (12%) with placebo.

More participants experienced at least one adverse event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5 (95% CI 1.4 to 1.7) and the number needed to treat to harm was 4.1 (95% CI 3.2 to 5.7). Adverse event and all-cause withdrawals were not different.

Authors' conclusions

Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all.

It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy.

PLAIN LANGUAGE SUMMARY

Amitriptyline for neuropathic pain and fibromyalgia in adults

The review set out to examine how well amitriptyline worked in treating neuropathic pain or fibromyalgia, where the definition of worked involved both a high level of pain relief and the ability to take the tablets over a longer time without side effects being intolerable. There were no studies that could provide an answer that was trustworthy or reliable, because most studies were relatively old, and used methods or reported results that we now recognise as making benefits seem better than they are. This is disappointing, but we can still make useful comments about the drug.

Amitriptyline probably does not work in neuropathic pain associated with HIV or treatments for cancer. Amitriptyline probably does work in other types of neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, and post-stroke pain, and in fibromyalgia), though we cannot be certain of this. Our best guess is that amitriptyline provides pain relief in about 1 in 4 (25%) more people than does placebo, and about 1 in 4 (25%) more people than placebo report having at least one adverse event, probably not serious but disconcerting; we cannot trust either figure based on the information available.

The most important message is that amitriptyline probably does give really good pain relief to some patients with neuropathic pain or fibromyalgia, but only a minority of them; amitriptyline will not work for most people.

BACKGROUND

Description of the condition

Neuropathic pain, unlike nociceptive pain such as gout and other forms of arthritis, is caused by nerve damage, often accompanied by changes in the central nervous system (CNS). Fibromyalgia is defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and is frequently associated with other symptoms such as poor sleep, fatigue, and depression. Its cause is not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Many people with these conditions are significantly disabled with moderate or severe pain for many years. Conventional analgesics are usually not effective, although opioids may be in some individuals. Others may derive some benefit from topical lidocaine patches or topical capsaicin. Treatment is more usually by unconventional analgesics such as antidepressants or anticonvulsants.

Data for the incidence of neuropathic pain is difficult to obtain, but a systematic review of prevalence and incidence in the Oxford Region of the UK indicates prevalence rates per 100,000 of 34 for postherpetic neuralgia, 400 for diabetic neuropathy and trigeminal neuropathy, and 2000 for fibromyalgia (McQuay 2007). Different estimates in the UK indicate incidences per 100,000 person-years observation of 40 (95% confidence interval (CI) 39 to 41) for postherpetic neuralgia, 27 (26 to 27) for trigeminal neuralgia, 1 (1 to 2) for phantom limb pain, and 15 (15 to 16) for painful diabetic neuropathy, with rates decreasing in recent years for phantom limb pain and postherpetic neuralgia and increasing for painful diabetic neuropathy (Hall 2006). The prevalence of neuropathic pain in Austria was reported as being 3.3% (Gustorff 2008). More recent surveys tend to agree that around 15% to 25% of patients with chronic pain (at least moderate pain lasting three months or longer) have neuropathic symptoms (Ohayon 2012; Toth 2009; Yawn 2009), and a systematic review of prevalence and incidence studies shows that the percentage with neuropathic symptoms varies with painful condition (Sadosky 2008).

Neuropathic pain and fibromyalgia are commonly 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 physical or cognitive, or both, therapies being combined with pharmacological interventions.

Description of the intervention

Amitriptyline is a tricyclic antidepressant. It is not licensed in the UK for treating neuropathic pain or fibromyalgia, but is commonly used for these indications, and it is commonly used for treating neuropathic pain around the world, irrespective of licensed indications. The drug is available as tablets (10, 25, 50 mg) and oral solutions. This medicine is usually given at night time in an attempt to reduce any sedative effects during the day. There were over 9.5 million prescriptions for amitriptyline in England in 2011 (mainly for 10 mg and 25 mg tablets) (PCA 2012); some of these prescriptions may be for relief of depression. The main side effects are due to its anticholinergic activity, and include dry mouth, weight gain, and drowsiness.

How the intervention might work

The mechanism of action of amitriptyline in the treatment of neuropathic pain and fibromyalgia remains uncertain, although it is known to inhibit both serotonin and noradrenalin 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 amitriptyline 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 patients with and without depression (Onghena 1992).

Why it is important to do this review

Amitriptyline is an established pharmacological intervention for chronic neuropathic pain. An earlier Cochrane review (Saarto 2007) of antidepressants for neuropathic pain included amitriptyline and found that about one in three participants treated experienced at least moderate pain relief with amitriptyline who would not have done so with placebo, when all types of neuropathic pain were combined. This review is the first of a number of revisions to the Saarto 2007 review. There may have been some new studies since the last review, including topical administration (Ho 2008), but it is also important to re-review existing evidence using more stringent criteria of validity, including both the level of response obtained, and duration of study.

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 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 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 (Moore 2010a; Moore 2012). To summarise some of the recent insights that make a new review necessary, over and above including more trials:

1. Analgesic results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2005) and 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 this 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; Straube 2010); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion 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 2010c; Straube 2010; 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. Imputation methods like 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 2012).

5. Finally, moderate or substantial pain relief in fibromyalgia predicts improvement in other outcomes and quality of life (Moore 2010c), and 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 and even ability to work (Straube 2011) in a significant way.

This Cochrane review therefore assesses evidence in ways that make both statistical and clinical sense, and in accordance with the current author guidance for pain reviews (AUREF 2012). Trials included and analysed have to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally a minimum of 400+ participants in a comparison in which numbers needed to treat (NNTs) are four or above (Moore 1998)). This does set high standards, and marks a departure from how reviews have been conducted previously.

Because amitriptyline is a crucially important drug in treating neuropathic, and sometimes other, pain, and because experience from previous reviews was that most studies would be older, be small, and have methodological deficiencies according to present standards of evidence, we felt it appropriate to accept lower standards than those currently demanded for part of our analyses. This included accepting shorter studies, cross-over studies, and studies where the outcome definition was uncertain; all studies had to minimally be both randomised and double-blind. We therefore report 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.

OBJECTIVES

1. To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia.

2. To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia.

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 treatment, and outcomes reported ideally after eight weeks of treatment or longer for the highest level of evidence, but accepted studies lasting four to eight weeks as a lower level. Full journal publication was required, with the exception of extended abstracts of otherwise unpublished clinical trials. We did not include short abstracts (usually meeting reports), studies that were non-randomised, studies of experimental pain, case reports, or clinical observations. Cross-over studies were not accepted unless there was clear reporting of the first phase only (essentially a parallel-group study). Studies with fewer than 10 participants in a treatment arm were rejected. Studies of topical administration were not considered.

Types of participants

We included adult participants aged 18 years and above with initial pain of at least moderate intensity. Participants could have one or more of a wide range of chronic neuropathic pain conditions including:

- painful diabetic neuropathy;
- postherpetic neuralgia;

- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome;
- cancer-related neuropathy;
- Guillain Barré;
- HIV neuropathy;
- spinal cord injury;
- fibromyalgia.

We included studies of participants with more than one type of neuropathic pain; we analysed results according to the primary condition.

Types of interventions

Amitriptyline in any dose, by any route other than topical, administered for the relief of neuropathic pain or fibromyalgia, and compared to placebo, no intervention, or any other active comparator. We did not include studies using amitriptyline to treat pain resulting from the use of other drugs.

Types of outcome measures

Studies needed to report pain assessment as either the primary or secondary outcome.

We anticipated that a variety of outcome measures would be used in the studies. The majority of studies were expected to use standard subjective scales for pain intensity or pain relief, or both, and we paid particular attention to IMMPACT definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those set out in the previous review (Saarto 2007), concentrating on dichotomous outcomes where pain responses are not normally distributed.

Primary outcomes

1. Patient-reported pain relief of 30% or greater
2. Patient-reported pain relief of 50% or greater
3. Patient-reported global impression of clinical change (PGIC) much or very much improved
4. Patient-reported global impression of clinical change (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
5. Withdrawals due to adverse events
6. Specific adverse events, particularly somnolence and dizziness

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 9);
- MEDLINE (via Ovid) (to September 2012);
- EMBASE (via Ovid) (to September 2012);
- Oxford Pain Relief database (Jadad 1996a).

See Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy

There was no language restriction.

Searching other resources

We searched reference lists of retrieved articles and reviews for any additional studies.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into RevMan (RevMan 2011) or any other analysis method. 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 'Risk of bias' tool available in RevMan 5 to report on sequence generation, allocation concealment, blinding, and other risks such as reporting of dropouts, and used the Oxford Quality Score (Jadad 1996b) as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum.

Measures of treatment effect

We calculated numbers needed to treat to benefit (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 used dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). Continuous data were not used in analyses.

Unit of analysis issues

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.

Dealing with missing data

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

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic. When I^2 was greater than 50%, we considered the reasons.

Assessment of reporting biases

The aim of this review is 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 with studies failing to report any dichotomous results. We extracted and used continuous data, which probably poorly reflect efficacy and utility, if useful for illustrative purposes only.
We undertook no assessment of publication bias due to the quality of the data identified, although we had planned to use 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 undertook meta-analysis using a fixed-effect model. A random-effects model for meta-analysis would have been used if there was significant clinical heterogeneity and it was considered appropriate to combine studies.
We determined that we would analyse data for each painful condition in two 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 for dropouts, reported an ITT analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants (preferably at least 400) in the comparison. These top-tier results are reported first.
- The second tier used any available data, but where one or more of these conditions were not met, for example reported at least 30% pain intensity reduction, used LOCF or a completer analysis, lasted four to eight weeks, and where the numbers of participants and studies were small.

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). We did not plan subgroup analyses since experience of previous reviews indicated that there would be too few data for any meaningful subgroup analysis.

Sensitivity analysis

We planned no sensitivity analysis because the evidence base was known to be too small to allow reliable analysis; results from neuropathic pain of different origins were not pooled in the primary analyses. We did examine details of dose escalation schedules in the unlikely situation that this could provide some basis for a sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.
See: Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification.

Results of the search

Results of the searches yielded 55 relevant studies with an amitriptyline treatment arm in a variety of neuropathic pain conditions. An additional unpublished study was brought to our attention by a peer reviewer (Anon 2000).

Three studies still await classification because of translation and other requirements. Ataoğlu 1997 is a Turkish report of a comparison of paroxetine and amitriptyline in fibromyalgia and, also in fibromyalgia, Jang 2010 is a Chinese report of a combination of acupuncture, cupping and medicine, which may include amitriptyline. Keskinbora 2006 is a Turkish report comparing gabapentin and amitriptyline in peripheral neuropathic pain.

Included studies

Twenty-two studies fulfilled the inclusion criteria. Studies reporting on efficacy or safety of amitriptyline were carried out in painful diabetic neuropathy (four studies, 478 participants; Anon 2000; Biesbroeck 1995; Jose 2007; Max 1992), postherpetic neuralgia (five studies, 227 participants; Graff-Radford 2000; Max 1988; Rowbotham 2005; Watson 1992; Watson 1998); spinal cord injury (two studies, 122 participants; Cardenas 2002; Rintala 2007) and one study each in mixed neuropathic pain (Vrethem 1997), cancer-related pain (Kautio 2008), HIV neuropathy (Shlay 1998), and post-stroke pain (Leijon 1989), with 230 participants in these four studies. There were seven studies in fibromyalgia, involving 548 participants (Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Goldenberg 1986; Goldenberg 1996; Hannonen 1998).

The total number of participants in these studies was 1437, but because 10 studies had a cross-over design (Carette 1995; Goldenberg 1996; Jose 2007; Leijon 1989; Max 1992; Max 1988; Rintala 2007; Vrethem 1997; Watson 1992; Watson 1998) and were not always clear about the number of participants completing each cross-over and providing data, we could only estimate the number of participants exposed to different interventions. The estimates of exposure were 774 to amitriptyline, 457 to placebo, and 596 to other active treatments.

The included studies individually involved between 15 and 235 participants, and only four involved over 100 participants (Biesbroeck 1995; Carette 1994; Hannonen 1998; Shlay 1998), and only one (Biesbroeck 1995) more than 100 participants in each treatment arm; the median study size was 44 participants. The median study duration was six weeks; four studies had a shorter duration (Leijon 1989; Vrethem 1997; Watson 1992; Watson 1998), while three studies had a duration of 12 weeks or more (Carette 1994; Hannonen 1998; Shlay 1998).

Excluded studies

We excluded 34 studies (Achar 2010; Bansal 2009; Bowsher 1997; Çapaci 2002; Carasso 1979; Fors 2002; Hampf 1989; Heymann 2001; Isomeri 1993; Jaeschke 1991; Kalso 1996; Kaur 2011; Kautio 2009; Kempenaers 1994; Kieburtz 1998; Lampl 2002; Max 1987; McQuay 1992; McQuay 1993; Mendel 1986; Mercadante 2002; Morello 1999; Özerbil 2006; Pilowsky 1990; Robinson 2004; Scudds 1989; Sharav 1987; Turkington 1980; Ventafridda 1987; Watson 1982; Wilder-Smith 2005; Zitman 1990; Zitman 1991). Reasons for exclusion of studies were: not being convincingly double-blind, not demonstrating that participants had initial pain of at least moderate intensity, lasting less than four weeks, having fewer than 10 participants in a treatment arm, not having a clear diagnosis of the painful condition, preventative treatments, having a high dropout rate, or not reporting any pain data. Details are in the Characteristics of excluded studies table.

