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Amitriptyline for fibromyalgia in adults (Review)

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

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Amitriptyline for fibromyalgia in adults.
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[Intervention Review]

Amitriptyline for fibromyalgia in adults

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 12, 2012. That review considered both fibromyalgia and neuropathic pain, but the efficacy of amitriptyline for neuropathic pain is now dealt with in a separate review.

Amitriptyline is a tricyclic antidepressant that is widely used to treat fibromyalgia, and is recommended in many guidelines. It is usually used at doses below those at which the drugs act as antidepressants.

Objectives

To assess the analgesic efficacy of amitriptyline for relief of fibromyalgia, and the adverse events associated with its use in clinical trials.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE to March 2015, together with reference lists of retrieved papers, previous systematic reviews and other reviews, and two clinical trial registries. We also used our own hand searched 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 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 three tiers of evidence. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks duration, parallel design), second tier from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison, and third tier from data involving small numbers of participants that were considered very likely to be biased or used outcomes of limited clinical utility, or both.

For efficacy, we calculated the number needed to treat to benefit (NNT), and for harm we calculated the number needed to treat to harm (NNH) for adverse events and withdrawals. We used a fixed-effect model for meta-analysis.

Main results

We included seven studies from the earlier review and two new studies (nine studies, 649 participants) of 6 to 24 weeks' duration, enrolling between 22 and 208 participants; none had 50 or more participants in each treatment arm. Two studies used a cross-over design. The daily dose of amitriptyline was 25 mg to 50 mg, and some studies had an initial titration period.

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There was no first or second tier evidence for amitriptyline in the treatment of fibromyalgia. Using third tier evidence the risk ratio (RR) for at least 50% pain relief, or equivalent, with amitriptyline compared with placebo was 3.0 (95% confidence interval (CI) 1.7 to 4.9), with an NNT) of 4.1 (2.9 to 6.7) (very low quality evidence). There were no consistent differences between amitriptyline and placebo or other active comparators for relief of symptoms such as fatigue, poor sleep, quality of life, or tender points.

More participants experienced at least one adverse event with amitriptyline (78%) than with placebo (47%). The RR was 1.5 (1.3 to 1.8) and the NNH was 3.3 (2.5 to 4.9). Adverse event and all-cause withdrawals were not different, but lack of efficacy withdrawals were more common with placebo (12% versus 5%; RR 0.42 (0.19 to 0.95)) (very low quality evidence).

Authors' conclusions

Amitriptyline has been a first-line treatment for fibromyalgia for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against years of successful treatment in many patients with fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline will be one option in the treatment of fibromyalgia, while recognising that only a minority of patients will achieve satisfactory pain relief.

It is unlikely that any large randomised trials of amitriptyline will be conducted in fibromyalgia to establish efficacy statistically, or measure the size of the effect.

PLAIN LANGUAGE SUMMARY

Amitriptyline for fibromyalgia in adults

Our understanding of fibromyalgia (a condition of persistent, widespread pain and tenderness, sleep problems, and fatigue) is poor. Common pain relieving medicines such as paracetamol and ibuprofen are not usually considered effective in fibromyalgia. Medicines that are sometimes used to treat epilepsy or depression can be very effective in some people with fibromyalgia, as they are in some other forms of chronic pain where there may be nerve damage (neuropathic pain).

Amitriptyline is an antidepressant, and antidepressants are recommended for treating fibromyalgia. Although amitriptyline is commonly used to treat fibromyalgia, a review in 2012 found no good quality evidence to support its use. Most studies were small, old, and used methods or reported results that we now recognise as making benefits seem better than they are.

This review is an update of the 2012 review, which considered both fibromyalgia and neuropathic pain conditions. Neuropathic pain is now considered in a separate review. Here we examine how well amitriptyline worked in treating fibromyalgia, using a definition of what worked that involved both a high level of pain relief and the ability to take the tablets over a longer time without side effects being intolerable.

In March 2015 we performed searches to look for new studies, and found only two additional small studies to include. Neither provided any good quality evidence for benefit or harm. There were still no studies that could provide an answer that was trustworthy or reliable, because most 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 provide good levels of pain relief for some people with fibromyalgia, although we cannot be certain of this. Our best guess is that amitriptyline provides good pain relief in about 1 in 4 (25%) more people than does placebo. About 1 in 3 (31%) more people than with placebo report having one or more adverse events, which are usually not serious but may be troublesome and interfere with taking the treatment. 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 fibromyalgia, but only a minority of them; amitriptyline will not work for most people.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Amitriptyline compared with placebo for fibromyalgia

Patient or population: adults with fibromyalgia

Settings: community

Intervention: amitriptyline 25 to 50 mg daily

Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with placebo	NNT or NNH and/or relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain or equivalent (substantial)	360 in 1000	110 in 1000	RR 2.9 (1.7 to 4.9) NNT 4.1 (2.9 to 6.7)	4 studies, 275 participants	Very low	Small number of studies and participants
At least 30% reduction in pain or equivalent (moderate)	no data					
Adverse event withdrawals	80 in 1000	90 in 1000	RR 1.03 (0.49 to 2.2) NNTp not calculated	4 studies, 298 participants	Very low	Small number of studies and participants
Serious adverse events	none reported					
Death	none reported					

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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BACKGROUND

This is an update of an earlier review of amitriptyline for neuropathic pain and fibromyalgia originally published in the Cochrane Library in 2012 (Moore 2012a). The efficacy of amitriptyline for neuropathic pain conditions is now dealt with in a separate review (Moore 2015).

In the update we have used a template for reviews of drugs used to relieve fibromyalgia. The aim is for all reviews to use the same methods, based on current criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

Fibromyalgia has been defined as widespread pain that lasts for longer than three months, with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990). It is frequently associated with other symptoms such as poor sleep, fatigue, and depression (Wolfe 2014). More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain, and which does not require palpation of tender points for diagnosis (Wolfe 2010). While some rheumatologists have thought of fibromyalgia as a specific pain disorder, other investigators have characterised it as a bodily distress syndrome or a physical symptom disorder, or somatoform disorder (Wolfe 2014). It is a heterogeneous condition in which there is abnormal processing of the sensation of pain. The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the central nervous system (CNS). Moreover, people with neuropathic pain and people with fibromyalgia experience similar sensory phenomena (Koroschetz 2011).

Many people with fibromyalgia are significantly disabled, and experience moderate or severe pain for many years. Chronic painful conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased health costs (Moore 2014a).

Fibromyalgia is common. Numerous studies have investigated prevalence in different settings and countries. The Queiroz 2013 review gives a global mean prevalence of 2.7% (range 0.4% to 9.3%), and a mean in the Americas of 3.1%, in Europe of 2.5%, and in Asia of 1.7%. Fibromyalgia is more common in women, with a female to male ratio of 3:1 (4.2%:1.4%). The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in those with repetitive strain injury; Queiroz 2013).

Fibromyalgia pain is known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions, or both. Conventional analgesics are usually not effective. Treatment is often by so-called unconventional analgesics, such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2014b; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least a 50% reduction in pain intensity; Moore 2013a) is small, generally only 5% to 15% more than with placebo, with numbers needed to treat to benefit (NNT) usually between 6 and 20 (Moore 2013b; Wiffen 2013). This is confirmed by individual patient level analyses for duloxetine and pregabalin (Moore 2014c; Straube 2010); and is somewhat less effective than with the same drugs in neuropathic pain (Kalso 2013).

