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Wiffen PJ, Derry S, Moore RA

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[Intervention Review]

Lamotrigine for chronic neuropathic pain and fibromyalgia in adults

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ABSTRACT

Background

This is an update of the original Cochrane review entitled *Lamotrigine for acute and chronic pain* published in Issue 2, 2007, and updated in Issue 2, 2011. Some antiepileptic medicines have a place in the treatment of neuropathic pain (pain due to nerve damage). This updated review adds no new additional studies looking at evidence for lamotrigine as an effective treatment for chronic neuropathic pain or fibromyalgia. The update uses higher standards of evidence than previously.

Objectives

To assess the analgesic efficacy of lamotrigine in the treatment of chronic neuropathic pain and fibromyalgia, and to evaluate adverse effects reported in the studies.

Search methods

We identified randomised controlled trials (RCTs) of lamotrigine for chronic neuropathic pain and fibromyalgia (including cancer pain) from MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We ran searches for the original review in 2006, in 2011 for the first update, and subsequent searches in August 2013 for this update. We sought additional studies from the reference lists of the retrieved papers. The original review and first update included acute pain, but no acute pain studies were identified.

Selection criteria

RCTs investigating the use of lamotrigine (any dose, by any route, and for any study duration) for the treatment of chronic neuropathic pain or fibromyalgia. Assessment of pain intensity or pain relief, or both, using validated scales. Participants were adults aged 18 and over. We included only full journal publication articles.

Data collection and analysis

Two review authors independently extracted efficacy and adverse event data, and examined issues of study quality. We performed analysis using three tiers of evidence. The first tier used data where studies reported the outcome of at least 50% pain reduction from baseline, lasted at least eight weeks, had a parallel group design, included 200 or more participants in the comparison, and reported an intention-to-treat analysis. First-tier studies did not use last observation carried forward (LOCF) or other imputational methods for dropouts. The second tier used data that failed to meet this standard and second-tier results were therefore subject to potential bias.

Main results

Twelve included studies in 11 publications (1511 participants), all with chronic neuropathic pain: central post-stroke pain (1), chemotherapy-induced neuropathic pain (1), diabetic neuropathy (4), HIV-related neuropathy (2), mixed neuropathic pain (2), spinal cord injury-related pain (1), and trigeminal neuralgia (1). We did not identify any additional studies. Participants were aged between 26 and 77 years. Study duration was two weeks in one study and at least six weeks in the remainder; eight were of eight-week duration or longer.

No study provided first-tier evidence for an efficacy outcome. There was no convincing evidence that lamotrigine is effective in treating neuropathic pain and fibromyalgia at doses of 200 mg to 400 mg daily. Almost 10% of participants taking lamotrigine reported a skin rash.

Authors' conclusions

Large, high-quality, long-duration studies reporting clinically useful levels of pain relief for individual participants provided no convincing evidence that lamotrigine is effective in treating neuropathic pain and fibromyalgia at doses of about 200 to 400 mg daily. Given the availability of more effective treatments including antiepileptics and antidepressant medicines, lamotrigine does not have a significant place in therapy based on the available evidence. The adverse effect profile of lamotrigine is also of concern.

PLAIN LANGUAGE SUMMARY

Lamotrigine (an antiepileptic drug) for chronic neuropathic pain or fibromyalgia

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages carried along healthy nerves from damaged tissue (a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines like paracetamol or ibuprofen are not effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain. Our understanding of fibromyalgia (a condition of persistent, widespread pain and tenderness, sleep problems, and fatigue) is lacking, but fibromyalgia can respond to the same medicines as neuropathic pain.

Lamotrigine is a medicine used to treat epilepsy, and so might be a useful medicine for neuropathic pain or fibromyalgia.

On 26 November 2013 we performed searches to look for clinical trials where lamotrigine was used to treat neuropathic pain or fibromyalgia. We found 12 studies of reasonable quality that tested lamotrigine against placebo for a number of weeks. Almost half of the 1511 people in the studies had painful limbs because of damaged nerves caused by diabetes, and seven different painful neuropathic conditions were examined. No studies looked at fibromyalgia.