Risk of bias in included studies

Risk of bias is shown in Figure 1 as a summary and in Figure 2 for each included study.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

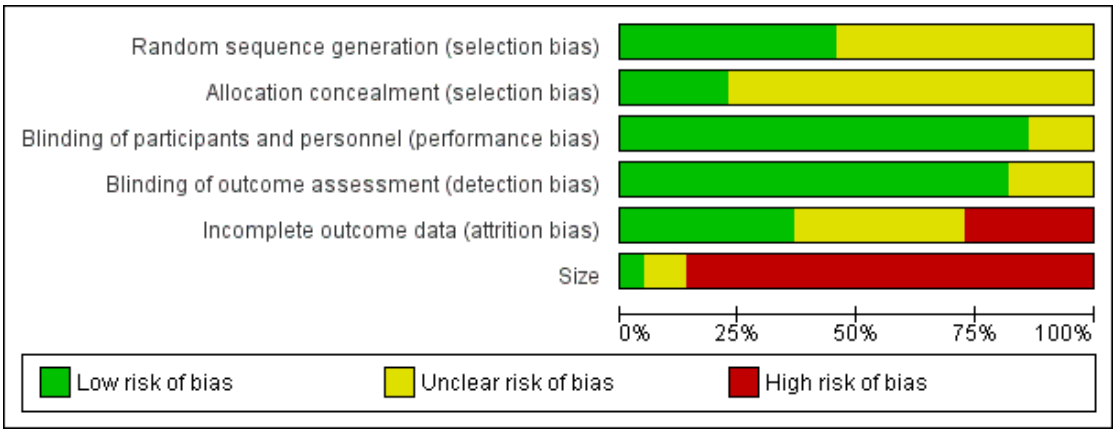
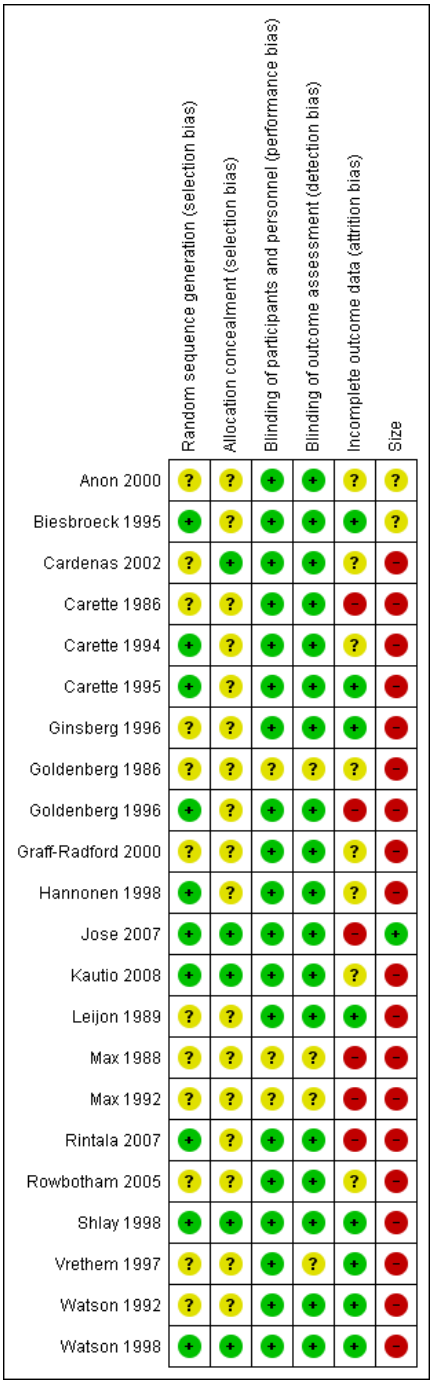


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Quality scores were good using the Oxford Quality Score; three studies scored 3/5 points, 12 scored 4/5, and 7 scored 5/5.

Allocation

Fewer than half of the studies adequately described the methods used to ensure that allocation of participants to treatment groups was concealed (Figure 1).

Blinding

Over two-thirds of the studies were convincingly double-blind from the descriptions of the measures taken.

Incomplete outcome data

Ten studies had a cross-over design. Five cross-over studies posed difficulties because data on all randomised participants were not available (Carette 1995; Goldenberg 1996; Max 1988; Max 1992; Rintala 2007). They tended to report on completers of all cross-over phases. In only about a third of studies was reporting of a high standard.

Selective reporting

The outcomes specified in the methods of most of these studies were not those sought for the review, so selective reporting bias was not an issue.

Other potential sources of bias

The major additional source of potential bias were:

- short duration: only 10 studies lasted eight weeks or longer, and four were shorter than six weeks;
- small size: only one study had more than the 100 participants in treatment arms, which has been shown to be associated with lower estimation of treatment effects in chronic pain studies (Nüesch 2010). Estimation of the magnitude of the treatment effect is suspect when the total number of participants is small (Moore 1998).

Effects of interventions

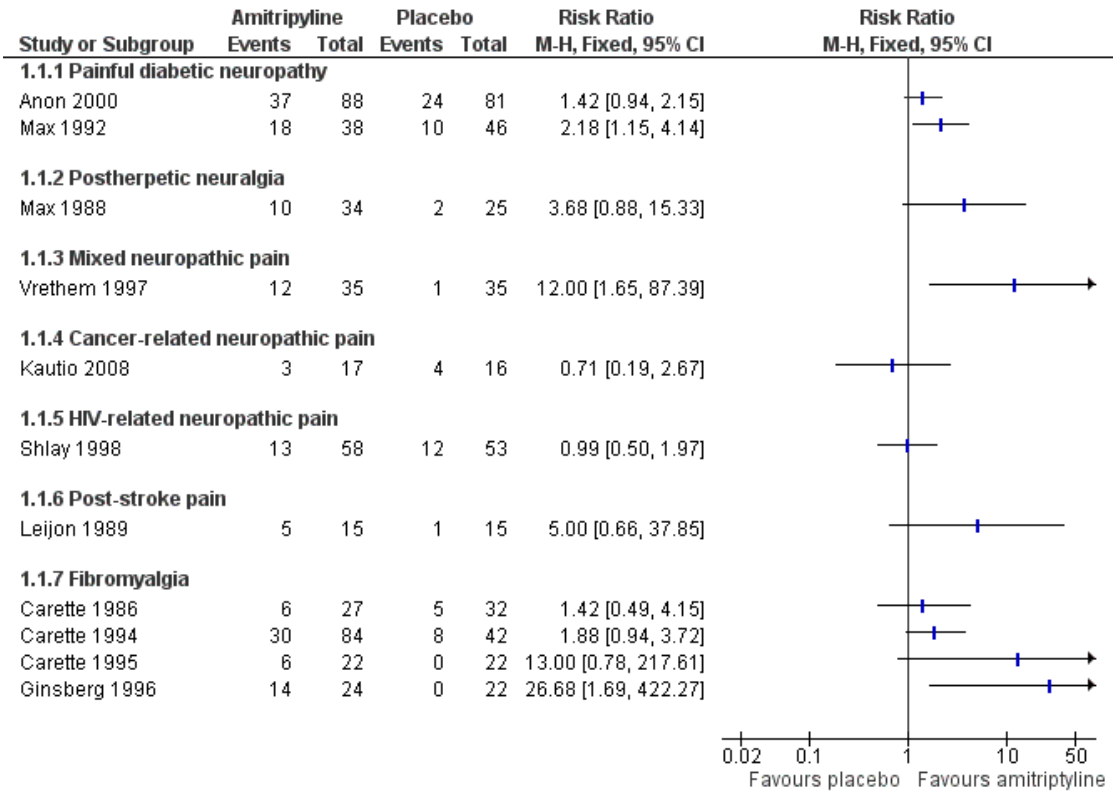
Efficacy

These analyses are performed in a two-tier manner. The first tier used data for each painful condition 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 for dropouts, reported an ITT analysis, lasted eight to 12 weeks or longer, were parallel-group design, and where there were at least 200 participants (preferably at least 400) in the comparison. These top-tier results are reported first.

No study met the criteria for first-tier evidence.

A second tier accepted less good quality data, for example at least 30% pain intensity reduction, LOCF or unexplained imputation, completer analyses, studies lasting four to eight weeks, and where any number of participants have contributed data (Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: 1 Amitriptyline versus placebo, outcome: 1.1 Second-tier efficacy.



Painful diabetic neuropathy

Four studies evaluated amitriptyline in painful diabetic neuropathy (Anon 2000; Biesbroeck 1995; Jose 2007; Max 1992). Two were of six weeks' duration (Jose 2007; Max 1992) and were small cross-over studies. All four were active controlled studies comparing amitriptyline with topical capsaicin (Biesbroeck 1995), oral lamotrigine (Jose 2007), oral pregabalin (Anon 2000), or oral desipramine or fluoxetine (Max 1992); the latter study also used a placebo control in its design. None of these studies found any difference between amitriptyline and other active interventions. The estimate of exposure to interventions was 286 for amitriptyline, 110 to placebo, and 279 to other interventions.

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in painful diabetic neuropathy.

Second-tier evidence

There was no convincing evidence that amitriptyline at doses of between 10 and 125 mg daily was better than topical capsaicin or oral lamotrigine. Only a small completer analysis from a multiple cross-over design offers some support for oral amitriptyline being any better than placebo.

Postherpetic neuralgia

Five studies evaluated amitriptyline in postherpetic neuralgia (Graff-Radford 2000; Max 1988; Rowbotham 2005; Watson 1992; Watson 1998); none involved more than 62 participants. Two (Watson 1992; Watson 1998) were of five, and two (Max 1988; Rowbotham 2005) of six weeks' duration. Three (Max 1988; Watson 1992; Watson 1998) were cross-over studies. One (Graff-Radford 2000) had no dichotomous outcomes. Two (Graff-Radford 2000; Max 1988) included a placebo, and included an active comparator. The estimate of exposure to interventions was 227 for amitriptyline, 53 to placebo, and 148 to other interventions.

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in postherpetic neuralgia.

Second-tier evidence

There was no convincing evidence that amitriptyline at various daily doses was better than nortriptyline, maprotiline, desipramine, or fluoxetine. Two studies pointed to amitriptyline being better than placebo (Graff-Radford 2000; Max 1988), but based on only 84 patients in the comparison. Amitriptyline was possibly better than lorazepam (Max 1988), but not desipramine (Rowbotham 2005), maprotiline (Watson 1992), or nortriptyline (Watson 1998).

Spinal cord injury

Two studies evaluated amitriptyline in spinal cord injury (Cardenas 2002; Rintala 2007); neither involved more than 84 participants. One (Cardenas 2002) was of six weeks' duration and the other (Rintala 2007) had a cross-over design with nine-week treatment periods. Both were placebo comparisons and one (Rintala 2007) also involved gabapentin as an active comparator. The estimate of exposure to interventions was 72 for amitriptyline, 65 to placebo, and 26 to other interventions.

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in spinal cord injury.

Second-tier evidence

The larger parallel-group study (Cardenas 2002) showed no difference between amitriptyline and placebo in a statistical analysis, but there was some suggestion that amitriptyline may have been somewhat better than placebo in a probable completer analysis in the other (Rintala 2007).

Mixed neuropathic pain

One four-week cross-over study involving 35 participants compared amitriptyline with maprotiline and placebo (Vrethem 1997).

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in mixed neuropathic pain.

Second-tier evidence

There was no convincing evidence that amitriptyline at 25 to 75 mg daily was better than placebo or maprotiline. This small study indicated that with amitriptyline about a third of participants were pain-free or much improved, and more than with placebo.

Cancer-related neuropathic pain

One eight-week study reporting on 33 participants compared amitriptyline with placebo (Kautio 2008).

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in cancer-related neuropathic pain.

Second-tier evidence

There was no convincing evidence that amitriptyline at 10 to 50 mg daily was better than placebo. This small study showed no difference between amitriptyline and placebo.

Painful HIV-related neuropathy

One 14-week study reporting on 136 participants compared amitriptyline with placebo (Shlay 1998).

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in painful HIV-related neuropathy.

Second-tier evidence

There was no convincing evidence that amitriptyline at 25 to 75 mg daily was better than placebo. This study showed no difference between amitriptyline and placebo.

Post-stroke pain

One four-week cross-over study involving 15 participants compared amitriptyline with carbamazepine and placebo (Leijon 1989).

First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in post-stroke pain.

Second-tier evidence

There was no convincing evidence that amitriptyline at 25 to 75 mg daily was better than placebo. This small study indicated that with amitriptyline about a third of participants were pain-free or much improved, and more than with placebo.

Fibromyalgia

Seven studies examined the efficacy of amitriptyline in fibromyalgia at daily doses of 25 mg or 50 mg (Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Goldenberg 1986; Goldenberg 1996; Hannonen 1998). Two lasted six weeks (Goldenberg 1986; Goldenberg 1996), and the others eight to 24 weeks. Two studies had a cross-over design (Carette 1995; Goldenberg 1996). Two were relatively large (Carette 1994; Hannonen 1998) with over 100 participants in total. All studies included a placebo comparison group. The estimate of exposure to interventions was 236 for amitriptyline, 196 to placebo, and 166 to other interventions.

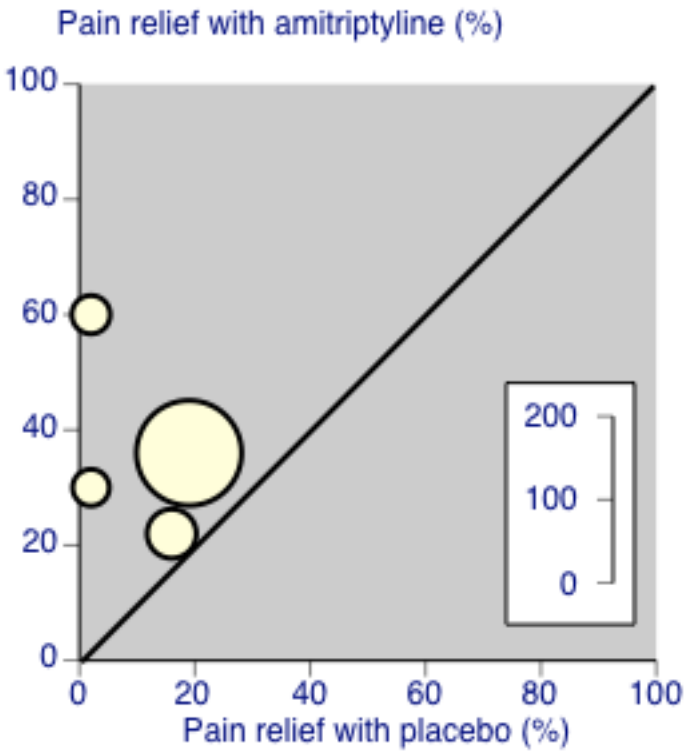
First-tier evidence

There was no first-tier evidence on the efficacy of amitriptyline in fibromyalgia.

Second-tier evidence

There was some evidence that amitriptyline at 25 or 50 mg daily was better than placebo. Four studies provided some data for second-tier evidence (Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Figure 3), but with considerable variation between studies (Figure 4). When pooled they showed that about 36% of participants treated with amitriptyline had a beneficial outcome (range 22% to 60% between studies), compared with 12% with placebo (range 2% to 19% between studies). This was statistically significant, with a risk ratio of 2.9 (95% confidence interval 1.7 to 4.9). The three studies that did not report dichotomous outcomes did however provide some support of greater analgesic effects from amitriptyline than placebo.

Figure 4. L'Abbé plot of second-tier outcome for amitriptyline 25 or 50 mg and placebo in fibromyalgia. Each circle represents one study. Size of circle is proportional to size of study (inset scale).



Amitriptyline was probably no better than cyclobenzaprine (Carette 1994), fluoxetine (Goldenberg 1996), or moclobemide (Hannonen 1998).