Those who do experience good levels of pain relief, however, also benefit from substantial reductions in other symptoms such as fatigue, function, sleep, depression, anxiety, and ability to work, with significant improvement in quality of life (Moore 2010b; Moore 2014a; Straube 2011). Fibromyalgia is not particularly different from other chronic pain in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

Description of the intervention

Amitriptyline is a tricyclic antidepressant. It is not licensed in the UK for treating fibromyalgia, but is commonly used for this indication, and it is commonly used for treating fibromyalgia around the world, irrespective of licensed indications. It is available as tablets (10, 25, 50 mg) and oral solutions, and is usually taken at night time to reduce any sedative effects during the day. There were over 11 million prescriptions for amitriptyline in England in 2013, mainly for 10 mg and 25 mg tablets (PCA 2014); some of these prescriptions would be for relief of depression or neuropathic pain. 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 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 little 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 fibromyalgia. The earlier review found some evidence of pain relief with amitriptyline compared with placebo for fibromyalgia, at the expense of increased adverse events, but this was based on small numbers of participants in studies that were susceptible to bias.

It was decided to split reviews combining neuropathic pain conditions with fibromyalgia into separate reviews, so an update was performed at the same time, to capture any new studies.

Like the earlier Cochrane review, this update assessed evidence in ways that make both statistical and clinical sense, and used developing criteria for what constitutes reliable evidence in chronic pain (Appendix 1; Moore 2010a). It followed standards set out in the *PaPaS Author and Referee Guidance* for pain studies of the Cochrane Pain, Palliative and Supportive Care Group (PaPaS 2012).

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OBJECTIVES

To assess the analgesic efficacy of amitriptyline for relief of fibromyalgia, and the adverse events associated with its use in clinical trials.

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. We required full journal publication, 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. We accepted cross-over studies only if there was clear reporting of the first phase only. We did not include studies with fewer than 10 participants in any treatment arm, or studies of topical administration.

Types of participants

We included adult participants with fibromyalgia diagnosed using the 1990 or 2010 criteria (Wolfe 1990; Wolfe 2010), aged 18 years and above, and with initial pain of at least moderate intensity

Types of interventions

Amitriptyline in any dose, by any route other than topical, administered for the relief of fibromyalgia pain, and compared to placebo or any active comparator.

Types of outcome measures

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

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

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

These outcomes were used in the earlier version of this review, but are different from many other earlier reviews, concentrating on dichotomous outcomes where pain responses are not normally distributed.

We have included a 'Summary of findings' table as set out in the author guide (PaPaS 2012), including outcomes of at least 30% and at least 50% pain intensity reduction, withdrawals due to adverse events, serious adverse events, and death, although there were no data for some of these outcomes. We used the GRADE approach to assess the quality of evidence related to each of the key outcomes listed in Types of outcome measures (Schünemann 2011), as appropriate.

Primary outcomes

1. Participant-reported pain relief of 30% or greater.
2. Participant-reported pain relief of 50% or greater.
3. PGIC much or very much improved.
4. PGIC very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy, adverse events, and for any cause
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.
5. Specific adverse events, particularly somnolence, dizziness, and dry mouth.
6. Any disability-related or mental health-related outcome.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (via *The Cochrane Library* 2012, Issue 9 for the earlier review and via CRSO from 2012 to 26 March 2015 for this update);
- MEDLINE (via Ovid) (from inception to September 2012 for the original review, and from 2012 to 26 March 2015 for this update);
- EMBASE (via Ovid) (from inception to September 2012 for the original review, and from 2012 to 26 March 2015 for this update);
- Oxford Pain Relief database (Jadad 1996a) for the earlier review. This database is no longer being updated.

See Appendix 2 for the MEDLINE search strategy, Appendix 3 for the EMBASE search strategy, and Appendix 4 for the CENTRAL search strategy.

There was no language restriction.

Searching other resources

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

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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 2014) 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 Oxford Quality Score (Jadad 1996b) as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors independently assessed the risk of bias for each study, using the criteria outlined in the 'Risk of bias' tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process such as random number table or computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
5. Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Kjaergard 2001; Nuesch 2010). Studies were considered to be at low risk of bias if they had 200 participants or more, at unclear risk if they had 50 to 200 participants, and at high risk if they had fewer than 50 participants.

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 unit of analysis was the individual participant. For cross-over studies we planned to use the first period data only, or any useable results if first period data were not available. 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 wherever possible.

Assessment of heterogeneity

We assessed statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic (Higgins 2003). 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 and of value to patients (Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). 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).

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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 three tiers, according to outcome and freedom from known sources of bias.

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

Subgroup analysis and investigation of heterogeneity

We 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. 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, and Characteristics of studies awaiting classification.

Results of the search

New searches from January 2012 to 26 March 2015 identified 37 potentially relevant studies in CENTRAL, 107 in MEDLINE, and 259 in EMBASE. Of these, two were obtained and read in full to determine inclusion status.

Three studies still await classification because of translation requirements. Ataoğlu 1997 is a Turkish study comparing amitriptyline with paroxetine in 68 participants for six weeks. Jang 2010 is a Chinese study comparing amitriptyline with acupuncture plus cupping and with the combined treatments over four weeks, involving 186 participants in three treatment arms. The details of NCT00381199 are not clear, but it involved a comparison of amitriptyline 10 mg to 25 mg daily with nabilone 0.5 mg to 1 mg daily over a period of about three weeks in 32 participants.

Included studies

In this update we included two new studies (101 participants; Braz 2013; de Zanette 2014) and seven studies (548 participants; Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Goldenberg 1986; Goldenberg 1996; Hannonen 1998) from the previous review that fulfilled the inclusion criteria; altogether there were nine included studies with 649 participants (Figure 1).

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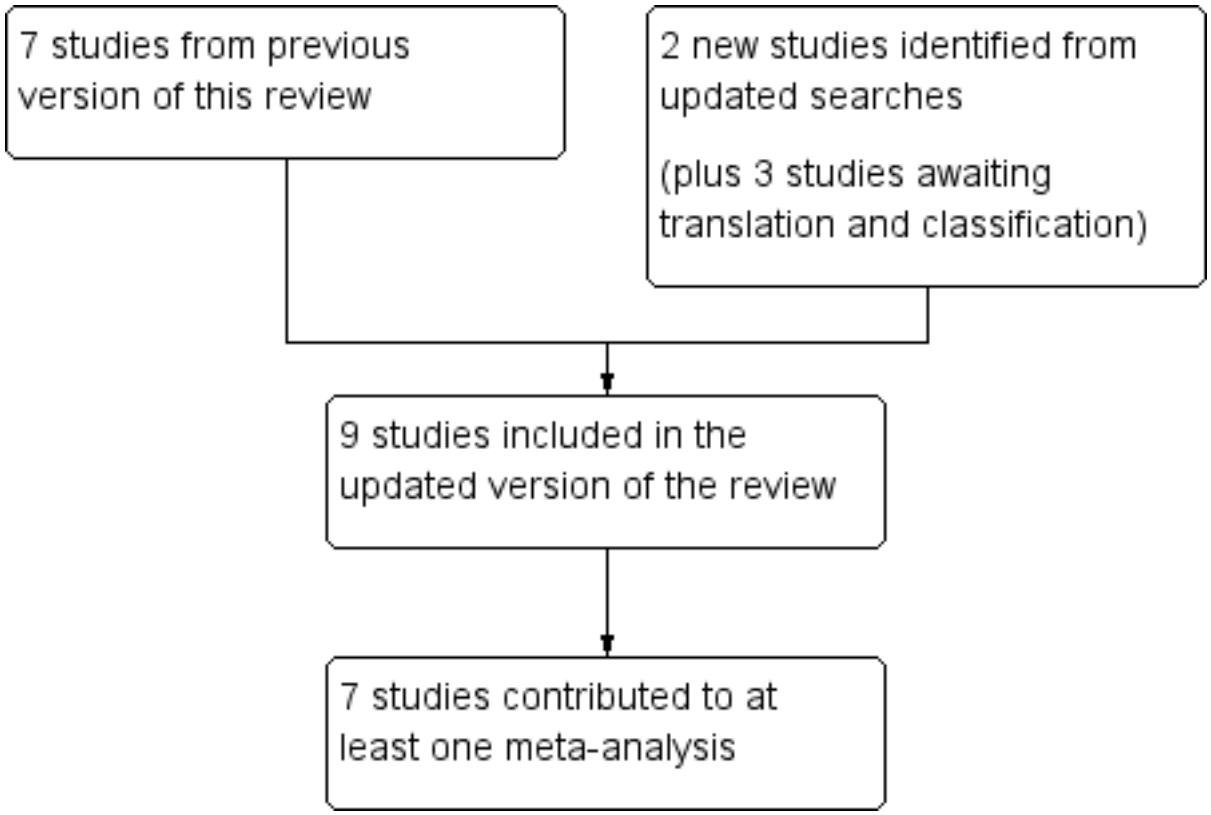
Figure 1. Flow diagram.