Lamotrigine did not help the pain, and was no different from placebo except in causing more side effects. Adverse events were more frequent with lamotrigine than placebo, with rash in 1 person in 27.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Lamotrigine compared with placebo for painful diabetic neuropathy

Patient or population: neuropathic pain (three studies in painful diabetic neuropathy)
Settings: Community
Intervention: oral lamotrigine 200 to 400 mg daily
Comparison: placebo

Outcomes	Probable outcome with		Risk ratio NNTor NNH (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
	comparator	intervention				
At least 50% of maximum pain relief	240 in 1000	260 in 1000	RR 1.1 (0.82 to 1.4) NNT not calculated	3 studies, 773 participants, 195 events	High	Unlikely that further research would reveal significant benefit, especially as potential high positive bias exists in the calculations we have because of LOCF imputation or completer analyses
Participants with at least 1 adverse event (all conditions)	622 in 1000	717 in 1000	RR 1.1 (1.01 to 1.2) NNH 10 (6.5 to 27)	7 studies, 1121 participants, 768 events	High	Large numbers of events
Participants with a serious adverse event (all conditions)	No data				Very low	No data
Participants with rash (all conditions)	56 in 1000	95 in 1000	RR 1.4 (1.01 to 2.0) NNH 27 (16 to 89)	12 studies, 1715 participants, 138 events	Moderate	Modest number of events
Deaths (all conditions)	No data				Very low	No data

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.

LOCF: last observation carried forward; NNT: number needed to treat for an additional beneficial outcome: NNH: number needed to treat for an additional harmful outcome; RR: risk ratio

BACKGROUND

This is an update of a review first published in 2007 (Wiffen 2007), which looked at lamotrigine to treat acute and chronic pain of any type. In 2011 we updated the review with the addition of five new studies (1111 participants, of whom 767 received lamotrigine), using stricter methodological criteria to reduce potential bias (Wiffen 2011a). We made the decision to update again, and to concentrate on chronic neuropathic pain and fibromyalgia. We changed the title from *Lamotrigine for acute and chronic pain*, because there have been further recent advances in the rigour with which we assess studies and report data. We also made this decision in order to conform with other reviews in the series on neuropathic pain and fibromyalgia, and because there is little or no use or intended use of lamotrigine and similar drugs in acute pain, or other forms of chronic pain.

In particular we considered study size and duration, outcomes reported, and method of imputation for withdrawals, and we now report results in two tiers according to outcome and freedom from known sources of bias. We wanted to bring this review in line with a template protocol so that it could easily be included in the overview of antiepileptics for chronic neuropathic pain and fibromyalgia in adults (Wiffen 2013a). Reviews of carbamazepine (Wiffen 2011b), clonazepam (Corrigan 2012), gabapentin (Moore 2011a), lacosamide (Hearn 2012), phenytoin (Birse 2012), pregabalin (Moore 2009a), topiramate (Wiffen 2013b), and valproic acid (Gill 2011) have been completed.

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; Moore 2012b; Appendix 1). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009a). This indicated 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. While fibromyalgia is considered to have a different aetiology from chronic neuropathic pain, it is a condition that responds to the same therapies. Because of limitations in the number of available clinical trials, it is convenient to consider fibromyalgia together with neuropathic pain. We make no presumption to pool data across individual neuropathic pain conditions or fibromyalgia, but will consider each condition separately.

Description of the condition

The 2011 International Association for the Study of Pain definition of *neuropathic pain* is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the central nervous system (CNS) (Moisset 2007). Neuropathic pain tends to be chronic and may be present for months or years. It is complex (Apkarian 2011; Tracey 2011), and neuropathic pain features can be found in patients with joint pain (Soni 2013).

Fibromyalgia is defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and is frequently associated with other symptoms such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Moreover, patients with neuropathic pain and those with fibromyalgia experience similar sensory phenomena (Koroschetz 2011). Many people with these conditions are significantly disabled with moderate or severe pain for many years.