Adverse events

Participants experiencing at least one adverse event

This outcome was reported by 10 studies with placebo treatment arms, with 669 participants in the comparison (Anon 2000; Cardenas 2002; Carette 1986; Carette 1994; Ginsberg 1996; Hannonen 1998; Kautio 2008; Leijon 1989; Shlay 1998; Vrethem 1997). At least one adverse event was experienced by 285/446 (64%) of participants taking amitriptyline, and 155/391 (40%) taking placebo. The risk ratio was 1.5 (95% confidence interval 1.4 to 1.7) (Analysis 1.2), and the number needed to treat to harm was 4.1 (95% confidence interval 3.2 to 5.7).

Serious adverse events

These were reported in only two studies (Anon 2000; Vrethem 1997). There were 8/122 (6.6%) events with amitriptyline and 2/114 (1.8%) with placebo.

Withdrawals

All-cause withdrawals were reported by eight studies (Anon 2000; Cardenas 2002; Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Goldenberg 1986; Hannonen 1998). Overall, 66/346 (19%) withdrew for any cause with amitriptyline and 56/298 (19%) with placebo. The risk ratio was 1.00 (95% confidence interval 0.74 to 1.4); the number needed to treat to harm (NNH) was not calculated (Analysis 1.3).

Adverse event withdrawals were reported by six studies (Anon 2000; Carette 1986; Carette 1994; Hannonen 1998; Max 1988; Rintala 2007). Overall, 37/312 (12%) withdrew because of adverse events with amitriptyline and 19/263 (12%) with placebo. The risk ratio was 1.7 (95% confidence interval 1.01 to 2.9); the NNH was not calculated (Analysis 1.4).

Lack of efficacy withdrawals were reported by four studies (Anon 2000; Carette 1986; Carette 1994; Hannonen 1998). Overall, 11/240 (5%) withdrew because of lack of efficacy with amitriptyline and 23/200 (12%) with placebo. The risk ratio was 0.38 (95% confidence interval 0.19 to 0.76); the NNTp was 14 (8.3 to 57) (Analysis 1.5).

DISCUSSION

The most important finding of this review was that there were no studies that met current standards of evidence for chronic pain that exclude all known biases (Moore 2010a; Moore 2012). All the studies accepted for second-tier evidence contained features of design, conduct, or reporting that are known to be associated with bias in favour of the active treatment. Particular problems were reporting of outcomes of less than 50% pain intensity reduction, or undefined 'improvement', having relatively short duration (though studies lasting less than four weeks were excluded), and studies being small, in circumstances where small studies in chronic pain are known to be associated with over-estimation of treatment effect (Nüesch 2010). That means that the second-tier efficacy results reported here offer only the best judgement possible on evidence that is not wholly trustworthy.

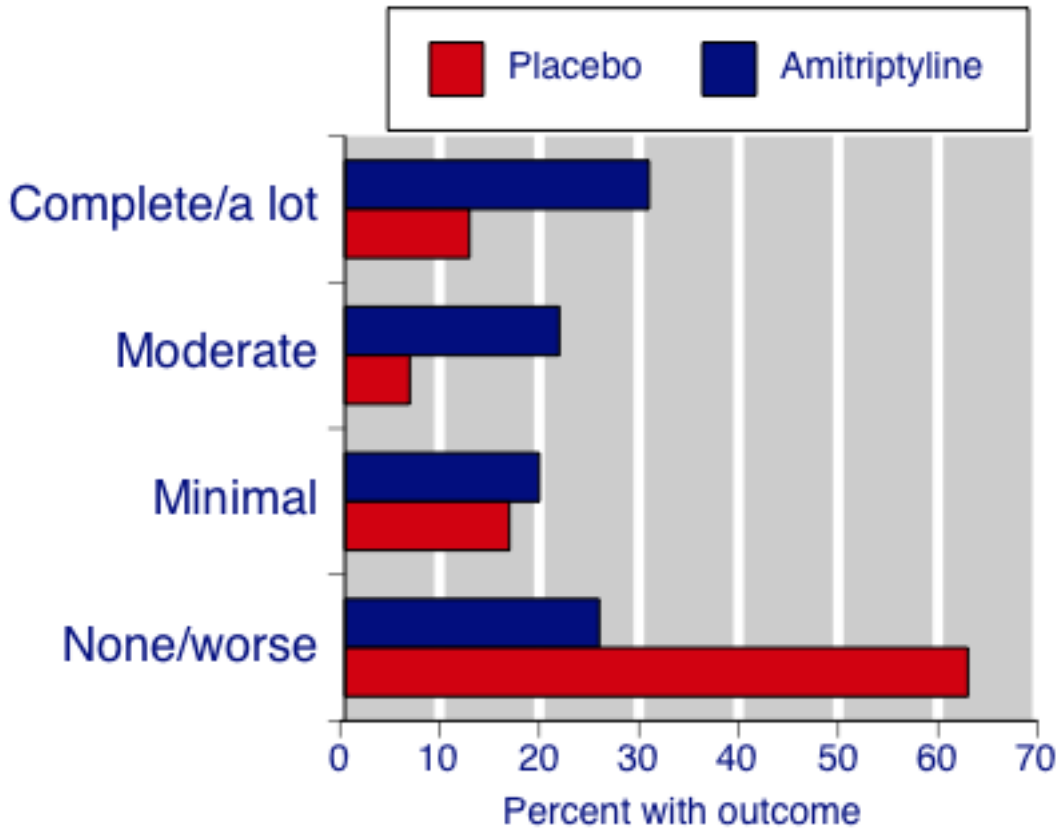
While it is possible that amitriptyline is effective in some patients with neuropathic pain or fibromyalgia, the evidence we have cannot rule out the possibility that amitriptyline is no better than placebo for any individual painful condition. This rather bleak conclusion should be tempered by the evidence that the most important message is that amitriptyline probably does give really good pain relief to some patients with neuropathic pain or fibromyalgia, but only a minority of them; amitriptyline will not work for most people.

Summary of main results

There is limited evidence based on small numbers of small studies that amitriptyline may have some benefit in neuropathic pain and fibromyalgia, with the exception of cancer-related and HIV-related neuropathic pain. These latter two conditions are notoriously difficult to treat, with growing evidence that most drugs fail in these conditions. Combining the classic neuropathic pain conditions of painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence gave, in nine studies and 687 participants, a statistically significant benefit (risk ratio 2.3, 95% confidence interval 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). Given the caveats above, this is almost certainly an overestimation of treatment effect, but the magnitude and consistency of effect within these eight studies does provide some confidence that amitriptyline benefits are real, at least for some patients. This is supported to some extent by the statistically significant, but small, reduction in participants withdrawing from studies because of the lack of analgesic efficacy compared with placebo (Analysis 1.5).

Moreover, six studies provided data concerning the levels of pain relief achieved by individual patients for amitriptyline and placebo (Carette 1986; Heymann 2001; Max 1988; Scudds 1989; Vrethem 1997). This shows a bimodal distribution with both placebo and amitriptyline (Figure 5). With placebo most participants had no or minimal pain relief. With amitriptyline more participants had moderate or complete pain relief, but for the best level of pain relief this was only 18% more than with placebo, meaning that most patients treated with amitriptyline would fail to achieve adequate levels of pain relief.

Figure 5. Bimodal distribution of benefits with amitriptyline and placebo in neuropathic pain and fibromyalgia



There are also problems with an assumption than amitriptyline is effective. For example, several studies could not differentiate between the efficacy found with amitriptyline and some other drugs, two of which, lamotrigine (Wiffen 2011) and topical capsaicin (Derry 2009), have evidence of little benefit in neuropathic pain.

Overall completeness and applicability of evidence

It is likely that all of the completed clinical trials have been found, but those we found and included had deficiencies because the design or reporting included features known to be associated with potential bias towards the active treatment over placebo. For example, almost half the studies had a cross-over design, most were small, some had a relatively short duration, and few had both a placebo group and reported outcomes based on individual patients obtaining a high degree of pain relief. For most specific painful conditions there was only a single small study.

This limits considerably the applicability of the evidence. Although amitriptyline is widely used as the mainstay of treatment of neuropathic pain, there is no unbiased evidence on which to base clinical practice, and no evidence for comparison with other potential treatments of neuropathic pain or fibromyalgia.

There are also significant limits in what the review can say about appropriate doses of amitriptyline. Most studies used dose titration and the range of doses was 10 mg to 125 mg daily.

Quality of the evidence

All studies had to be randomised and double-blind to be included, and all had to have participants with at least moderate pain relief to ensure that studies were sensitive. No single study fulfilled all the qualities of reliability now used in chronic pain.

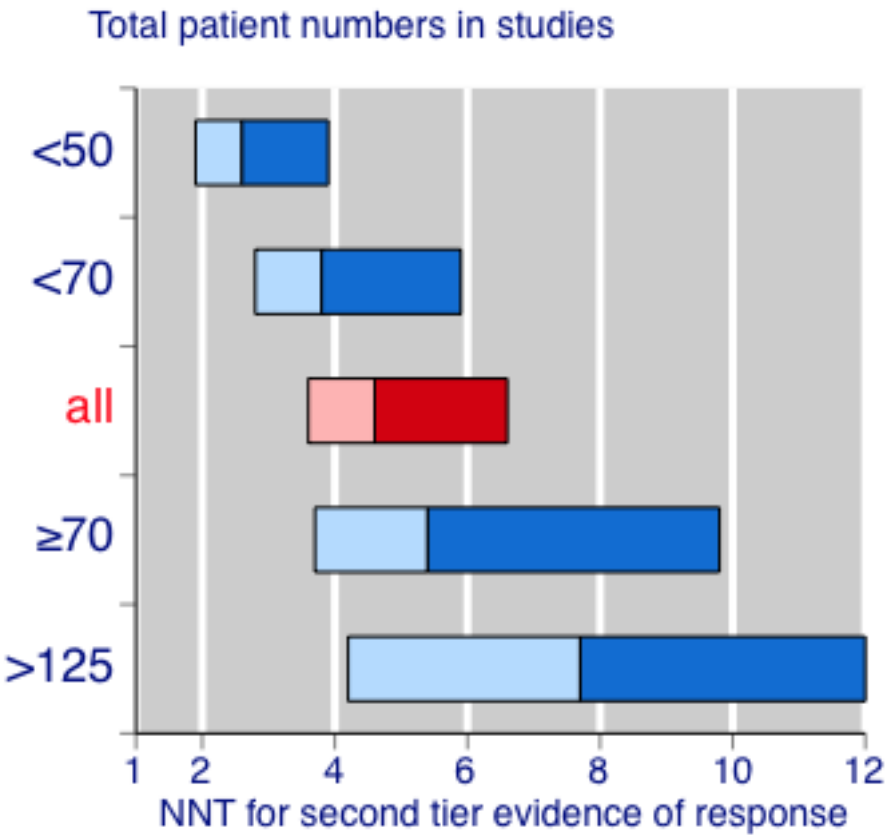
Potential biases in the review process

We used an extensive search strategy, which was based on previous Cochrane reviews and on other reviews with different strategies, and fundamental to all of these was a comprehensive manual journal search (Jadad 1996a). It is unlikely that relevant high-quality

large studies of amitriptyline in neuropathic pain or fibromyalgia have been overlooked, especially because amitriptyline is the mainstay of treatment. The addition of an unpublished study (Anon 2000), brought to our attention by a peer reviewer, was consistent with published data.

In osteoarthritis, studies with fewer than 100 participants per treatment arm had larger treatment effects than studies with more than 100 participants (Nüesch 2010). No study in this review had as many as 100 participants per treatment arm, but an analysis of NNT for second-tier outcomes by total study size showed a distinct relationship between size and treatment effect, with larger studies having higher (worse) NNTs (Figure 6).

Figure 6. Relationship between NNT and total size of study



Agreements and disagreements with other studies or reviews

Most previous systematic reviews have tended to examine all antidepressants or tricyclic antidepressants as a class of drugs (Attal 2010; Collins 2000; Finnerup 2005; Hempenstall 2005; McQuay 1996; Moulin 2007; Saarto 2007; Wong 2007), mainly because there are few studies with any single antidepressant drug in any single neuropathic pain condition before the advent of duloxe-

tine (Lunn 2009). None of these reviews has considered the additional sources of potential bias revealed in the recent past, and have occasionally concluded that the evidence for antidepressants or tricyclic antidepressant drugs is of high quality, including recent European guidelines (Attal 2010). It is notable how many authors have been prepared to produce firm guidelines based on tiny amounts of trial data with known evidence problems (Wong 2007). Other recent reviews have downgraded the quality of evidence regarding amitriptyline (Bril 2011).

This review is considerably more critical of the quality and quantity of useful data for amitriptyline for treating neuropathic pain or fibromyalgia, and is part of a series of reviews examining individual drugs rather than combining all together. This is appropriate because there is no good evidence that failure with one molecule will preclude success with another. For example a comparison of amitriptyline with nortriptyline in a cross-over study in postherpetic neuralgia found that out of 31 participants five had mild or no pain with amitriptyline but moderate to severe pain with nortriptyline, while four had good pain relief with nortriptyline but none with amitriptyline (Watson 1998). This small sample suggests that up to 30% of patients may react differently even to closely related drugs.

The second-tier estimates of efficacy for amitriptyline in neuropathic pain and fibromyalgia are of the same order as found for duloxetine in painful diabetic neuropathy (Lunn 2009) and painful diabetic neuropathy and fibromyalgia (Sultan 2008), though with much larger studies with many more participants, and studies that were parallel-group, generally longer, and better controlled, though with last observation carried forward (LOCF) imputation.

AUTHORS' CONCLUSIONS

Implications for practice

Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact is that there is no supportive unbiased evidence for a beneficial effect as defined as substantial pain relief has to be balanced against decades of successful treatment in many tens of thousands of patients with neuropathic pain or fibromyalgia. There is no evidence of a lack of effect, rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but we should be cognisant of the fact that only a minority of patients will achieve satisfactory pain relief.