Two studies used a cross-over design (Carette 1995; Goldenberg 1996) and the remainder used a parallel group design. All the studies except de Zanette 2014 included a placebo control, six included an active comparator (Braz 2013; Carette 1994; de Zanette 2014; Goldenberg 1986; Goldenberg 1996; Hannonen 1998), and three additionally included a treatment arm using a combination of amitriptyline and the active comparator being tested (de Zanette 2014; Goldenberg 1986; Goldenberg 1996). Two hundred and seventy participants took amitriptyline, 209 took placebo, 195 took various active comparators, and 55 took combinations. The active comparators were:

- Panax ginseng extract (100 mg daily, 27% of ginsenosides);
- cyclobenzaprine 30 mg daily;
- melatonin 10 mg daily;
- naproxen 2 x 500 mg daily;
- fluoxetine 20 mg daily;
- moclobemide 450 mg daily.

The included studies individually involved between 22 and 208 participants, and only two involved over 100 participants (Carette 1994; Hannonen 1998). The vast majority of participants were female (626 women and 33 men) with three studies enrolling only women (Braz 2013; de Zanette 2014; Hannonen 1998). Study duration ranged from 6 to 24 weeks.

Excluded studies

We excluded 15 studies (Çapaci 2002; Fors 2002; Hampf 1989; Heymann 2001; Isomeri 1993; Jaeschke 1991; Kempenaers 1994; McQuay 1992; McQuay 1993; Özerbil 2006; Pilowsky 1982; Pilowsky 1990; Scudds 1989; 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, having fewer than 10 participants in a treatment arm, or not having a clear diagnosis of the painful condition. Details are in the Characteristics of excluded studies table.

Risk of bias in included studies

Risk of bias is shown in Figure 2 as a summary and in Figure 3 for each included study.

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

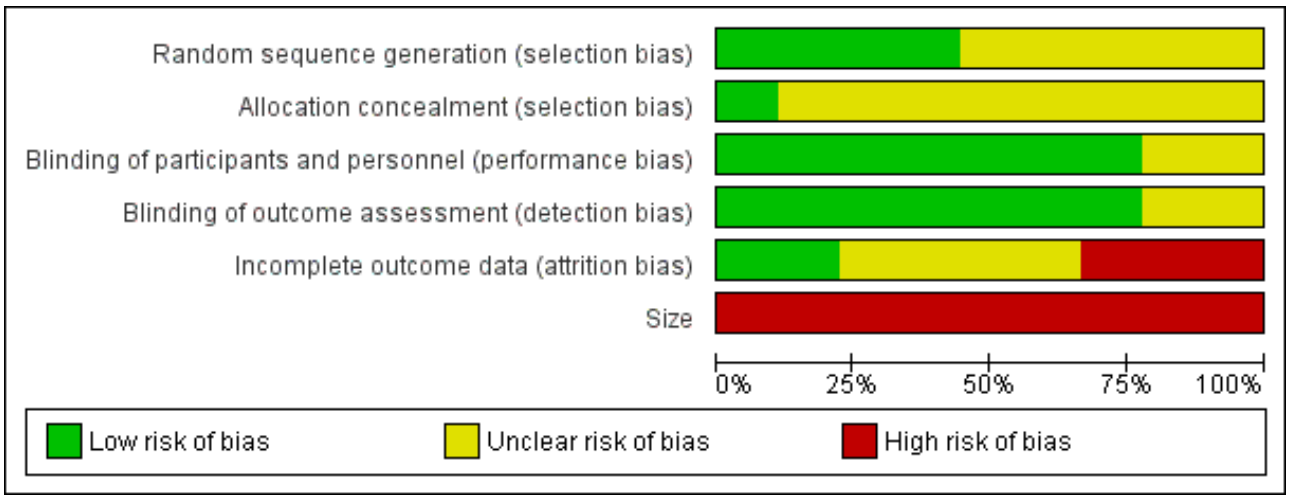

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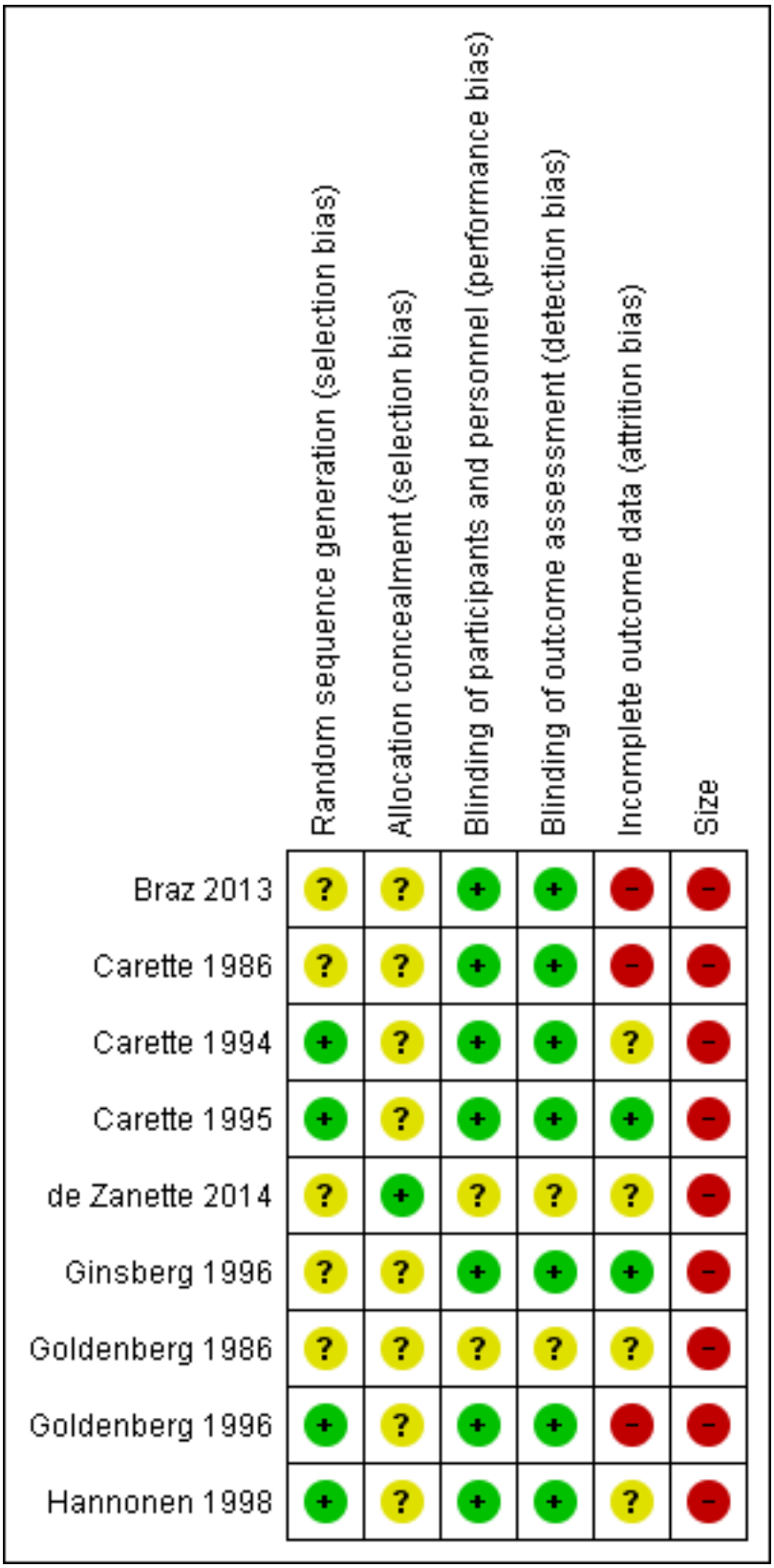
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Quality scores were good using the Oxford Quality Score; one study scored 3/5 points, three scored 4/5, and five scored 5/5.