Implications for research

It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy. Such trials are expensive. The bigger implication is for research in clinical practice, with knowledge of whether there is a sequence of using drugs that will provide overall better clinical effectiveness (Moore 2010d). Another area for research, though extremely difficult, is to identify characteristics that predict which patients are likely to benefit from amitriptyline.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anon 2000

Methods	R, DB, PC and AC, parallel groups, duration 9 weeks Amitriptyline 75 mg/day (25 mg x 3 daily), pregabalin 600 mg/day (200 mg x 3 daily), placebo Pain assessed periodically up to 9 weeks
Participants	Adults with painful diabetes neuropathy and pain ≥ 4/10 for at least 1 week N = 254 Mean age 60 years, 37% female Mean baseline score 6.3 to 6.9
Interventions	Amitriptyline, n = 87 Pregabalin, n = 86 Placebo, n = 81
Outcomes	Pain score Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matched" capsules and placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"matched" capsules and placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned
Size	Unclear risk	50 to 200 participants/treatment arm

Biesbroeck 1995

Methods	R, DB (DD), PC and AC, parallel groups, duration 8 weeks Amitriptyline taken as single dose, but split (morning and bedtime) if warranted. Initial daily dose of amitriptyline 25 mg, increased to maximum of 125 mg during first 4 weeks. Cream applied to painful area x 4 daily Pain assessed at baseline and every 2 weeks
Participants	Inclusion: diabetic neuropathy involving feet, ≥ moderate daily pain interfering with activities or sleep N = 235, mean age 60 years (range 21 to 85), M 132/F 103 Mean duration of symptoms > 4 years, mean baseline pain > 60/100
Interventions	Amitriptyline capsule (titrated from x 1 to x 5 25 mg/day) + placebo cream, n = 117 Topical capsaicin 0.075% cream + placebo capsule(s), n = 118 Topical capsaicin 0.075% cream + oral amitriptyline capsule(s) - not analysed For first 2 weeks, placebo cream contained methyl nicotinate, a rubefacient that can produce a stinging/burning sensation and erythema (to mimic capsaicin). Placebo capsules contained 0.25 mg benztropine to mimic dry mouth of amitriptyline, and also for first 2 weeks 2 mg diazepam to mimic CNS effects such as sedation 7 day washout for all topical medication and tricyclic antidepressants. Other long-term oral therapy permitted with no changes to dose or frequency
Outcomes	Pain intensity Pain relief Interference with activities of life Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomisation schedule"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy method described. Attempt to control for unmasking by adverse effects
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis for efficacy, but no data suitable for analysis. ITT analysis for adverse events

Biesbroeck 1995 (*Continued*)

Size	Unclear risk	50 to 200 participants/treatment arm

Cardenas 2002

Methods	R, DB, PC, parallel-group, treatment duration 6 weeks Medication taken as single dose 1 to 2 hours before bedtime. Initial daily dose of amitriptyline 10 mg, increased to 25 mg after 1 week, then by 25 mg each week to maximum of 125 mg if tolerated Pain intensity assessed at baseline and then weekly (average of 3 assessments used in weeks 1 and 6)
Participants	Inclusion: spinal cord injury > 6 months previously, age 18 to 65 years pain ≥ 3 months with average pain in last month ≥ 3/10 Exclude: history cardiovascular disease, abnormal ECG, seizures, major depressive episode or requiring antidepressant medication, consuming > 2 alcoholic drinks/day N = 84, mean age 42 years, M 67/F 17 Baseline pain intensity > 5/10
Interventions	Amitriptyline 25 to 125 mg/day, n = 44 Placebo, n = 40 Placebo contained 0.5 mg benztropine to mimic dry mouth
Outcomes	Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described other than stated as done by Center Pharmacy Investigational Drug Services
Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical gelatin capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical gelatin capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported

Cardenas 2002 (*Continued*)

Size	High risk	Fewer than 50 participants/treatment arm

Carette 1986

Methods	Multicentre, R, DB, PC, parallel groups, duration 9 weeks Medication taken as single dose at bedtime. Initial daily dose of amitriptyline 10 mg, increased to 25 mg after 1 week, and to 50 mg after 4 weeks. Dose reduction allowed if not tolerated Pain, sleep, overall change in disease assessed at baseline, week 5 and week 9
Participants	Inclusion: primary fibrositis (Smythe's criteria) Exclusion: evidence of traumatic, neurologic, muscular, infectious, osseous, endocrine, or other rheumatic conditions. History of glaucoma, urinary retention, cardiovascular abnormalities. Use of amitriptyline within previous year N = 70 enrolled, 57 completed, mean age 41 years, M 5/F 54 Mean duration of symptoms ~85 months (significantly longer in placebo group), mean baseline pain ~6/10
Interventions	Amitriptyline 50 mg/day, n = 27 Placebo, n = 32 All NSAIDs, antidepressants and hypnotic medication stopped ≥ 3 weeks before start of study Paracetamol permitted throughout study
Outcomes	Patient global impression of change Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - stated to be "randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules "were identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Capsules "were identical"

Carette 1986 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Size	High risk	Fewer than 50 participants/treatment arm

Carette 1994

Methods	Multicentre, R, DB (DD), PC and AC, parallel groups, treatment period 24 weeks Amitriptyline taken as single dose at bedtime; initial daily dose 10 mg, increased to 25 mg after 1 week, and to 50 mg after 12 weeks Cyclobenzaprine initial daily dose 10 mg at bedtime, increased to 20 mg at bedtime after 1 week, and to 10 mg in the morning +20 mg at bedtime after 12 weeks. Dose reduction permitted if not tolerated Pain, fatigue, sleep, fibromyalgia symptoms assessed at baseline, and each month
Participants	Inclusion: fibromyalgia (ACR 1990), age ≥ 18 years, ≥ 4/10 for pain and/or global assessment of fibromyalgia symptoms Exclusion: evidence of inflammatory rheumatic disease, untreated endocrine, neurologic, infectious, or osseous disorder. Glaucoma, urinary retention, cardiovascular abnormalities. Previous treatment with study drugs N = 208, mean age 45 years, M 13/F 195 Median duration of symptoms 5 years, baseline pain ≥ 66/100
Interventions	Amitriptyline 50 mg/day, n = 84 Cyclobenzaprine 30 mg/day, n = 82 Placebo, n = 42 All NSAIDs, hypnotics, and antidepressants discontinued ≥ 3 weeks before start of study Paracetamol permitted throughout study
Outcomes	Responder (at least 4/6 from ≥ 50% improvement in pain, sleep, fatigue, patient global assessment, physician global assessment, and increase of 1 kg in total myalgic score) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"generated using a table of random numbers .... assigned in blocks of 5"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method described. "Either amitriptyline 25mg or an identical appearing inert cyclobenzaprine placebo or active cyclobenzaprine and inert amitripty-

Carette 1994 (*Continued*)

		line placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy method described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Responder analysis, but unclear whether withdrawal = non responder or LOCF
Size	High risk	Fewer than 50 participants in placebo treatment arm

Carette 1995

Methods	Single centre, R, DB, PC, cross-over study. 2 x 8-week treatment periods with no washout Medication taken as single dose, 1 hour before bedtime Pain, fibromyalgia, sleep, and fatigue assessed at baseline and end of each treatment period
Participants	Inclusion: fibromyalgia (ACR), age ≥ 18 years, baseline pain and/or global assessment of fibromyalgia ≥ 4/10 Excluded: evidence of neurologic, muscular, infectious, endocrine, osseous, or other rheumatological diseases, history of glaucoma, urinary retention, cardiovascular disease, sleep apnoea N = 22, mean age 44 years, M 1/F 21 Mean (SD) duration of fibromyalgia 83 (± 75) months, mean baseline pain 7/10
Interventions	Amitriptyline 25 mg/d (reduced to 10 mg/day if not tolerated), n = 22 Placebo, n = 20 Washout before start of study: 2 weeks for NSAIDs and hypnotics, minimum 4 weeks for antidepressants Paracetamol permitted throughout study
Outcomes	Responder (at least 4/6 from ≥ 50% improvement in pain, sleep, fatigue, patient global assessment, physician global assessment, and increase of 1 kg in total myalgic score) Mean pain intensity Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"generated using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported

Carette 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identically appearing placebo tablet"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identically appearing placebo tablet"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in responder analysis. Unclear how missing data were handled for mean data
Size	High risk	Fewer than 50 participants/treatment arm

Ginsberg 1996

Methods	Single centre, R, DB, PC, parallel groups, 8-week treatment period Medication taken as single dose, 1 hour before bedtime Pain, fibromyalgia, sleep, and fatigue assessed at baseline and end of weeks 4 and 8
Participants	Inclusion: fibromyalgia (ACR) Exclusion: glaucoma, urinary retention, cardiovascular problems, epilepsy, treatment with amitriptyline within 6 months N = 46, mean age 46 years, M 8/F 38 Duration of fibromyalgia 0.3 to 20 years, mean baseline pain 7/10
Interventions	Amitriptyline 25 mg/day n = 24 (sustained-release formulation) Placebo, n = 22 Not permitted during study: vitamin D/magnesium, muscle relaxants, analgesics/anti-inflammatory except paracetamol, antidepressants, hypnotics, tranquillisers Paracetamol permitted throughout study for severe pain
Outcomes	Responder (at least 3/4 from $\geq$ 50% improvement in patient global, physician global, pain, and $\geq$ 25% reduction in tender point score) Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported - stated as "randomly assigned"

Ginsberg 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was "identical to the amitriptyline capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo was "identical to the amitriptyline capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in responder analysis. Unclear how missing data were handled for mean data
Size	High risk	Fewer than 50 participants/treatment arm

Goldenberg 1986

Methods	R, DB, AC, and PC, parallel groups, 6-week treatment period Amitriptyline taken as single dose at night, naproxen as divided dose morning and night - implication is DD Assessments at baseline, 2, 4, and 6 weeks for patient global fibromyalgia symptoms, pain or stiffness, fatigue, sleep
Participants	Inclusion: fibromyalgia (not ACR, but probably equivalent), baseline pain and/or fibromyalgia symptoms $\geq$ 4/10 Excluded: peptic ulcer disease or cardiac arrhythmias N = 62, mean age 44 years, M 3/F 59 Duration of chronic pain 0.3 to 20 years
Interventions	Amitriptyline 25 mg/day, n = assume 16 Naproxen 2 x 500 mg/day, n = assume 15 Amitriptyline 25 mg + naproxen 2 x 500 mg/day, n = assume 15 Placebo, n = assume 16 All analgesics, antiinflammatory medications, antidepressants, sleeping medication and CNS-active medications stopped $\geq$ 72 h before start Paracetamol (2 x 650 mg every 4 hours) allowed for severe pain throughout study
Outcomes	Mean pain intensity Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Goldenberg 1986 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not reported - stated to be "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be 'blinded'. Describes double-dummy design but not stated to be matching
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be 'blinded'. Describes double-dummy design but not stated to be matching
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported. No responder data
Size	High risk	Fewer than 50 participants/treatment arm

Goldenberg 1996

Methods	Single centre, R, DB, PC, and AC, cross-over study. 4 x 6-week treatment periods with 2-week washout between periods Amitriptyline taken as single dose at bedtime, fluoxetine as single dose in the morning Pain, fibromyalgia, sleep, and fatigue assessed at baseline and end of each treatment period
Participants	Inclusion: fibromyalgia (ACR), age 18 to 60 years, baseline pain $\geq$ 30/100, baseline HRS-D $\leq$ 18 Exclusion: current or history of systemic disease N = 31, mean age 43 years, M 3/F 28 Duration of symptoms 24 to 240 months, mean baseline pain 67/100
Interventions	Amitriptyline 25 mg/day, n = 21 Fluoxetine 20 mg/day, n = 22 Amitriptyline 25 mg + fluoxetine 20 mg, n = 19 Placebo, n = 19 All CNS-active medications, NSAIDs, analgesics other than paracetamol stopped $\geq$ 7 days before start Paracetamol permitted
Outcomes	Mean pain intensity Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5
Risk of bias	

Goldenberg 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"order of treatment was generated from a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All tablets were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All tablets were identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF implied
Size	High risk	Fewer than 50 participants/treatment arm

Graff-Radford 2000

Methods	R, DB (DD), PC, and AC, parallel groups, treatment period 8 weeks Medication taken as single dose at bedtime. Initial daily dose of amitriptyline was 12.5 mg, increased by 25 mg each week to maximum of 200 mg or maximum tolerated dose. Initial daily dose of fluphenazine was 1 mg, titrated to maximum of 3 mg, depending on response Pain intensity and side effects assessed each week
Participants	Postherpetic neuralgia with pain for ≥ 6 months - no further details about inclusion/exclusion criteria N = 50 (49 completed), mean age 73 years, M 27/F 22 Mean duration of pain symptoms 33 months, baseline pain 55/100
Interventions	Amitriptyline 12.5 mg to 200 mg/day, n = 11 Fluphenazine 1 to 3 mg/day, n = 13 Amitriptyline + fluphenazine 25 to 300/1 to 3 mg/day, n = 12 Placebo, n = 13 No details of washout or permitted medication
Outcomes	Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5
Risk of bias	

Graff-Radford 2000 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described - states "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method. "Active" placebo (glycopyrrolate) to mimic anticholinergic side effects
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy method. "Active" placebo (glycopyrrolate) to mimic anticholinergic side effects
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not described
Size	High risk	Fewer than 50 participants/treatment arm

Hannonen 1998

Methods	Multicentre, R, DB, PC, and AC, parallel groups, 12-week treatment period Amitriptyline taken 2 h before bedtime, moclobemide taken as divided dose in morning and afternoon. Initial daily dose amitriptyline 12.5 mg, increased to 25 mg at 2 weeks, and again to 37.5 mg at 6 weeks if response unsatisfactory. Initial daily dose of moclobemide 300 mg, increased to 450 mg at 2 weeks, and again to 600 mg if response unsatisfactory Pain, general health (fibromyalgia), sleep, and fatigue assessed at baseline and 2, 6, 12 weeks
Participants	Inclusion: fibromyalgia (ACR 1990), female, age 18 to 65 years, score $\geq$ 4/10 for at least three of pain, general health (fibromyalgia), sleep, and fatigue Exclusion: severe cardiovascular, pulmonary, hepatic, haematological or renal disease N = 130, mean age 49 years, all F Mean duration of symptoms 8 years, baseline pain $\geq$ 5.7/10
Interventions	Amitriptyline 25 mg/day, n = 42 Moclobemide 450 mg/day, n = 43 Placebo, n = 45 All CNS-active medications, NSAIDs, and analgesics (other than paracetamol) discontinued before start of study Paracetamol permitted throughout study
Outcomes	Mean pain intensity, global health Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Hannonen 1998 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomisation was organised centrally with sequentially numbered envelopes consisting of blocks of six". Probably low risk
Allocation concealment (selection bias)	Unclear risk	Does not state that envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"placebo capsules were identical to the active drugs". Implies double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"placebo capsules were identical to the active drugs". Implies double-dummy method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported. No obvious imbalance for discontinuations between groups, but > 25% withdrawals in all groups
Size	High risk	Fewer than 50 participants/treatment arm