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Allocation

All studies were randomised, but only four adequately described the method used to generate the random sequence, and only one adequately described the method used to conceal the allocation of the random sequence.

Blinding

Seven studies adequately described the methods used to maintain blinding.

Incomplete outcome data

Two studies had a cross-over design, and data on all randomised participants were not available for all outcomes (Carette 1986; Goldenberg 1996), while another study reported results only for participants who completed the study (Braz 2013). Only two studies convincingly reported on all participants (Carette 1995; Ginsberg 1996).

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

None of the studies included over 50 participants per treatment arm, and all were judged at high risk of bias for this domain.

Effects of interventions

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

Results from individual studies are in Appendix 5 (efficacy) and Appendix 6 (adverse events and withdrawals).

Efficacy

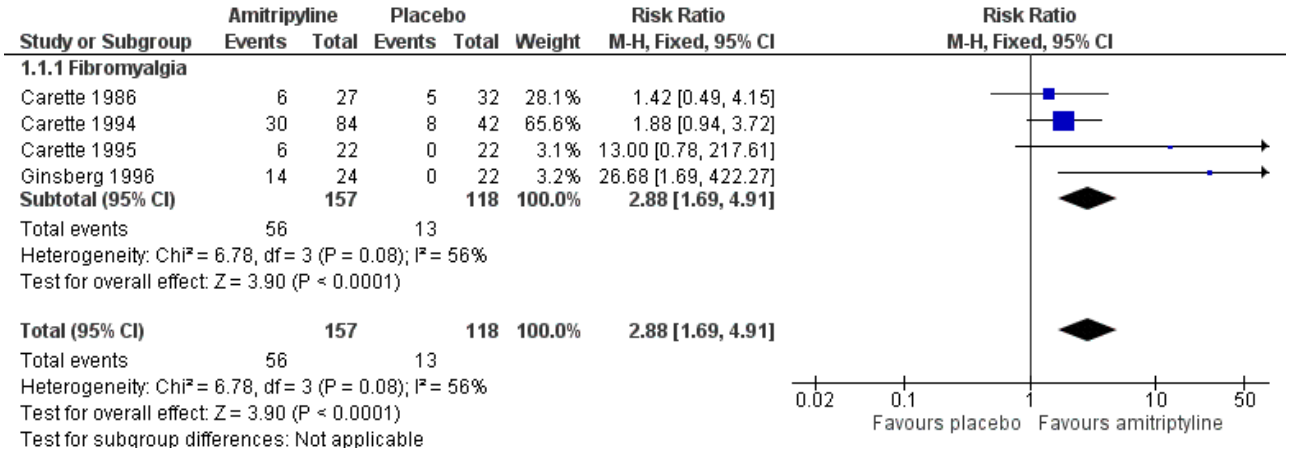
No study met the criteria for first- or second-tier evidence.

Participants with substantial pain relief

There was some third-tier evidence that amitriptyline at 25 mg or 50 mg daily was better than placebo from four studies (Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996).

- The proportion of participants with substantial pain relief with amitriptyline was 36% (56/157, range 22% to 58%)
- The proportion of participants with substantial pain relief with placebo was 11% (13/118, range 0% to 19%)
- The RR for amitriptyline compared with placebo was 2.9 (1.7 to 4.9) (Figure 4), and the NNT was 4.1 (2.9 to 6.7).

Figure 4. Forest plot of comparison: 1 Amitriptyline versus placebo, outcome: 1.1 Third-tier efficacy.



These statistics should be interpreted with caution, in particular because of the small number of participants and events. The L'Abbe plot and I^2 statistic estimate show no greater variation than would be expected in this number of small studies (Figure 5). Three of the four placebo-controlled studies that did not report dichotomous outcomes also provided some support of greater analgesic effects from amitriptyline than placebo (Goldenberg 1986; Goldenberg 1996; Hannonen 1998).

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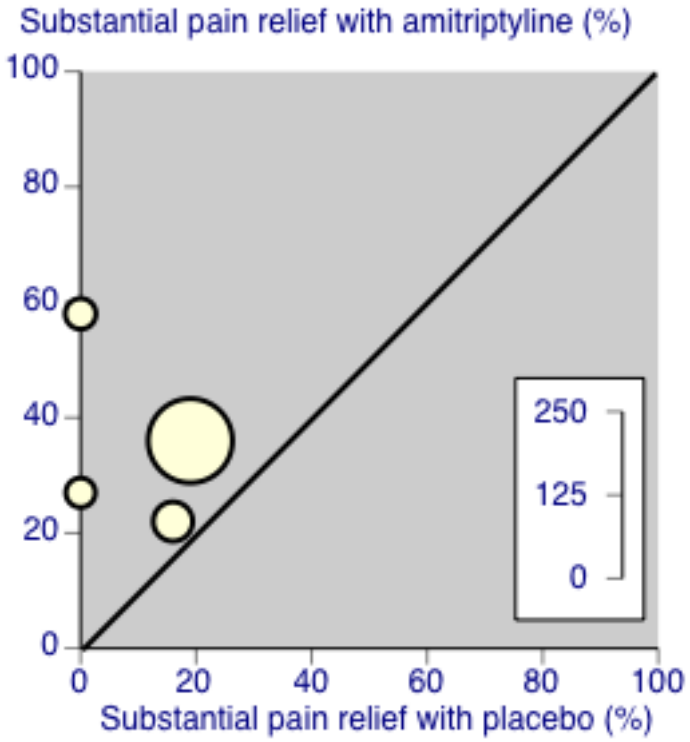
Figure 5. Third-tier evidence: substantial pain relief



Amitriptyline was probably no better than cyclobenzaprine (Carette 1994), fluoxetine (Goldenberg 1996), moclobemide (Hannonen 1998) or Panax ginseng (Braz 2013) in individual small studies of limited ability to discriminate. One study claimed a benefit of melatonin over amitriptyline (de Zanette 2014).

Any disability-related or mental health-related outcome

All the included studies provided some information about the effects of amitriptyline on symptoms such as fatigue, sleep, tender points and quality of life (Appendix 5). These were reported as group means, but it was not always clear whether all participants were included in the analysis or what imputation method was used for missing data. Most studies reported no significant difference between treatment groups at the end of treatment for most measures, although occasionally a single measure was significantly different. There was no discernable pattern to this, and we would expect occasional significant results by chance in such a data set.

Adverse events

Participants experiencing at least one adverse event

This outcome was reported by four studies with placebo treatment arms, with 318 participants in the comparison (Carette 1986; Carette 1994; Ginsberg 1996; Hannonen 1998). At least one adverse event was experienced by 137/177 (77%) of participants taking amitriptyline, and 66/141 (47%) taking placebo. The risk ratio was 1.5 (1.3 to 1.8) (Analysis 1.2), and the number needed to treat to harm was 3.3 (2.5 to 4.9).

Serious adverse events

No studies reported any serious adverse events.

Individual adverse events

There were insufficient data for analysis of individual events. The most common events reported were dry mouth and drowsiness, somnolence or fatigue. Other events included dizziness, headache, nightmares, behavioural change, neuropsychiatric symptoms, weight gain, dyspepsia, and diarrhoea.

Withdrawals

All-cause withdrawals were reported by seven placebo-controlled studies (418 participants, Braz 2013; Carette 1986; Carette 1994; Carette 1995; Ginsberg 1996; Goldenberg 1986; Hannonen 1998). Overall, 38/228 (17%) withdrew for any cause with amitriptyline and 41/190 (22%) with placebo. The risk ratio was 0.77 (0.53 to 1.1) (Analysis 1.3); the number needed to treat to harm (NNH) was not calculated.