Jose 2007

Methods	R, DB, AC, cross-over study. 2 x 6-week treatment periods separated by 2-week washout Amitriptyline taken as single dose at bedtime, lamotrigine as divided dose, morning and night. Initial daily dose of amitriptyline 10 mg, increasing to 25 mg, and 50 mg after 2 weeks at each dose. Initial daily dose of lamotrigine 25 mg, increasing to 50 mg and 100 mg after 2 weeks at each dose
Participants	Inclusion: painful diabetic neuropathy, type 2 diabetes, stable glucose-lowering medication, pain $\geq$ 5/10 for $\geq$ 1 month Exclusion: renal or liver disease, epilepsy, psychiatric or cardiac disease, uncontrolled hypertension, peripheral vascular disease, other cause of neuropathy or painful conditions N = 53 (46 completed both periods), mean age 56 years, M 16/F 30 Mean duration of pain symptoms 12 months; mean baseline pain $\geq$ 70/100
Interventions	Amitriptyline 10 to 50 mg/day, n = 53 Lamotrigine 50 to 200 mg/day, n = 46 Antidepressants, anticonvulsants, local anaesthetics and opioids discontinued $\geq$ 1 month, other PDN medication $\leq$ 1 week before start of study. Paracetamol $\leq$ 3 g/day permitted during run-in and washout periods, except before assessments

Jose 2007 (*Continued*)

Outcomes	Patient global impression of change (≥ 50% and ≥ 30% improvement) Pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"generated using random number tables by block randomisation"
Allocation concealment (selection bias)	Low risk	"Drugs were blinded, packed and numbered serially, and allocated remotely" "Drug codes maintained under lock and key"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method. "matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy method. "matching placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis of completers
Size	Low risk	Fewer than 50 participants/treatment arm

Kautio 2008

Methods	R, DB, PC, parallel groups, 8-week treatment period Initial daily dose 10 mg, increased by 10 mg/week to maximum dose 50 mg if tolerated Pain symptoms assessed twice weekly, and global improvement of symptoms at end of study
Participants	Inclusion: cancer patient with chemotherapy-induced neuropathy, age 18 to 65 years, baseline pain ≥ 3/10, expected survival time ≥ 3 months and neurotoxic chemotherapy of ≥ 2 months Exclusion: other neurological disease, other possible causes of neuropathy, contraindications to amitriptyline therapy N = 42 (33 completed), mean age 54 years, M 12/F 32

Kautio 2008 (*Continued*)

Interventions	Amitriptyline 10 to 150 mg/day, n = 21 (17 in analysis) Placebo, n = 21 (16 in analysis) Concomitant medication for neuropathic symptoms that inhibits norepinephrine uptake prohibited
Outcomes	Responder (complete or major relief of neuropathic symptoms)
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Remote allocation (hospital pharmacy)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF on completer analysis as reported. Relevant participants added back for responder analysis
Size	High risk	Fewer than 50 participants/treatment arm

Leijon 1989

Methods	R, DB (DD), AC, and PC, cross-over study. 3 x 4 weeks separated by 1-week washout Medication taken as divided doses, morning and night Initial daily dose of amitriptyline 25 mg, increased to 50 mg on day 2, and 75 mg on day 6. Initial daily dose of carbamazepine 200 mg, increased to 400 mg on day 2, 600 mg on day 6, 700 mg on day 15, and 800 mg on day 18. Dose reduction allowed for moderate adverse events Pain assessed twice daily, and global evaluation of effect on pain at end of each period
Participants	Inclusion: unequivocal stroke episode, constant or intermittent pain which started after stroke and requires treatment, and is not nociceptive, peripheral neuropathic or psychogenic in origin Exclusion: contraindication to study drug, condition would make evaluation difficult N = 15, mean age 66 years, M 12/F 3

Leijon 1989 (*Continued*)

	Duration of pain 54 months (range 11 to 154), mean baseline pain intensity ~5/10
Interventions	Amitriptyline 25 to 75 mg/day, n = 15 Carbamazepine 200 to 800 mg, n = 14 Placebo, n = 15
Outcomes	Patient global evaluation (much improved + pain-free, and ≥ improved) Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - described only as randomised
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique", "identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double dummy technique", "identical capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in patient global evaluation, no withdrawals
Size	High risk	Fewer than 50 participants/treatment arm

Max 1988

Methods	R, DB, PC, and AC, cross-over study. 2 x 6-week treatment periods (placebo to active, or active to active) separated by 1-week washout Medication taken as divided dose morning and evening (unless intolerable daytime sedation). Initial daily dose of amitriptyline 12.5 mg, titrated over first 3 weeks to 150 mg or maximum tolerated dose. Initial daily dose of lorazepam 0.5 mg, titrated over first 3 weeks to 6 mg or maximum tolerated dose Pain intensity assessed 5 x daily and pain relief at end of each treatment period
Participants	Postherpetic neuralgia Inclusion: daily pain persisting ≥ 3 months after eruption Exclusion: presence of another type of pain as severe as PHN, depression requiring treatment

Max 1988 (*Continued*)

	N = 62 (41 completed both periods, 58 completed at least part of at least one period), median age 72 years, M 31/F 27 Median duration of pain 19 months, baseline pain (in completers) moderate
Interventions	Amitriptyline 12.5 to 150 mg/day, n = 34 Lorazepam 0.5 to 6 mg/day, n = 40 Placebo, n = 25 2-week drug-free washout period before start of study
Outcomes	Patient global evaluation of treatment at 6 weeks (all periods) Mean pain intensity (first period only) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported - states patients were "randomised into one of four treatment pairs"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported - stated "under double blind conditions"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Size	High risk	Fewer than 50 participants/treatment arm

Max 1992

Methods	Two R, DB, AC, cross-over studies. 2 x 6-week treatment periods separated by 2-week washout, then option to enter the other study Medication taken as single dose at 9 pm. Dose titrated to maximum tolerated over first 4 weeks of study Pain assessed daily (Gracely scale), and global evaluation of treatment made at end of each treatment phase

Max 1992 (*Continued*)

Participants	Inclusion: painful diabetic neuropathy, stable control of diabetes mellitus, ≥ 3 months of daily pain ≥ moderate intensity, not attributable to another cause Exclusion: other pain more severe than neuropathic pain, severe depression, symptomatic coronary artery or peripheral vascular disease, postural hypotension, nephropathy Study 1: N = 29 initially, but unclear how many included in analyses Study 2: N = 28 initially, but unclear how many included in analyses Median age ~58 years, M:F 3:2 Median duration of pain ~3 years, mean baseline pain intensity moderate to severe
Interventions	Study 1 Amitriptyline 12.5 to 150 mg/day Desipramine 12.5 to 150 mg/day Study 2 Fluoxetine 20 to 40 mg/day Placebo Placebo contained 0.125 to 1.5 mg benztropine/day to mimic dry mouth Antidepressant medication stopped ≥ 3 weeks before start of baseline observations. Other analgesic medication stopped if possible, or limited to 1 dose/day for severe pain
Outcomes	Patient global evaluation of treatment at end of each treatment period. No usable data Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - stated to be "randomised"
Allocation concealment (selection bias)	Unclear risk	Not clearly described - stated to be "double blind randomisation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described - stated to be "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Size	High risk	Fewer than 50 participants/treatment arm

Rintala 2007

Methods	R, DB, PC, and AC, cross-over study. 3 x 9-week treatment periods separated by 1-week washout Medication taken as 3 daily doses. Daily dose of amitriptyline 25 mg (days 1 to 3), increased to 50 mg (4 to 5), 75 mg (6 to 7), 100 mg (8 to 14), 125 mg (15 to 21), and 150 mg (22 to 56), then reduced during 9th week of treatment. Daily dose of gabapentin 300 mg (days 1 to 3), increased to 600 mg (4 to 5), 900 mg (6 to 7), 1800 mg (8 to 14) , 2400 mg (15 to 21), 3600 mg (22 to 56), then reduced during 9th week of treatment Pain intensity assessed at baseline and end of each treatment period
Participants	Inclusion: spinal cord injury ≥ 12 months previously, ≥ 1 pain component characteristic of neuropathic pain, present for > 6 months, pain intensity ≥ 5/10, age 18 to 70 years Exclusion: significant cardiac conduction disturbance, history of seizures, liver dysfunction, renal insufficiency, serious psychological disturbance, abuse problem, use of contraindicated medication N = 38 (22 completed all 3 phases), mean age ~40 years, M 36/F 2 Median duration of pain 5 years, median pain at baseline 6/10
Interventions	Amitriptyline 25 to 150 mg/day, n = 28 Gabapentin 300 to 1200 mg/day, n = 26 All pain medication stopped > 1 week before start
Outcomes	Responder (≥ 30% reduction in pain), by depressive symptoms Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"based on table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules" prepared by commercial compounding company. Each single capsule contained the required dose for the schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical capsules" prepared by commercial compounding company. Each single capsule contained the required dose for the schedule
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported

Size	High risk	Fewer than 50 participants/treatment arm

Rowbotham 2005

Methods	R, DB (DD), AC, parallel groups, 6-week treatment period then 2-week taper Medication taken as divided dose, twice daily. Initial doses were amitriptyline 25 mg/day, desipramine 25 mg/day, fluoxetine 20 mg every other day. Dose increased every 2 to 7 days over first 3 weeks to maximum tolerated or daily doses of amitriptyline 150 mg, desipramine 150 mg, and fluoxetine 60 mg
Participants	Inclusion: postherpetic neuralgia, age > 40 years, pain ≥ 3 months after healing of rash Exclusion: previous adequate trial of antidepressant for postherpetic neuralgia, previous neurosurgical or neurolytic therapy, separate pain problem of ≥ severity N = 47, mean age 72 years, M 20/F 27 Mean duration of symptoms 42 months, mean baseline pain 54/100
Interventions	Amitriptyline 25 to 150 mg/day, n = 17 Desipramine 25 to 150 mg/day, n = 15 Fluoxetine 10 to 60 mg/day, n = 15
Outcomes	Responder (≥ moderate pain relief) Mean pain intensity Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - states "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy technique - states "under double blind conditions...all subjects took 2 capsules twice a day"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy technique
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF implied for mean data and categorical data. Comparison shows differences between completers and non-completers

Rowbotham 2005 (*Continued*)

Size	High risk	Fewer than 50 participants/treatment arm

Shlay 1998

Methods	Multicentre, R, DB (part DD), PC, parallel groups, study duration 14 weeks Initial daily dose of amitriptyline 25 mg, increased by 25 mg every 2 to 3 days to maximum 75 mg/day. Medication taken 1 to 2 hours before bedtime. Acupuncture at standard and control points carried out twice weekly, with needles inserted to different depths Initially participants randomised to 2 x 2 factorial study, where participants received amitriptyline + control acupuncture, standard acupuncture + placebo amitriptyline, amitriptyline + standard acupuncture, or placebo amitriptyline + control acupuncture. Subsequently, participants randomised to amitriptyline versus placebo amitriptyline, or standard acupuncture versus control acupuncture Pain assessed daily using Gracely Scale, and at end of titration and maintenance periods by Patient Global Pain Relief
Participants	Inclusion: documented history of HIV and symptoms of HIV-related lower extremity neuropathy, age $\geq$ 13 years Exclusion: treatment for opportunistic infection or malignancy (except Kaposi sarcoma) Antiretroviral medication allowed throughout study. Analgesic medication could be maintained or reduced, but new treatments discouraged. Tricyclic antidepressants and Monoamine oxidase inhibitors discontinued $\geq$ 2 weeks before start N = 125, mean age 41 years, M 124/F 12
Interventions	Amitriptyline 25 to 75 mg/day + control acupuncture, n = 33 Acupuncture (standard technique) x 2/week + placebo amitriptyline, n = 31 Amitriptyline + standard acupuncture, n = 32 Placebo amitriptyline + control acupuncture, n = 29 Amitriptyline alone, n = 6 Placebo amitriptyline alone, n = 5 Standard acupuncture alone, n = 58 Control acupuncture alone, n = 56 Antiretroviral therapy permitted, dosages of analgesic medication or herbal therapies maintained or reduced. Initiation of new treatment discouraged
Outcomes	Global pain relief at 6 and 14 weeks Mean pain intensity Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Shlay 1998 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation schedules prepared "using random blocks stratified by unit" by university statistical centre
Allocation concealment (selection bias)	Low risk	Remote allocation "by study units by telephoning the statistical center"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules were of "identical" appearance to amitriptyline. Acupuncture control used "control points". Unit pharmacists were only people not blinded to drug assignment, and acupuncturists were only people not blinded to acupuncture assignment. Application of drug treatment effectively blinded, application of acupuncture potentially compromised
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo capsules were of "identical" appearance to amitriptyline. Acupuncture control used "control points". Unit pharmacists were only people not blinded to drug assignment, and acupuncturists were only people not blinded to acupuncture assignment. Diaries and pain assessments collected by staff blinded to assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two methods used. LOCF - if pain score for week 6 or 14 not available, closest score (4 to 10 week or 11 to 16 week) used. BOCF - assumes no change from pain at baseline. Did not change results
Size	High risk	Fewer than 50 participants/treatment arm

Vrethem 1997

Methods	R, DB (DD), PC and AC, cross-over study. 3 x 4-week treatment periods separated by 1-week washouts Medication taken at night
Participants	Inclusion: polyneuropathic pain (diabetic and non-diabetic) for $\geq$ 6 months, with $\geq$ 2 of distal sensory impairment, distal muscle weakness or atrophy, bilateral decrease, loss of tendon reflexes N = 37, age 35 to 83, M 17/F 19 (no data for one participant) Duration of pain 6 to 168 months

Vrethem 1997 (*Continued*)

Interventions	Amitriptyline 25 to 75 mg/day, n = 35 Maprotiline 25 to 75 mg/day, n = 35 Placebo, n = 35 2 participants took ≤ 1 dose and provided no data
Outcomes	Patient global evaluation ("much improved or pain-free" and "≥ improved") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - stated to be 'randomised'
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique", "identical capsules". Adverse events reported to research assistant, then to two independent neurologists if dose changes required; investigators blinded to adverse events
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double dummy technique", "identical capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	True responder data available for all participants for global analysis
Size	High risk	Fewer than 50 participants/treatment arm

Watson 1992

Methods	R, DB (DD), AC, cross-over. 2 x 5-week treatment periods separated by 2-week washout Medication probably taken as single dose. Initial dose of amitriptyline or maprotiline 25 mg (12.5 mg if age > 65 years), increased by 12.5 mg every 3 to 5 days to maximum tolerated dose within 3 weeks Pain intensity assessed at baseline and weekly intervals
Participants	Inclusion: postherpetic neuralgia, pain symptoms ≥ 3 months and ≥ moderate for half of the day Exclusion: cardiac disease, seizure disorder, other significant pain problem, previous brain damage through injury, stroke etc, alcoholism N = 35, mean age 71 years, M 18/F 17

Watson 1992 (*Continued*)