Adverse event withdrawals were reported by four studies (298 participants, Braz 2013; Carette 1986; Carette 1994; Hannonen 1998). Overall, 14/166 (8%) withdrew because of adverse events with amitriptyline and 12/132 (9%) with placebo. The risk ratio was 1.03 (0.49 to 2.2) (Analysis 1.4); the NNH was not calculated.

Lack of efficacy withdrawals were reported by three studies (272 participants, Carette 1986; Carette 1994; Hannonen 1998). Overall, 8/153 (5%) withdrew because of lack of efficacy with amitriptyline and 14/119 (12%) with placebo. The risk ratio was 0.42 (0.19 to 0.95) (Analysis 1.5); the number needed to treat to prevent (NNTp) was 14 (7.2 to 980).

DISCUSSION

Because amitriptyline is a crucially important drug in treating various forms of chronic pain, including fibromyalgia, and because

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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. 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.

The most important finding of this review was that there were no studies that met current standards of evidence for chronic pain that minimise all known biases (Moore 2010a; Moore 2012b). All the studies accepted for third-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 (although two thirds of the studies had treatment periods of eight weeks or more), and studies being small, in circumstances where small studies in chronic pain are known to be associated with over-estimation of treatment effect (Dechartres 2013; Kjaergard 2001; Nüesch 2010), beyond the large random variation that occurs with small pain studies (Moore 1998). That means that the third-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 fibromyalgia, the evidence we have cannot rule out the possibility that amitriptyline is no better than placebo for this condition. This rather bleak conclusion should be tempered by many years of clinical experience indicating that amitriptyline can give really good pain relief to some patients with 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 provide good pain relief in fibromyalgia. Our best estimate is that for every four people treated, one will experience a good level of pain relief (equivalent to at least 50% pain reduction) who would not have done with placebo (very low quality evidence; Summary of findings for the main comparison). Given the caveats above, this is probably an overestimation of treatment effect, but the consistency of effect within these four studies does provide some confidence that amitriptyline benefits are real, at least for some patients.

The effect of amitriptyline on other fibromyalgia symptoms, such as fatigue, quality of sleep, and tender points is less clear. Mean data indicate that all treatment groups show an overall improvement during the study, but there were no consistent findings of significant differences between amitriptyline and placebo or other comparators. This differs from results of individual patient level analyses linking improvements in pain with changes in other outcomes; these demonstrate that pain reduction is closely linked with improvements in sleep, depression, quality of life, and ability to work (Moore 2010c; Straube 2011). The small number of studies and participants and the use of mean data for these outcomes may have limited the ability to demonstrate a significant difference.

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, two had a cross-over design, all were small, and fewer than half reported efficacy outcomes based on individual participants obtaining a high degree of pain relief.

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

There are also significant limits in what the review can say about appropriate doses of amitriptyline. Studies used daily doses of 25 mg to 50 mg, with titration in some.

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. It is disappointing that the more recent studies were not of higher reporting quality.

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 included a comprehensive manual journal search (Jadad 1996a). It is unlikely that relevant high-quality large studies of amitriptyline in fibromyalgia have been overlooked, especially because amitriptyline is the mainstay of treatment.

Agreements and disagreements with other studies or reviews

Our earlier review looked at both neuropathic pain and fibromyalgia, although different conditions were analysed separately for efficacy. The new studies did not contribute to efficacy data and did not change the conclusions for the analyses of withdrawals to which they did contribute.

A review of amitriptyline, duloxetine, and milnacipran in fibromyalgia included seven of the nine studies in this review, and three studies that we excluded because they had no baseline pain requirement or baseline pain data (Heymann 2001; Scudds 1989), or had fewer than 10 participants in each treatment arm (Kempenaers 1994). The authors acknowledged the poor quality of the studies, reporting an NNT of 3.5 (2.7 to 5.0) for at least 30% pain relief compared with placebo, and small or moderate effects on fatigue, quality of life, and sleep, using mean data. These results are consistent with those found in this review. Corresponding NNTs for duloxetine and milnacipran were 8 and 11, with similar small to moderate effects on other symptoms. The higher (worse) NNTs may in part be due to inclusion of larger studies of better quality for these two drugs. There were no significant differences in overall withdrawal rates between each drug and placebo, or between the three drugs, but adverse event withdrawals were not specifically reported (Hausser 2011).

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An earlier review of amitriptyline for fibromyalgia again included seven of the nine studies in this review, and three studies that we excluded because they had no baseline pain requirement or baseline pain data (Fors 2002; Heymann 2001; Scudds 1989). The authors chose not to pool data, but reported a therapeutic response for amitriptyline 25 mg, but not 50 mg, compared with placebo for pain, sleep, fatigue, and global impression. Neither dose had an effect on tender points. No clear statement was made about adverse events because of inconsistent reporting, although there was no difference between amitriptyline and placebo for adverse event withdrawals (Nishishinya 2008).

Amitriptyline had similar effects on the intensity of care in a large cohort of US patients treated with a variety of antidepressant and antiepileptic drugs (Kim 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Amitriptyline has been a first-line treatment for fibromyalgia for many years. The fact that there is no supportive unbiased evidence for substantial pain relief has to be balanced against decades of successful treatment in many tens of thousands of patients with fibromyalgia. There is no reliable evidence of a lack of effect: rather our concern should be of overestimation of treatment effect.

For clinicians

Amitriptyline will continue to be used as part of the treatment of fibromyalgia, but we should be cognisant of the fact that only a small number of patients will achieve satisfactory pain relief.

For policy makers

Amitriptyline will continue to be used as part of the treatment of fibromyalgia, but a range of drugs will be needed to provide good pain relief for a population of people with fibromyalgia.

For Funders

Amitriptyline will continue to be used as part of the treatment of fibromyalgia, but a range of drugs will be needed to provide good pain relief for a population of people with fibromyalgia.

Implications for research

General

There is no convincing evidence about effectiveness of the most commonly used first line therapy for fibromyalgia.

It is unlikely that any large randomised trials of amitriptyline will be conducted in fibromyalgia to establish efficacy. Such trials are expensive. The bigger implication is for research in clinical practice, to determine 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.

Design

This review highlights the design weaknesses of older trials in fibromyalgia. It is notable that probably the only treatment in fibromyalgia that reaches first tier level of evidence is duloxetine, and then because of a post-hoc individual-patient-level analysis to change LOCF to BOCF, and use a common defined outcome (Moore 2014c).

Measurement (endpoints)

There are no lessons here about endpoints. We know that individuals with high levels of pain relief obtain benefit in a range of other symptoms, like sleep, depression, quality of life, and function.

Comparison between active treatments

This is not possible given the present state of knowledge, with generally inadequate trials and reporting for older therapies. More recently introduced therapies for fibromyalgia - duloxetine, milnacipran, and pregabalin - have been licensed in the USA and elsewhere based on large, high quality, clinical trials. While issues around imputation methods in those trials remains, we can be confident that they work well in a small proportion of people with fibromyalgia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Braz 2013

Methods	R, DB, AC, PC, parallel groups, duration 12 weeks Medication taken once daily at 6 pm Assessment at baseline and 1, 3, 6, 9, 12 weeks
Participants	Inclusion: women with fibromyalgia (ACR 1990), age 21 to 60 years, normal laboratory tests Exclusion: untreated inflammatory or endocrine disease; neurological, renal, infectious or bone disease; glaucoma, urinary retention, cardiovascular abnormalities; use of tricyclics within 3 months, any contraindication to study medication N = 38, mean age 43 years, all F Mean duration of symptoms > 33 months (least in placebo group, mean baseline pain 9/10 (5.7 to 9.6)
Interventions	Amitriptyline 25 mg daily, n = 13 Panax ginseng extract (100 mg daily, 27% of ginsenosides), n = 12 Placebo, n = 13 Analgesics, opioids, anti-inflammatory drugs all stopped for ≥ 3 weeks before start of study
Outcomes	Mean pain intensity AE 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	Method of generation of random sequence not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical form as capsules .... in sealed black bottles"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical form as capsules .... in sealed black bottles"