	Median duration of pain 14 months
Interventions	Amitriptyline ≥ 12.5 mg/day, n = 35 Maprotiline ≥ 12.5 mg/day, n = 35 All antidepressant or neuroleptic medications withdrawn over 3 weeks before start of study. Stable analgesics continued as needed
Outcomes	Responder (mild or no pain at end of study) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described - stated to be "randomized"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy technique described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy technique described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Imputation method not reported. Completer analysis reported, but all participants included in responder outcome
Size	High risk	Fewer than 50 participants/treatment arm

Watson 1998

Methods	R, DB, AC, cross-over study. 2 x 5-week treatment periods separated by 2-week washout Initial daily dose 20 mg (10 mg if age > 65 years), increased by 10 mg every 3 to 5 days to maximum tolerated within 3 weeks Pain intensity and pain relief assessed at baseline and weekly intervals
Participants	Inclusion: postherpetic neuralgia, pain symptoms ≥ 3 months and ≥ moderate for half of the day Exclusion: cardiac disease, seizure disorder, other significant pain problem, severe depression, previous brain damage through injury, stroke etc, alcoholism N = 33, mean age 71 years, M 18/F 17

Watson 1998 (*Continued*)

	Median duration of pain 14 months
Interventions	Amitriptyline ≥ 10 mg/day, n = 33 Nortriptyline ≥ 10 mg/day, n = 33 All antidepressant or neuroleptic medications withdrawn over 3 weeks before start of study. Stable analgesics continued as needed
Outcomes	Responder (satisfaction with pain relief and tolerable side effects) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated "by computer"
Allocation concealment (selection bias)	Low risk	Remote allocation and "sequence concealed in sequential, numbered, sealed envelopes" "Code kept in central pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical blue gelatin capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical blue gelatin capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis
Size	High risk	Fewer than 50 participants/treatment arm

AC: active control
ACR: American College of Rheumatology
BOCF: baseline observation carried forward
CNS: central nervous system
DB: double-blinding
DD: double dummy
ECG: electrocardiogram
HRS-D: Hamilton Rating Scale - Depression
ITT: intention-to-treat
LOCF: last observation carried forward
NSAIDs: non-steroidal anti-inflammatory drugs

PC: placebo controlled
PDN: painful diabetic neuropathy
PHN: postherpetic neuralgia
R: randomisation
W: withdrawals

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

Study	Reason for exclusion
Achar 2010	Not double-blind
Bansal 2009	Fewer than half of participants completed 4 weeks of treatment
Bowsher 1997	Pre-emptive study
Carasso 1979	Single-blind study
Fors 2002	No initial pain requirement for inclusion, no baseline pain reported
Hampf 1989	Fewer than 10 participants in amitriptyline treatment arm
Heymann 2001	No initial pain requirement for inclusion, no baseline pain reported
Isomeri 1993	Study not blinded
Jaeschke 1991	Fewer than 10 participants/treatment group (N of 1 trials)
Kalso 1996	Duration of study < 4 weeks
Kaur 2011	Study described as double-blind, but tablets supplied by two different pharmaceutical companies as free samples. All authors considered that they were extremely unlikely to be indistinguishable, so study not convincingly double-blind
Kautio 2009	Prophylactic treatment, no initial pain requirement
Kempenaers 1994	Fewer than 10 participants/treatment group
Kieburtz 1998	Inadequate levels of pain at baseline (using Gracely Scale and use of pain medication at baseline)
Lampl 2002	Prophylactic treatment
Max 1987	Some participants had inadequate levels of pain at baseline (using Gracely Scale)
McQuay 1992	Duration of study < 4 weeks
McQuay 1993	Duration of study < 4 weeks

(*Continued*)

Mendel 1986	Fewer than 10 participants per treatment arm
Mercadante 2002	Duration of study < 4 weeks
Morello 1999	Some participants had inadequate levels of pain at baseline (using Gracely Scale)
Pilowsky 1982	Unclear diagnosis of pain condition ("a wide range of intractable pain problems ..... without readily treatable somatic pathology")
Pilowsky 1990	Study not double-blind
Robinson 2004	Some participants had inadequate levels of pain at baseline (using categorical scale)
Scudds 1989	No initial pain requirement for inclusion, no baseline pain reported
Sharav 1987	Mixed pain conditions. "Most patients had evidence of musculoskeletal pain"
Turkington 1980	No initial pain requirement for inclusion, no baseline pain reported, no pain measurement reported
Ventafridda 1987	Duration of study < 4 weeks
Watson 1982	Duration of study < 4 weeks
Wilder-Smith 2005	Amitriptyline comparison was not blinded
Zitman 1990	Unclear diagnosis of pain condition ("somatoform pain disorder"). Included some participants with < moderate baseline pain intensity
Zitman 1991	Unclear diagnosis of pain condition ("chronic pain .....no selection on organic or psychogenic aetiology"). Included some participants with < moderate baseline pain intensity
Özerbil 2006	No pain evaluation, duration of each treatment period only 2 weeks
Ç apaci 2002	Study not convincingly double-blind, no patient evaluation of pain

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ataoğ lu 1997

Methods	Randomised, 6-week trial
Participants	Fibromyalgia
Interventions	Amitriptyline Paroxetine

Ataoğlu 1997 (*Continued*)

Outcomes	
Notes	Turkish (with English abstract) - awaiting translation

Jang 2010

Methods	RCT
Participants	Fibromyalgia syndrome
Interventions	Oral amitriptyline (Western medicine), once daily Acupuncture combined with cupping and Western medicine Acupuncture combined with cupping
Outcomes	
Notes	Chinese (with English abstract) - awaiting translation

Keskinbora 2006

Methods	RCT, double-blind
Participants	Peripheral neuropathic pain - burning, stabbing, shooting N = 46
Interventions	Amitriptyline Gabapentin
Outcomes	Improvement in pain intensity Patient satisfaction Adverse events
Notes	Turkish (with English abstract) - awaiting translation, but probably no evaluable data

DATA AND ANALYSES

Comparison 1. Amitriptyline versus placebo

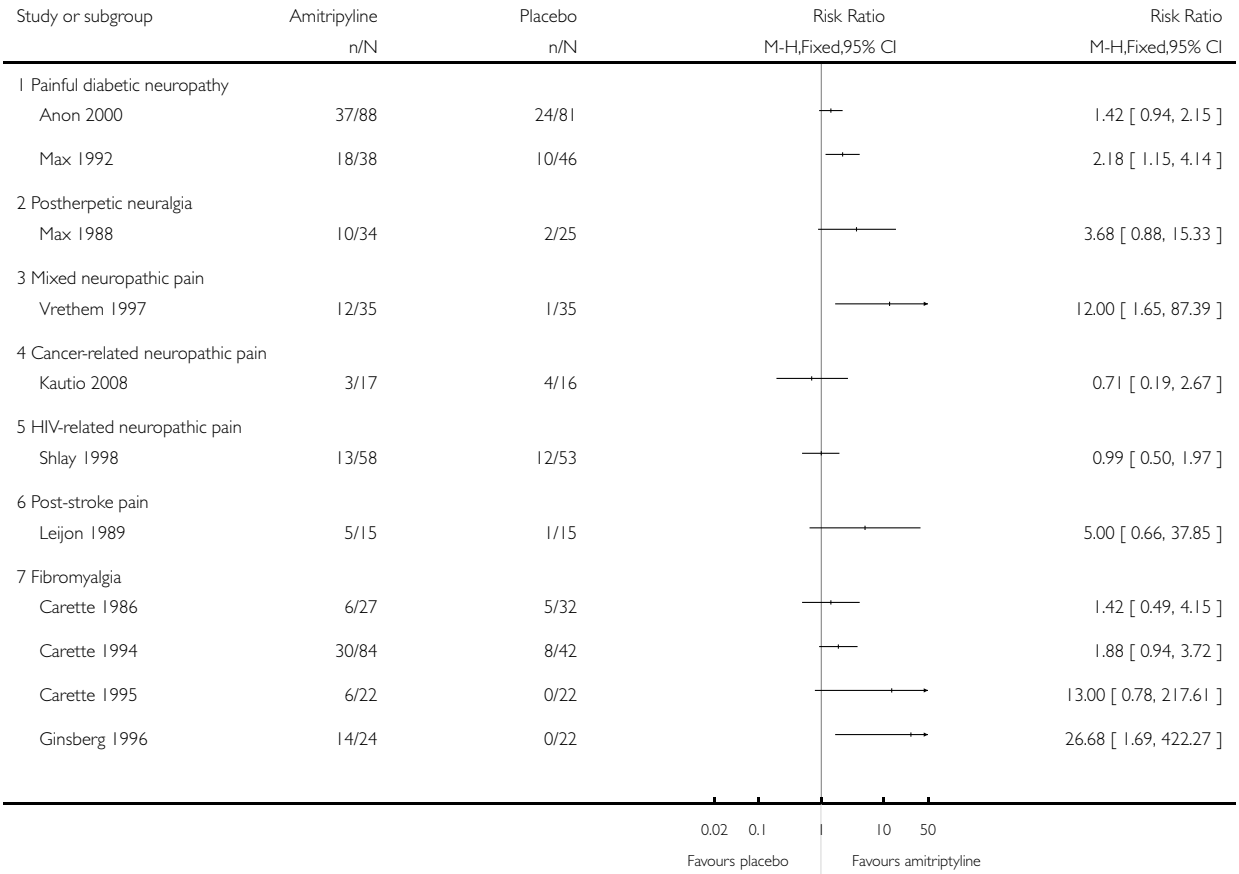
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-tier efficacy	11		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Painful diabetic neuropathy	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Postherpetic neuralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Mixed neuropathic pain	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Cancer-related neuropathic pain	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 HIV-related neuropathic pain	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Post-stroke pain	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Fibromyalgia	4		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 At least 1 adverse event	10	837	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.37, 1.74]
3 All-cause withdrawal	8	644	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.36]
4 Adverse event withdrawal	6	575	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.01, 2.92]
5 Lack of efficacy withdrawal	4	440	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.19, 0.76]

Analysis 1.1. Comparison 1 Amitriptyline versus placebo, Outcome 1 Second-tier efficacy.

Review: Amitriptyline for neuropathic pain and fibromyalgia in adults

Comparison: 1 Amitriptyline versus placebo

Outcome: 1 Second-tier efficacy



Analysis 1.2. Comparison 1 Amitriptyline versus placebo, Outcome 2 At least 1 adverse event.

Review: Amitriptyline for neuropathic pain and fibromyalgia in adults

Comparison: 1 Amitriptyline versus placebo

Outcome: 2 At least 1 adverse event

Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anon 2000	59/87	38/81		23.6 %	1.45 [1.10, 1.90]
Cardenas 2002	43/44	36/40		22.7 %	1.09 [0.97, 1.22]
Carette 1986	19/27	4/32		2.2 %	5.63 [2.18, 14.54]
Carette 1994	80/84	26/42		20.8 %	1.54 [1.21, 1.96]
Ginsberg 1996	7/24	0/22		0.3 %	13.80 [0.83, 228.33]
Hannonen 1998	31/42	36/45		20.9 %	0.92 [0.73, 1.16]
Kautio 2008	2/17	0/16		0.3 %	4.72 [0.24, 91.41]
Leijon 1989	14/15	7/15		4.2 %	2.00 [1.15, 3.49]
Shlay 1998	6/71	2/65		1.3 %	2.75 [0.57, 13.13]
Vrethem 1997	24/35	6/33		3.7 %	3.77 [1.77, 8.05]
Total (95% CI)	**446**	**391**		**100.0 %**	**1.54 [1.37, 1.74]**

Total events: 285 (Amitripyline), 155 (Placebo)

Heterogeneity: Chi^2 = 72.84, df = 9 (P<0.00001); I^2 =88%

Test for overall effect: Z = 7.12 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Amitriptyline versus placebo, Outcome 3 All-cause withdrawal.

Review: Amitriptyline for neuropathic pain and fibromyalgia in adults

Comparison: 1 Amitriptyline versus placebo

Outcome: 3 All-cause withdrawal

Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anon 2000	23/87	19/81		31.9 %	1.13 [0.67, 1.91]
Cardenas 2002	8/44	3/40		5.1 %	2.42 [0.69, 8.51]
Carette 1986	7/27	4/32		5.9 %	2.07 [0.68, 6.34]
Carette 1994	14/84	14/42		30.3 %	0.50 [0.26, 0.95]
Carette 1995	2/22	0/20		0.8 %	4.57 [0.23, 89.72]
Ginsberg 1996	1/24	0/22		0.8 %	2.76 [0.12, 64.41]
Goldenberg 1986	1/16	1/16		1.6 %	1.00 [0.07, 14.64]
Hannonen 1998	10/42	15/45		23.5 %	0.71 [0.36, 1.41]
Total (95% CI)	**346**	**298**		**100.0 %**	**1.00 [0.74, 1.36]**

Total events: 66 (Amitripyline), 56 (Placebo)

Heterogeneity: Chi^2 = 10.58, df = 7 (P = 0.16); I^2 =34%

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Amitriptyline versus placebo, Outcome 4 Adverse event withdrawal.

Review: Amitriptyline for neuropathic pain and fibromyalgia in adults

Comparison: 1 Amitriptyline versus placebo

Outcome: 4 Adverse event withdrawal

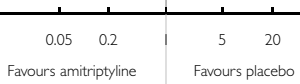
Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anon 2000	16/87	5/81		25.9 %	2.98 [1.14, 7.76]
Carette 1986	2/27	2/32		9.2 %	1.19 [0.18, 7.86]
Carette 1994	5/84	2/42		13.4 %	1.25 [0.25, 6.18]
Hannonen 1998	5/42	5/45		24.2 %	1.07 [0.33, 3.44]
Max 1988	5/34	3/25		17.3 %	1.23 [0.32, 4.66]
Rintala 2007	4/38	2/38		10.0 %	2.00 [0.39, 10.28]
Total (95% CI)	**312**	**263**		**100.0 %**	**1.72 [1.01, 2.92]**

Total events: 37 (Amitripyline), 19 (Placebo)

Heterogeneity: Chi^2 = 2.48, df = 5 (P = 0.78); I^2 =0.0%

Test for overall effect: Z = 2.01 (P = 0.044)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Amitriptyline versus placebo, Outcome 5 Lack of efficacy withdrawal.