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Braz 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Results for completers only
Size	High risk	< 50 participants per 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"

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Carette 1986 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Capsules "were identical"
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"

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Carette 1994 *(Continued)*

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 amitriptyline 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

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Carette 1995 *(Continued)*

Random sequence generation (selection bias)	Low risk	"generated using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
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

de Zanette 2014

Methods	R, DB (DD), AC, parallel groups, duration 6 weeks Medication taken as single dose at bedtime Assessment at baseline and end of treatment
Participants	Inclusion: fibromyalgia (ACR), refractory to current treatment and PI ≥ 50/100 Exclusion: inflammatory rheumatic disease or other painful conditions that might confound assessment; history of substance abuse, neurologic or oncologic disease, ischaemic heart disease, kidney or hepatic insufficiency N = 63, mean age 48 years, mean baseline pain 66/100
Interventions	Amitriptyline 25 mg daily, n = 21 Melatonin 10 mg daily, n = 21 Amitriptyline 25 mg + melatonin 10 mg daily, n = 21 Current analgesics continued unchanged (paracetamol, ibuprofen, codeine, tramadol) Rescue medication: paracetamol (maximum 4 x 750 mg daily) and ibuprofen (maximum 4 x 20 mg daily)
Outcomes	Pain intensity Fibromyalgia Impact Questionnaire Use of additional analgesics in final week
Notes	Oxford Quality Score: R1, DB2, W1. Total = 5/5
Risk of bias	

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de Zanette 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	"Before the recruitment phase, envelopes containing the protocol materials were prepared. Each envelope was sealed and numbered sequentially" "Two investigators who were not involved in patient evaluations were responsible for the blinding and randomization procedures"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Placebo and active treatment [capsules] had the same size, color, smell and flavor"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Placebo and active treatment [capsules] had the same size, color, smell and flavor"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method for mean data unclear. No dichotomous data
Size	High risk	< 50 participants per 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 ≥ 50% improvement in patient global, physician global, pain, and ≥ 25% reduction in tender point score) Mean pain intensity Adverse events

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Ginsberg 1996 *(Continued)*

	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"
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 (DD), 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 ≥ 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, anti-inflammatory medications, antidepressants, sleeping medication and CNS-active medications stopped ≥ 72 h before start

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Goldenberg 1986 *(Continued)*

	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
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 ≥ 30/100, baseline HRS-D ≤ 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 ≥ 7 days before start

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Goldenberg 1996 *(Continued)*

	Paracetamol permitted
Outcomes	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	"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

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 ≥ 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 ≥ 5.7/10
Interventions	Amitriptyline 25 mg/day, n = 42 Moclobemide 450 mg/day, n = 43 Placebo, n = 45

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Hannonen 1998 *(Continued)*

	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

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

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
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)

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Study	Reason for exclusion
Kempenaers 1994	Fewer than 10 participants/treatment group
McQuay 1992	Predominantly neuropathic or musculoskeletal pain
McQuay 1993	Neuropathic pain
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
Scudds 1989	No initial pain requirement for inclusion, no baseline pain reported
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
Çapaci 2002	Study not convincingly double-blind, no patient evaluation of pain

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

Ataoğlu 1997

Methods	Randomised, 6-week trial
Participants	Fibromyalgia N = 68
Interventions	Amitriptyline Paroxetine
Outcomes	
Notes	Turkish (with English abstract) - awaiting translation

Jang 2010

Methods	Randomised, controlled trial, 4 weeks
Participants	Fibromyalgia syndrome N = 186
Interventions	Oral amitriptyline (Western medicine), once daily Acupuncture combined with cupping and Western medicine

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Jang 2010 *(Continued)*

	Acupuncture combined with cupping
Outcomes	
Notes	Chinese (with English abstract) - awaiting translation

NCT00381199

Methods	Randomised, double-blind, cross-over study. Duration 43 days (possibly 2 x 3 weeks) Assessment at 1, 15, 29, 43 days
Participants	Fibromyalgia (ACR 1990) with self-reported sleep disturbance. Age 18 years or over N = 32
Interventions	Amitriptyline 10 to 25 mg daily Nabilone 0.5 to 1 mg daily
Outcomes	Pain intensity (VAS) Pain quality (McGill Pain Questionnaire) Quality of Life (Fibromyalgia Impact Questionnaire) Mood (Profile of Mood States)
Notes	Reported complete in May 2007

ACR: American College of Rheumatology; N: number of participants; VAS: visual analogue scale

DATA AND ANALYSES

Comparison 1. Amitriptyline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Third-tier efficacy	4	275	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [1.69, 4.91]
1.1 Fibromyalgia	4	275	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [1.69, 4.91]
2 At least 1 adverse event	4	318	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.29, 1.84]
3 All-cause withdrawal	7	418	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.11]
4 Adverse event withdrawal	4	298	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.16]
5 Lack of efficacy withdrawal	3	272	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.19, 0.95]

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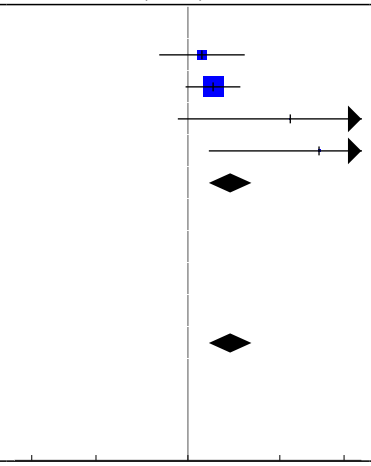
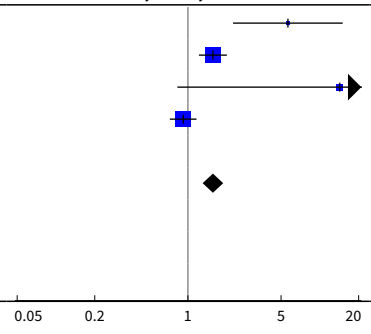
Analysis 1.1. Comparison 1 Amitriptyline versus placebo, Outcome 1 Third-tier efficacy.

Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Fibromyalgia					
Carette 1986	6/27	5/32		28.14%	1.42[0.49,4.15]
Carette 1994	30/84	8/42		65.59%	1.88[0.94,3.72]
Carette 1995	6/22	0/22		3.07%	13[0.78,217.61]
Ginsberg 1996	14/24	0/22		3.2%	26.68[1.69,422.27]
Subtotal (95% CI)	**157**	**118**		**100%**	**2.88[1.69,4.91]**
Total events: 56 (Amitripyline), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.78, df=3(P=0.08); I^2=55.73%					
Test for overall effect: Z=3.9(P<0.0001)					
Total (95% CI)	**157**	**118**		**100%**	**2.88[1.69,4.91]**
Total events: 56 (Amitripyline), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.78, df=3(P=0.08); I^2=55.73%					
Test for overall effect: Z=3.9(P<0.0001)					



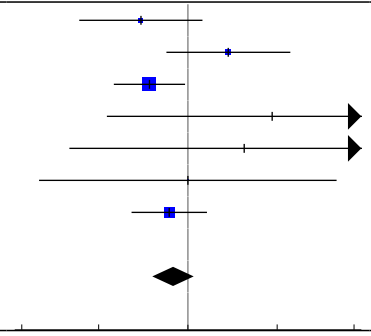
Analysis 1.2. Comparison 1 Amitriptyline versus placebo, Outcome 2 At least 1 adverse event.

Study or subgroup	Amitripyline n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Carette 1986	19/27	4/32		4.97%	5.63[2.18,14.54]
Carette 1994	80/84	26/42		47.1%	1.54[1.21,1.96]
Ginsberg 1996	7/24	0/22		0.71%	13.8[0.83,228.33]
Hannonen 1998	31/42	36/45		47.22%	0.92[0.73,1.16]
Total (95% CI)	**177**	**141**		**100%**	**1.54[1.29,1.84]**
Total events: 137 (Amitripyline), 66 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.18, df=3(P<0.0001); I^2=89.35%					
Test for overall effect: Z=4.72(P<0.0001)					



Analysis 1.3. 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
Braz 2013	3/13	7/13		15.27%	0.43[0.14,1.3]
Carette 1986	7/27	4/32		7.98%	2.07[0.68,6.34]
Carette 1994	14/84	14/42		40.71%	0.5[0.26,0.95]
Carette 1995	2/22	0/20		1.14%	4.57[0.23,89.72]
Ginsberg 1996	1/24	0/22		1.14%	2.76[0.12,64.41]
Goldenberg 1986	1/16	1/16		2.18%	1[0.07,14.64]
Hannonen 1998	10/42	15/45		31.58%	0.71[0.36,1.41]
Total (95% CI)	**228**	**190**		**100%**	**0.77[0.53,1.11]**
Total events: 38 (Amitripyline), 41 (Placebo)					



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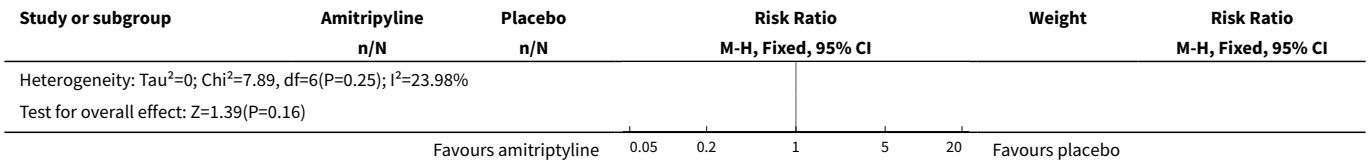
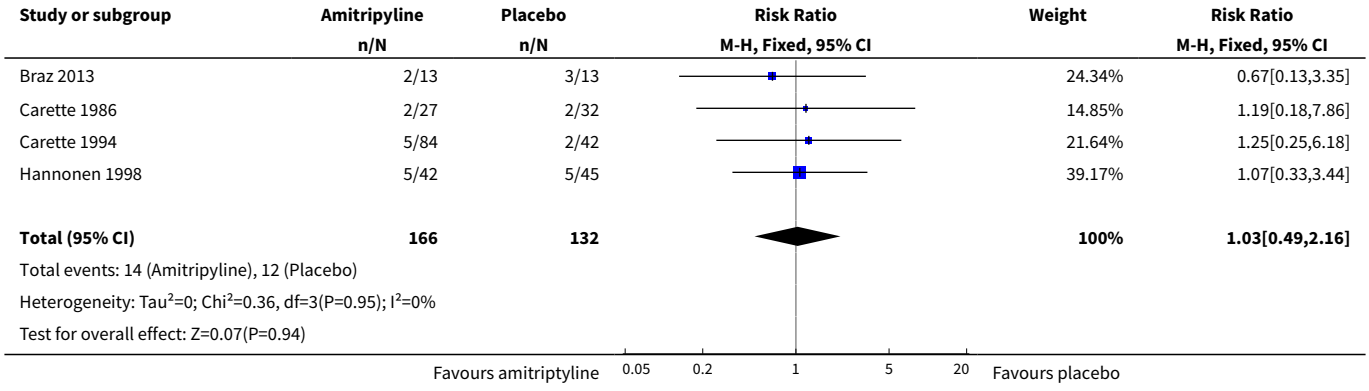
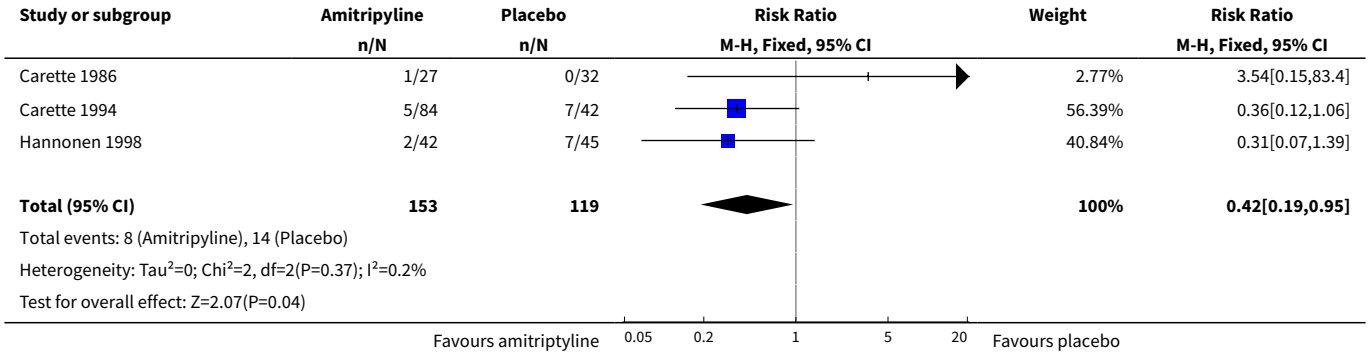


Analysis 1.4. Comparison 1 Amitriptyline versus placebo, Outcome 4 Adverse event withdrawal.



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



APPENDICES

Appendix 1. Methodological considerations for chronic pain

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

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results

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usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.

2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014b; 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. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014a).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. 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 3. 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

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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 4. 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 5. Summary of outcomes in individual studies: efficacy

Study	Treatment (taken at night, unless stated)	Pain outcome	Other efficacy outcome
Braz 2013	Amitriptyline 25 mg = 13 P. ginseng extract = 12 Placebo = 13	VAS PI reduced in all groups compared with baseline, but no statistically significant difference between groups	No significant differences between groups on any of the measures: fatigue, sleep, QoL
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	Global impression of change - moderate or marked at 9 weeks Amitriptyline = 17/27 Placebo = 10/32 Global impression of change - marked Amitriptyline = 6/27	No difference in tender points, but improved sleep with amitriptyline

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(Continued)

		Placebo = 5/32	
Carette 1994	Amitriptyline 25 mg = 84 Cyclobenzaprine 30 mg = 82 Placebo = 42 Dose titration: Amitriptyline week 1 - 10 mg/d Weeks 2 to 12 - 25 mg/d Weeks 13 to 24 - 50 mg/d Cyclobenzaprine 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): Amitriptyline = 30/84 Cyclobenzaprine = 27/82 Placebo = 8/42 No difference for change in mean pain score (from graph): Amitriptyline dropped 67 to 48 mm Placebo 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) Amitriptyline = 6/22 Placebo = 0/22 VAS pain at 8 weeks (mean ± SD) Amitriptyline = 5.1 ± 3.2 Placebo = 7.1 ± 2.1	Significant difference for sleep, patient global, fatigue, but not tender points
de Zanette 2014	Amitriptyline 25 mg daily = 21 Melatonin 10 mg daily = 21 Amitriptyline 25 mg + melatonin 10 mg daily = 21	Mean PI in last 24 h during last week of treatment (100 mm VAS) vs before treatment Amitriptyline 63 to 50 = 13 Melatonin 65 to 48 = 17 Amitriptyline + melatonin 69 to 49 = 20	No significant difference observed between groups in the numbers of analgesic used in last week of treatment, sleep quality and number of tender points
Ginsberg 1996	Amitriptyline 25 mg = 24 Placebo = 22	Responder (at least 50% improvement pain and or global) at 8 weeks: Amitriptyline = 14/ 24 Placebo = 0/22 VAS pain (mean ± SD) Amitriptyline baseline 3.8 ± 2.4 Amitriptyline end 7.0 ± 1.3 Placebo baseline 7.0 ± 1.4 Placebo 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: Amitriptyline 25 mg = 16 Placebo = 16 (Also included naproxen 2 x 500 mg and amitripty-	VAS pain at 6 weeks (mean, from graph): Amitriptyline = 5.4 Placebo = about 7.4 Significant difference only at 4 weeks, not at 6 weeks. No dispersion given	End of trial - significant benefit for amitriptyline versus placebo for fatigue, sleep, and patient global assessment, but not tender points