Review: Amitriptyline for neuropathic pain and fibromyalgia in adults

Comparison: 1 Amitriptyline versus placebo

Outcome: 5 Lack of efficacy withdrawal

Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anon 2000	3/87	9/81		36.0 %	0.31 [0.09, 1.11]
Carette 1986	1/27	0/32		1.8 %	3.54 [0.15, 83.40]
Carette 1994	5/84	7/42		36.1 %	0.36 [0.12, 1.06]
Hannonen 1998	2/42	7/45		26.1 %	0.31 [0.07, 1.39]
Total (95% CI)	**240**	**200**		**100.0 %**	**0.38 [0.19, 0.76]**

Total events: 11 (Amitripyline), 23 (Placebo)

Heterogeneity: $Chi^2 = 2.11$, df = 3 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 2.75 (P = 0.0059)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. MEDLINE (via OVID) search strategy

1. exp PAIN/
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/
3. exp SOMATOSENSORY DISORDERS/
4. FIBROMYALGIA/ or exp MYOFASCIAL PAIN SYNDROMES/ or POLYMYALGIA RHEUMATICA/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. (fibromyalgi* or fibrosti* or FM or FMS).mp.
7. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Amitriptyline/
10. (am?tr?pt?lin* or amitriptyliini).mp.
11. 9 or 10
12. 8 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.

18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 23 and 12

Appendix 2. EMBASE (via OVID) search strategy

1. exp chronic pain/
2. exp peripheral neuropathy/
3. exp somatosensory disorder/
4. fibromyalgia/ or exp myofascial pain/ or rheumatic polymyalgia/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. (fibromyalgi* or fibrosti* or FM or FMS).mp.
7. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. amitriptyline/
10. (am?tr?pt?lin* or amitriptyliini or Tryptomer or Elavil or Tryptizol or Laroxyl or Sarotex or Lentizol or Endep).mp.
11. 9 or 10
12. 8 and 11
13. random*.ti,ab.
14. factorial*.ti,ab.
15. (crossover* or cross over* or cross-over*).ti,ab.
16. placebo*.ti,ab.
17. (doubl* adj blind*).ti,ab.
18. assign*.ti,ab.
19. allocat*.ti,ab.
20. RANDOMIZED CONTROLLED TRIAL.sh.
21. DOUBLE-BLIND PROCEDURE.sh.
22. CROSSOVER PROCEDURE.sh.
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 12 and 23

Appendix 3. CENTRAL search strategy

1. MeSH descriptor Pain explode all trees
2. MeSH descriptor Peripheral Nervous System Diseases explode all trees
3. MeSH descriptor Somatosensory Disorders explode all trees
4. MeSH descriptor Fibromyalgia, this term only
5. MeSH descriptor Myofascial Pain Syndromes explode all trees
6. MeSH descriptor Polymyalgia Rheumatica explode all trees
7. ((pain* or discomfort*) and (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):ti,ab,kw
8. (fibromyalgi* or fibrosti* or FM or FMS):ti,ab,kw
9. ((neur* or nerv*) and (compress* or damag*)):ti,ab,kw
10. (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9)
11. MeSH descriptor Amitriptyline
12. (am?tr?pt?lin* or amitriptyliini or Tryptomer or Elavil or Tryptizol or Laroxyl or Sarotex or Lentizol or Endep).ti,ab,kw
13. 11 or 12

14. 10 and 13
15. Limit 14 to CENTRAL

Appendix 4. Summary of outcomes in individual studies: efficacy

Study	Treatment (taken at night, unless stated)	Pain outcome	Other efficacy outcome	
Anon 2000	Amitriptyline 75 mg/d = 87 Pregabalin 600 mg/d = 86 Placebo = 81 Treatment taken in divided doses, 3 times daily Titration over first 2 weeks	Participants with ≥ 50% reduction of pain from baseline P = 24/81 A = 40/87 Pregabalin = 34/86		
Biesbroeck 1995	Amitriptyline 25 to 125 mg/d = 117 Capsaicin cream 0.075% = 118 Placebos contained mimicking agents Titration of A over first 4 weeks	Both treatments produced substantial pain relief - statistically significant from baseline, but no difference between groups Only physician global reported	Both treatments improved interference with daily activities due to pain, with no difference between groups	
Cardenas 2002	Amitriptyline 10 to 125 mg/d = 44 Placebo = 40 Placebo contained 0.5 mg/d benztropine to mimic dry mouth Titration Week 1 - 10 mg/d Week 2 - 25 mg/d Increased by 25 mg/d each week to max 125 mg/d determined by complete pain relief or max tolerated dose Median max dose = 50 mg/d	Mean data only No significant difference between groups for any measures except satisfaction with life (favours placebo)		
Carette 1986	Amitriptyline 50 mg = 27 Placebo = 32	Global impression of change - moderate or marked at 9 weeks	No difference in tender points, but improved sleep with A	

(*Continued*)

	Dose titration: Week 1 - 10 mg/d Weeks 2 to 4 - 25 mg/d Weeks 5 to 9 - 50 mg/d	P = 10/32 A = 17/27 Global impression of change - marked P = 5/32 A = 6/27		
Carette 1994	Amitriptyline 25 mg = 84 Cyclobenzaprine 30 mg = 82 Placebo = 42 Dose titration: A week 1 - 10 mg/d Weeks 2 to 12 - 25 mg/d Weeks 13 to 24 - 50 mg/d C week 1 - 10 mg/d Weeks 2 to 12 - 20 mg/d Weeks 13 to 24 - 30 mg/d	Significant improvers (50% improvement in pain, sleep, fatigue, global, myalgic score, 4 of 6): P = 8/42 A = 30/84 C = 27/82 No difference for change in mean pain score (from graph): A dropped 67 to 48 mm P dropped 69 to 54 mm	No significant end of trial difference for sleep, fatigue, global, tender points	
Carette 1995	Amitriptyline 25 mg = 22 Placebo = 20 Cross-over	Significant improvers (50% improvement in pain, sleep, fatigue, global, myalgic score, 4 of 6) A = 6/22 P = 0/22 VAS pain at 8 weeks (mean ± SD) P = 7.1 ± 2.1 A = 5.1 ± 3.2	Significant difference for sleep, patient global, fatigue, but not tender points	
Ginsberg 1996	Amitriptyline 25 mg = 24 Placebo = 22	Responder (at least 50% improvement pain and or global) at 8 weeks: A = 14/ 24 P = 0/22 VAS pain (mean ± SD) A baseline 3.8 ± 2.4 A end 7.0 ± 1.3 P baseline 7.0 ± 1.4 P end 5.0 ± 2.1	Major changes in patient global, tender point count and score, sleep, fatigue, and stiffness	
Goldenberg 1986	Balanced assignment quoted, but actual numbers in each group not given Therefore we assume:	VAS pain at 6 weeks (mean, from graph): A = 5.4 P = about 7.4	End of trial - significant benefit for A versus P for fatigue, sleep, and patient global assessment, but not tender points	

(*Continued*)

	Amitriptyline 25 mg = 16 Placebo = 16 (Also included naproxen 2 x 500 mg and amitriptyline + naproxen treatment arms)	Significant difference only at 4 weeks, not at 6 weeks. No dispersion given		
Goldenberg 1996	Amitriptyline 25 mg = 21 Fluoxetine 20 mg = 22 A + Fluox = 19 Placebo = 19 Cross-over	VAS pain at 6 weeks (mean ± SD) A = 64 ± 28 Fluox = 58 ± 26 A + Fluox = 43 ± 29 P = 82 ± 17	Apparent significant results, probably A versus P, for pain, FIQ, sleep, and global, but not fatigue or tender points Generally effect A + Fluox > Fluox ≥ A > P % change before/after calculated for each patient gave similar pattern to group means - numbers given for > 25% improvement in FIQ only: A = 5/21, Fluox = 7/22, A + Fluox = 12/19, P = 1/19	
Graff-Radford 2000	Amitriptyline 12.5 to 200 mg/d = 12 Fluphenazine 1 to 3 mg/d = 12 A + Fluph = 13 Placebo = 13 Placebo contained glycopyrrolate to mimic dry mouth and constipation Titration A by 25 mg each week to max tolerated dose or 200 mg/d Fluph by 1 mg each week to max 3 mg/d Cross-over	Significant decrease in mean pain (using VAS) for A and A + Fluph, but not Fluph alone or P A + Fluph not better than A alone		
Hannonen 1998	Amitriptyline 25 mg = 42 Moclobemide 450 mg (am and pm) = 43 Placebo = 45 Titration to max 37.5 mg A, 600 mg M	VAS (mean ± SD) A baseline 6.0 ± 2.1 A end 4.5 ± 2.8 M baseline 5.7 ± 2.1 M end 4.5 ± 2.7 P baseline 5.7 ± 2.3	General health, sleep fatigue tender points, and clinician severity all improved with A and P, but no obvious between group difference, except	

(*Continued*)

		P end 5.2 ± 2.7 Number of responders not given, but some response in 74% (A) versus 49% (P), 54% (M)	perhaps sleep	
Jose 2007	Amitriptyline 10 to 50 mg/d = 53 Lamotrigine 50 to 200 mg/d (divided dose) = 46 Titration after 2 weeks if response and tolerated A - 10, 25, 50 mg L - 50, 100, 200 mg Cross-over	PGIC 50% improvement (efficacy and safety, 100 mm VAS) A = 13/46 L = 19/46 PGIC improvement 25% to 50% A = 5/46 L = 6/46 Majority of patients remained above 30 mm at end (IQR A = 40 to 70, L = 30 to 70)	No significant difference between groups using median Likert pain and McGill pain Improvements seen from 2nd week onwards	
Kautio 2008	Amitriptyline 10 to 50 mg/d = 20 Placebo = 22 Titration by 10 mg/d every week to target dose if tolerated	In patients who remained in study ≥ 4 weeks Patient global assessment at 14 weeks (5-point scale) 'Complete relief' and 'major relief' A = 3/17 P = 4/16 ≥ 'some relief' A = 8/17 P = 5/16	Patient global using numeric scale showed NSD trend for A better than P NSD between groups for sensory neuropathy (which was generally mild) No significant changes in depression	
Leijon 1989	Amitriptyline 25 to 75 mg/d = 15 Carbamazepine 200 to 800 mg/d = 15 Placebo = 15 All medications given in divided doses, am and evening Forced titration to day 6 for A and day 18 for C. Reduction allowed for moderate AEs Cross-over	Patient global assessment of PR at end of period (5-point scale) Much improved and pain free (top 2) A = 5/15 Car = 2/15 P = 1/15 ≥ Improved (top 3) A = 10/15 Car = 5/15 P = 1/15	Mean PI reduced compared with placebo from 2nd week for A, only at 3rd for C Depression scores (means) not reduced compared with placebo	

(*Continued*)

Max 1988	Amitriptyline 12.5 to 150 mg/d = 34 Lorazepam 0.5 to 6 mg/d = 40 Placebo = 25 Titration over first 3 weeks to max tolerated dose (rate dependent on age and weight) Medications taken as divided dose, unless patients complained of daytime sedation	From graph Patient global evaluation - 6-point scale: 'complete' or 'a lot' A = 10/34 Lor = 2/40 P = 2/25 'complete", 'a lot' or 'moderate' A = 13/34 Lor = 4/40 P = 6/25	At baseline 43 patients not depressed, 15 depressed (mostly mild). NSD between depressed and non-depressed for pain relief	
Max 1992	Study 1 Amitriptyline 12.5 to 150 mg/d = 29 + 5 + 20 Desipramine 12.5 to 150 mg/d = 29 + 5 + 20 Study 2 Fluoxetine 20 to 40 mg/d = 28 + 9 Placebo = 28 + 9 Placebo contained 0.125 to 1.5 mg benztropine to mimic dry mouth Doses titrated up to max tolerated during weeks 1 to 4 Cross-over. Patients could enter other study after completion of first: 38 completed A versus D, and 46 completed F versus P	Global rating of pain relief (6-point scale) at end of treatment period for completers 'complete' or 'a lot: A = 18/38 D = 15/38 Fluox = 15/46 P = 10/46	NSD between A and D for mean weekly pain scores	
Rintala 2007	Amitriptyline 25 to 150 mg/d = 28 (as 3 doses daily) Gabapentin 300 to 1200 mg/d = 26 (as 3 doses daily) Placebo = 25 Placebo contained diphenhydramine 25 to 150 mg/d as 3 doses	≥ 30% PR Patients with low depression score A = 50% G = 42.9% P = 35.7% Patients with high depression score A = 62.5% G = 12.5% P = 25%	Change in average pain from baseline to week 8: NSD between treatments for patients with low depression scores (n = 2 5) A significantly greater than P, and NS greater than G for patients with high depression scores (n = 13)	

(*Continued*)

	daily, to mimic side effects of A and G Cross-over	Denominators unknown: unclear whether %ages are for patients completing all three phases (do not back calculate to whole numbers) or for all patients taking medication (do not know distribution of depression within groups)		
Rowbotham 2005	Amitriptyline 25 to 150 mg/d = 17 Desipramine 25 to 150 mg/d = 15 Fluoxetine 10 to 60 mg/d = 15 Titration Doses increased every 2 to 7 days over first 21 days, then kept stable if tolerated Mean dose A = 77 mg/d, D = 93 mg/d, F = 44 mg/d	PR at end of treatment (6 weeks) of 'moderate' or better (= ≥ 50% PR) A = 9/17 D = 12/15 Fluox = 5/15	NSD between treatments for %age change in daily diary VAS from baseline to start of taper NSD between groups for mean final pain category 2.1 to 3.2 (scale 0 to 5) Minimal changes seen in all groups for symptom checklist scores	
Shlay 1998	Amitriptyline 25 to 75 mg/d = 71 Placebo = 65 Titration A increased every 2 to 3 days to max (Also included acupuncture treatment arms)	Complete or a lot of relief 6 weeks A = 9/61 P = 13/60 14 weeks A = 13/58 P = 12/53	Mean changes in PI at weeks 6 and 14, NSD between groups - both improved NSD in QoL or neurologic summary scores	
Vrethem 1997	Amitriptyline 25 to 75 mg/d = 36 Maprotiline 25 to 75 mg/d = 36 Placebo = 36 Titration 25 mg on days 1 to 3 50 mg on days 4 to 6 75 mg from day 7 Cross-over	Patient global at end of each treatment period (5-point scale) 'Pain free' and 'much improved' (top 2) A = 12/35 Map = 4/35 P = 1/35 ≥ 'improved' (top 3) A = 22/35 Map = 14/35	Responder' = PR 20% from baseline A = 20/35 Map = 15/35 P = 7/35 No difference between responses of diabetics and non-diabetics	

(*Continued*)

		P = 8/35		
Watson 1992	Amitriptyline = 35 Maprotiline = 35 Titration over first 3 weeks to max tolerated dose 12.5 mg/d increased by 12.5 mg to 25 mg/d mg every 3 to 5 d Cross-over	PI at final or 5th week (none, mild, moderate, no changes) None or mild: A = 15/35 Map = 12/35 'Effectiveness' (excellent, good, improved but unsatisfactory, no change) Excellent or good: A = 14/35 Map = 6/35	NSD between groups for patient estimate of %age improvement in pain NSD between treatments for depression scores Equal sedative scores for groups	
Watson 1998	Amitriptyline = 33 Nortriptyline = 33 Titration over first 3 weeks to max tolerated dose 10 or 20 mg/d increased by 10 mg/d every 3 to 5 d Cross-over	Satisfaction with pain relief and tolerable of side effects A = 17/33 N = 15/33	NSD between groups for pain VAS NSD between groups for pt estimate of %age improvement in pain	

A: amitriptyline
AE: adverse effect
C: cyclobenzaprine
Car: carbamazepine
d: day
D: desipramine
Fluox: fluoxetine
Fluph: fluphenazine
G: gabapentin
L: lamotrigine
Lor: lorazepam
M: moclobemide
Map: maprotiline
NS: non-significant
NSD: non-significant difference
P: placebo
PGIC: Patient Global Impression of Change
QoL: quality of life
SD: standard deviation
VAS: visual analogue scale

Appendix 5. Summary of outcomes in individual studies: adverse events and withdrawals

Study	Treatment (taken at night, unless stated)	Adverse events	Withdrawals
Anon 2000	Amitriptyline 75 mg/d = 87 Pregabalin 600 mg/d = 86 Placebo = 81 Treatment taken in divided doses, 3 times daily Titration over first 2 weeks	Patients with ≥ 1 AE: P = 38/81 A = 59/87 Pregabalin = 57/86 Most mild or moderate, 26 severe Patients with SAE: P = 2/81 A = 5/87 Pregabalin = 5/86 (1 death, unrelated)	All-cause: P = 19/81, A = 23/87, Pregabalin = 24/86 AE: P = 5/81, A = 16/87, Pregabalin = 11/86 LoE: P = 9/81, A = 3/87, Pregabalin = 7/86
Biesbroeck 1995	Amitriptyline 25 to 125 mg/d = 117 Capsaicin cream 0.075% = 118 Placebos contained mimicking agents Titration of A over first 4 weeks	A - GI, anticholinergic, CNS/neuromuscular, CV, sedative, skin, other Cap - skin, transient cough/sneeze	Not reported
Cardenas 2002	Amitriptyline 10 to 125 mg/d = 44 Placebo = 40 Placebo contained 0.5 mg/d benztropine to mimic dry mouth Titration Week 1 - 10 mg/d Week 2 - 25 mg/d Increased by 25 mg/d each week to max 125 mg/d determined by complete pain relief or max tolerated dose Median max dose = 50 mg/d	Patients with ≥1 AE: A = 43/44 P = 36/40 Both drugs: mainly dry mouth, drowsiness, constipation Increased spasticity A > P (details for individual events available)	All-cause: A = 8/44, P = 3/40 AE: A = 8/44 (urinary retention ± autonomic dysreflexia (3), constipation (1), other systemic complaints (3)) P = 3/40 (constipation (1), urinary retention/constipation (1), unrelated hospital admission (1))
Carette 1986	Amitriptyline 50 mg = 27 Placebo = 32 Dose titration: Week 1 - 10 mg/d Weeks 2 to 4 - 25 mg/d Weeks 5 to 9 - 50 mg/d	Patients with ≥1 AE: A = 19/27 P = 4/32 "minor side effects" - mostly drowsiness and xerostomia	Total: A = 7/27, P = 4/32 LoE: A = 1/27 P = 0/32 AE: A = 2/27 P = 2/32 Other: A = 4/27 P = 2/32
Carette 1994	Amitriptyline 25 mg = 84 Cyclobenzaprine 30 mg = 82 Placebo = 42	Patients with ≥1 AE: A = 80/84 C = 80/82	Total: A = 14/84, C = 24/82, P = 14/42 LoE:

(*Continued*)

	Dose titration: A week 1 - 10 mg/d Weeks 2 to 12 - 25 mg/d Weeks 13 to 24 - 50 mg/d C week 1 - 10 mg/d Weeks 2 to 12 - 20 mg/d Weeks 13 to 24 - 30 mg/d	P = 26/42 Most common - dry mouth, somnolence, dizziness weight gain	A = 5/84, C = 6/82, P = 7/42 AE: A = 5/84, C = 11/82, P = 2/42 Other: A = 4/84, C = 7/82, P = 5/42
Carette 1995	Amitriptyline 25 mg = 22 Placebo = 20 Cross-over	Not reported	2 withdrawals after first period A (not drug-related)
Ginsberg 1996	Amitriptyline 25 mg = 24 Placebo = 22	A = 7/24 (3 dry mouth, 2 digestive symptoms, 1 vertigo, 2 neuro-psychic symptoms) P = 0/22	1 in A due to AE
Goldenberg 1986	Balanced assignment quoted, but actual numbers in each group not given. Therefore we assume: Amitriptyline 25 mg = 16 Placebo = 16 (Also included naproxen 2 x 500 mg, and amitriptyline + naproxen treatment arms)	8 patients (across groups) complained of side effects but did not discontinue medication (dry mouth, dyspepsia, diarrhoea)	A = 1 (lost to follow-up) N = 1 (lost to follow-up) A + N = 1 (AE - somnolence) P = 1 (AE - epigastric distress)
Goldenberg 1996	Amitriptyline 25 mg = 21 Fluoxetine 20 mg = 22 A + Fluox = 19 Placebo = 19 Cross-over	Not reported	12/31 did not complete A = 1 (other) Fluox = 4 (1 AE, 3 LoE) A + Fluox = 5 (3 AE, 2 other) P = 1 (AE) Washout after A + Fluox = 1 (LoE)
Graff-Radford 2000	Amitriptyline 12.5 to 200 mg/d = 12 Fluphenazine 1 to 3 mg/d = 12 A + Fluph = 13 Placebo = 13 Placebo contained glycopyrrolate to mimic dry mouth and constipation Titration A by 25 mg each week to max tolerated dose or 200 mg/d Fluph by 1 mg each week to max 3	1 patient in A due to AE (excessive sedation)	A worst for dry mouth Fluph worst for sleepiness

(*Continued*)

	mg/d Cross-over		
Hannonen 1998	Amitriptyline 25 mg = 42 Moclobemide 450 mg (am and pm) = 43 Placebo = 45 Titration to max 37.5 mg A, 600 mg M	Patients with ≥1 AE: A = 31/42 (dry mouth, fatigue) M = 33/43 (headache, difficulty falling asleep) P = 36/45 (fatigue, headache)	Withdrawals: A = 10/42 (2 LoE, 5 AE, 3 other) M = 13/43 (4 LoE, 6 AE, 3 other) P = 15/45 (7 LoE, 5 AE, 3 other)
Jose 2007	Amitriptyline 10 to 50 mg/d = 53 Lamotrigine 50 to 200 mg/d (divided dose) = 46 Titration after 2 weeks if response and tolerated A - 10, 25, 50 mg L - 50, 100, 200 mg Cross-over	Total number of events: A = 33 (mainly sedative, CNS), L = 11 (mainly skin, creatinine)	Lost to follow-up: A = 7/53, L = 0/46 AE: A = 19/53 (dizziness (4), postural hypertension (2), difficulty urination (1), constipation (1), dry mouth (1), increased sleep (10)) L = 8/46 (rash (3), itching (1), increased creatinine (4)) LoE (titration stopped because no benefit with 2 doses): A = 16/53, L = 22/46
Kautio 2008	Amitriptyline 10 to 50 mg/d = 20 Placebo = 22 Titration by 10 mg/d every week to target dose if tolerated	Requiring dose reduction - in patients who remained in trial ≥ 4 weeks: A = 2/17 (tiredness, tachycardia) P = 0/16	Exclusion/withdrawal within first 4 weeks: A = 3 (2 chemo stopped, 1 non compliance) P = 6 (3 AE, 2 chemo stopped, 1 non compliance)
Leijon 1989	Amitriptyline 25 to 75 mg/d = 15 Carbamazepine 200 to 800 mg/d = 15 Placebo = 15 All medications given in divided doses, am and evening Forced titration to day 6 for A and day 18 for Car Reduction allowed for moderate AEs Cross-over	Patients with ≥ 1 AE A = 14/15 Car = 14/15 P = 7/15 Mostly mild Most common A - tiredness, dry mouth Car - vertigo, dizziness, gait problems No dose reduction due to AE for A 4 dose reductions due to AE for Car	1 pt with carbamazepine had treatment stopped at day 25 due to interaction with warfarin
Max 1988	Amitriptyline 12.5 to 150 mg/d = 34 Lorazepam 0.5 to 6 mg/d = 40 Placebo = 25 Titration over first 3 weeks to max	Patients with ≥ 1 AE: A = 88% Lor = 98% P = 72% Most common:	AE: A = 5/34 (urinary retention, sedation, dizziness, palpitations, rash) Lor = 6/40 (acute depression (4), ataxia, nightmares) P = 3/25 (dizziness, disorientation,

(*Continued*)

	tolerated dose (rate dependent on age and weight) Medications taken as divided dose, unless patients complained of daytime sedation	A - dry mouth, sedation, dizziness, difficulty urinating Lor - sedation, dizziness, dry mouth, mood change P - dry mouth, sedation, dizziness	rash) LoE: 3 (group not given) Mediation error: 1 (group not given) Other unrelated: 4 (group not given)
Max 1992	Study 1 Amitriptyline 12.5 to 150 mg/d = 29 + 5 + 20 Desipramine 12.5 to 150 mg/d = 29 + 5 + 20 Study 2 Fluoxetine 20 to 40 mg/d = 28 + 9 Placebo = 28 + 9 Placebo contained 0.125 to 1.5 mg benztropine to mimic dry mouth Doses titrated up to max tolerated during weeks 1 to 4 Cross-over. Patients could enter other study after completion of first: 38 completed A versus D, and 46 completed Fluox versus P	In patients taking both drugs Patients with ≥ 1 AE: A = 31/38 D = 29/38 Majority were dose limiting Most common (≥ 5%): A = dry mouth, tiredness headache, palpitations, increased sweating, constipation, lightheadedness, orthostatic symptoms D = dry mouth, tiredness, constipation, insomnia, increased sweating, headache, lightheadedness	AE: A = 7/54 (confusion 2, ortho hypertension, fatigue, malaise, hypomania, rash) D = 7/54 (rash 3, ortho hypertension, bundle-branch block, tremor, fever) A total of 16 patients did not complete A-D study due to adverse events or 'voluntary withdrawal'
Rintala 2007	Amitriptyline 25 to 150 mg/d = 28 (as 3 doses daily) Gabapentin 300 to 1200 mg/d = 26 (as 3 doses daily) Placebo = 25 Placebo contained diphenhydramine 25 to 150 mg/d as 3 doses daily, to mimic side effects of A and G Cross-over	Most commonly reported: A - dry mouth, drowsiness, fatigue, constipation, increased spasticity, dizziness, nausea G - dry mouth, drowsiness, fatigue, constipation, dizziness P - dry mouth, drowsiness, fatigue, constipation, increased spasticity	AE: A = 4/38, G = 5/38, P = 2/38 Medical problem: A = 2/38, G = 1/38, P = 1/38 Other: A = 1/38, G = 0/38, P = 3/38
Rowbotham 2005	Amitriptyline 25 to 150 mg/d = 17 Desipramine 25 to 150 mg/d = 15 Fluoxetine 10 to 60 mg/d = 15 Titration Doses increased every 2 to 7 days over first 21 days, then kept stable if tolerated Mean dose A = 77 mg/d, D = 93 mg/d, F = 44 mg/d	No usable data	All-cause A = 2/17, D = 2/15, F = 5/15 (4 were on opioids) AE: A and D = 3/32 (sedation/cognitive impairment, orthostasis) F = 2/15 (recurrence of AF, hospitalisation for nausea/weakness with hyponatraemia)

(*Continued*)

Shlay 1998	Amitriptyline 25 to 75 mg/d = 71 Placebo = 65 Titration A increased every 2 to 3 days to max (Also included acupuncture treatment arms)	Grade 4 AE (serious) A = 6/71 P = 2/65	By 14 weeks 35% of patients in either group had discontinued treatment
Vrethem 1997	Amitriptyline 25 to 75 mg/d = 36 Maprotiline 25 to 75 mg/d = 36 Placebo = 36 Titration 25 mg on days 1 to 3 50 mg on days 4 to 6 75 mg from day 7 Cross-over	Patients with ≥ 1 AE: A = 24/35 Map = 23/34 P = 6/33 Most common dry mouth, sedation, vertigo Patients with SAE: A = 3/35 Map = 2/34 P = 0/33	2 patients did not provide any data for any treatment AE: A = 3/35 (hyperglycaemia, severe thirst, urinary retention) M = 2/35 (sedation, vertigo and urticaria)
Watson 1992	Amitriptyline = 35 Maprotiline = 35 Titration over first 3 weeks to max tolerated dose 12.5 mg/d increased by 12.5 mg to 25 mg/d mg every 3 to 5 d Cross-over	Patients with ≥ 1 AE A = 20/32 M = 28/32 (details in table V)	Excl (added back for efficacy): A = 2 (mouth ulcer, pain remission during washout between treatments) M = 1 (pain remission during washout between treatments) AE: A = 5/35 (dry mouth, constipation, sedation, dizziness, lethargy, mouth ulcers, nausea) M = 4/35 (dry mouth, nausea, vomiting, restless legs)
Watson 1998	Amitriptyline = 33 Nortriptyline = 33 Titration over first 3 weeks to max tolerated dose 10 or 20 mg/d increased by 10 mg/d every 3 to 5 d Cross-over	Patients with ≥ 1 AE A = 31/33 M = 31/33 (details in table 1)	Patients "left the study" A = 1/33 (slurred speech, urinary retention) N = 1/33 (increased pain, fever, epigastric pain, bad dreams, perspiration) Patients with "intolerable AE - treatment stopped" A = 10/33 N = 5/33

A: amitriptyline
AE: adverse effect
AF: atrial fibrillation
Cap: capsaicin
C: cyclobenzaprine

CV: coefficient of variation
Car: carbamazepine
NS: central nervous system
D: desipramine
FIQ: fibromyalgia impact questionnaire
Fluox: fluoxetine
Fluph: fluphenazine
G: gabapentin
GI: gastrointestinal
IQR: interquartile range
L: lamotrigine
LOE: lack of efficacy
Lor: lorazepam
Map: maprotiline
M: moclobemide
N: naproxen
P: placebo
PI: pain intensity
PR: pain relief
SAE: serious adverse effect

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 12, 2012

Date	Event	Description
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

SD, RAM, and PW have received research support from charities, government, and industry sources at various times. RAM, DA, and PW have consulted for various pharmaceutical companies. RAM, DA, PC, and PW have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions.

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Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update we have used recently revised guidelines for reviews in pain, which take into account our better understanding of potential biases both in studies and in the review process (AUREF 2012).