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(Continued)

	line + naproxen treatment arms)		
Goldenberg 1996	Amitriptyline 25 mg = 21 Fluoxetine 20 mg = 22 Amitriptyline + Fluoxetine = 19 Placebo = 19 Cross-over	VAS pain at 6 weeks (mean ± SD) Amitriptyline = 64 ± 28 Fluoxetine = 58 ± 26 Amitriptyline + Fluoxetine = 43 ± 29 Placebo = 82 ± 17	Apparent significant results, probably amitriptyline versus placebo, for pain, FIQ, sleep, and global, but not fatigue or tender points Generally effect amitriptyline + fluoxetine > fluoxetine ≥ amitriptyline > placebo % change before/after calculated for each patient gave similar pattern to group means - numbers given for > 25% improvement in FIQ only: Amitriptyline = 5/21, Fluoxetine = 7/22, Amitriptyline + Fluoxetine = 12/19, Placebo = 1/19
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) Amitriptyline baseline 6.0 ± 2.1 Amitriptyline end 4.5 ± 2.8 Moclobemide baseline 5.7 ± 2.1 Moclobemide end 4.5 ± 2.7 Placebo baseline 5.7 ± 2.3 Placebo end 5.2 ± 2.7 Number of responders not given, but some response in 74% (amitriptyline) versus 49% (placebo), 54% (moclobemide)	General health, sleep fatigue tender points, and clinician severity all improved with amitriptyline and placebo, but no obvious between group difference, except perhaps sleep

AE: adverse effect; d: day; FIQ: Fibromyalgia Impact Questionnaire; QoL: quality of life; SD: standard deviation; VAS: visual analogue scale

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

Study	Treatment (taken at night, unless stated)	Adverse events	Withdrawals
Braz 2013	Amitriptyline 25 mg = 13 P. ginseng extract = 12 Placebo = 13	Not reported	All cause: Amitriptyline 3/13 P. ginseng 4/12 Placebo 7/13 AE: Amitriptyline 2/13 P. ginseng 3/12 Placebo 3/13 No specific LoE withdrawals
Carette 1986	Amitriptyline 50 mg = 27 Placebo = 32 Dose titration: Week 1 - 10 mg/d	Patients with ≥ 1 AE: Amitriptyline = 19/27 Placebo = 4/32	Total: Amitriptyline = 7/27, Placebo = 4/32 LoE: Amitriptyline = 1/27 Placebo = 0/32 AE:

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	Weeks 2 to 4 - 25 mg/d Weeks 5 to 9 - 50 mg/d	"minor side effects" - mostly drowsiness and xerostomia	Amitriptyline = 2/27 Placebo = 2/32 Other: Amitriptyline = 4/27 Placebo = 2/32
Carette 1994	Amitriptyline 25 mg = 84 Cyclobenzaprine 30 mg = 82 Placebo = 42 Dose titration: Amitriptyline week 1 - 10 mg/d Weeks 2 to 12 - 25 mg/d Weeks 13 to 24 - 50 mg/d Cyclobenzaprine week 1 - 10 mg/d Weeks 2 to 12 - 20 mg/d Weeks 13 to 24 - 30 mg/d	Patients with ≥ 1 AE: Amitriptyline = 80/84 Cyclobenzaprine = 80/82 Placebo = 26/42 Most common - dry mouth, somnolence, dizziness, weight gain	Total: Amitriptyline = 14/84, Cyclobenzaprine = 24/82, Placebo = 14/42 LoE: Amitriptyline = 5/84, Cyclobenzaprine = 6/82, Placebo = 7/42 AE: Amitriptyline = 5/84, Cyclobenzaprine = 11/82, Placebo = 2/42 Other: Amitriptyline = 4/84, Cyclobenzaprine = 7/82, Placebo = 5/42
Carette 1995	Amitriptyline 25 mg = 22 Placebo = 20 Cross-over	Not reported	2 withdrawals after first period A (not drug-related)
de Zanette 2014	Amitriptyline 25 mg daily = 21 Melatonin 10 mg daily = 21 Amitriptyline 25 mg + melatonin 10 mg daily = 21	Minor Amitriptyline 8/21 (nausea, dizziness, weight gain, dry mouth, headache) Melatonin 5/21 (no details) Amitriptyline + melatonin not reported Major Amitriptyline 5/21 (dizziness, nightmares, drowsiness, headache, behavioural change, worsening pain) Melatonin 6/21 (no details) Amitriptyline + melatonin not reported	AE: Amitriptyline 2/21 Melatonin 2/21 Amitriptyline + melatonin 2/21 No other withdrawals reported
Ginsberg 1996	Amitriptyline 25 mg = 24 Placebo = 22	Amitriptyline = 7/24 (3 dry mouth, 2 digestive symptoms, 1 vertigo, 2 neuro-psychic symptoms) Placebo = 0/22	1 in amitriptyline 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)	Amitriptyline = 1 (lost to follow-up) N = 1 (lost to follow-up) Amitriptyline + naproxen = 1 (AE - somnolence) Placebo = 1 (AE - epigastric distress)
Goldenberg 1996	Amitriptyline 25 mg = 21	Not reported	12/31 did not complete

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(Continued)

	Fluoxetine 20 mg = 22 Amitriptyline + Fluoxetine = 19 Placebo = 19 Cross-over		Amitriptyline = 1 (other) Fluoxetine = 4 (1 AE, 3 LoE) Amitriptyline + Fluoxetine = 5 (3 AE, 2 other) Placebo = 1 (AE) Washout after Amitriptyline + Fluoxetine = 1 (LoE)
Hannonen 1998	Amitriptyline 25 mg = 42 Moclobemide 450 mg (am and pm) = 43 Placebo = 45 Titration to max 37.5 mg amitriptyline, 600 mg moclobemide	Patients with ≥ 1 AE: Amitriptyline = 31/42 (dry mouth, fatigue) Moclobemide = 33/43 (headache, difficulty falling asleep) Placebo = 36/45 (fatigue, headache)	Withdrawals: Amitriptyline = 10/42 (2 LoE, 5 AE, 3 other) Moclobemide = 13/43 (4 LoE, 6 AE, 3 other) Placebo = 15/45 (7 LoE, 5 AE, 3 other)

AE: adverse effect; LoE: lack of efficacy; SAE: serious adverse effect

WHAT'S NEW

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

HISTORY

Review first published: Issue 7, 2015

Date	Event	Description
31 July 2015	Review declared as stable	This review will be assessed for further updating in 2020.
31 March 2015	New citation required but conclusions have not changed	Previous review split into two new reviews, with separate reviews dealing with neuropathic pain and with fibromyalgia. Title changed from Amitriptyline for neuropathic pain and fibromyalgia in adults to Amitriptyline for fibromyalgia in adults New studies did not provide data that changed conclusions
26 March 2015	New search has been performed	New searches run. Two new included studies identified, with 101 participants (Braz 2013; de Zanette 2014)
24 September 2010	Amended	Contact details updated.

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CONTRIBUTIONS OF AUTHORS

PW, RAM, and SD wrote the protocol.

For the original review, and again for this update, 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 has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

DA has no conflicts relating to this review or any similar product.

PC has received research support from industry sources at various times but none related to this review.

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

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Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- The National Institute for Health Research (NIHR), UK.

  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update considers fibromyalgia only. Neuropathic pain conditions are the subject of a separate review. It is based on a template for reviews of drugs used to relieve fibromyalgia. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

We have used three-tiers of evidence, not two, to better distinguish the strength of evidence and in line with other reviews of interventions for neuropathic pain. We assessed the data according to different neuropathic pain conditions, and planned no further subgroup analysis because the amount of data was expected to be small.

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