In primary care in the United Kingdom (UK), the incidences per 100,000 person-years' observation have been reported as 28 (95% confidence interval (CI) 27 to 30) for postherpetic neuralgia, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for painful diabetic neuropathy (Hall 2008). Estimates varied between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person-years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007). The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008) and as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). Some forms of neuropathic pain, such as diabetic neuropathy and post surgical chronic pain (which is often neuropathic in origin) are increasingly common (Hall 2008). Fibromyalgia is common, especially in women, with an all-age prevalence of 12%, and a female to male ratio of 6:1 (McNally 2006).

Neuropathic pain and fibromyalgia are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions or both. Conventional analgesics are usually not effective. Some patients with neuropathic pain may derive some benefit from topical lidocaine patch or low concentration topical capsaicin, although evidence of benefit is uncertain (Derry 2012; Khaliq 2013). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia (Derry 2013). Treat-

ment is more usually by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2009; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009a; Moore 2011a). The proportion of patients who achieve worthwhile pain relief (typically defined as at least 50% pain intensity reduction (Moore 2013b)) is small, typically 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNTs) usually between 4 and 10.

Description of the intervention

Lamotrigine, a phenyltriazine, is chemically unrelated to other antiepileptic drugs. The drug is available as standard oral tablets (25 mg to 200 mg) and chewable, dispersible tablets (2 mg to 100 mg), and a new extended release tablet is available in some parts of the world.

How the intervention might work

Lamotrigine is an antiepileptic drug exerting its antiepileptic effect via sodium channels. There is some evidence that agents that block sodium channels are useful in the treatment of neuropathic pain (McCleane 2000). There is evidence from animal models supporting the use of lamotrigine in neuropathic pain, and for an effect in experimental pain models such as cold-induced pain in humans (McCleane 2000). Lamotrigine is chemically unrelated to existing antiepileptic agents. There has also been discussion of the role of lamotrigine as a pre-emptive analgesic to reduce postsurgical pain (Bonicalzi 1997). More recently it has been shown that neuronal alpha4 beta2 nicotinic acetylcholine receptors may be a target for lamotrigine, and this may mediate its antiepileptic effects (Zheng 2010).

Why it is important to do this review

The standards used to assess evidence in chronic pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to using the number of participants who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the reference guide for pain studies (AUREF 2012) and reflect what patients with chronic pain want from treatment (Moore 2013a).

This Cochrane review assesses evidence in ways that make both statistical and clinical sense, and uses developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 500 participants in a comparison in which the NNT is four or more (Moore 1998)).

Lamotrigine is not widely prescribed for neuropathic pain, though it is prescribed for some cases of painful HIV-related neuropathy. It is important to know its place in the range of drugs used to treat the various types of neuropathic pain. This updated review brings the evidence for lamotrigine into line with that for other medicines used in these conditions, and will form part of an overview of antiepileptic drugs for chronic neuropathic pain and fibromyalgia.

OBJECTIVES

To assess the analgesic efficacy of lamotrigine in the treatment of chronic neuropathic pain and fibromyalgia, and to evaluate adverse effects reported in the studies.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with at least 10 participants per treatment group and double-blind (participant and observers) assessment of participant-reported outcomes, following two weeks of treatment or longer, although the emphasis of the review is on studies of six weeks or longer. We required full journal publication, with the exception of extended abstracts of otherwise unpublished clinical trials (for example, detailed information from PDFs of posters that typically included all important details of methodology used and results obtained). We did not include short abstracts (usually meeting reports with inadequate or no reporting of data). We excluded studies of experimental pain, case reports, and clinical observations.

In the earlier review, we excluded studies of lamotrigine used to treat pain produced by other drugs; in this version we have included one study for chemotherapy-induced pain, but have not combined results from this study in the analysis (Rao 2008).

Types of participants

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

- cancer-related neuropathy;

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

and

- fibromyalgia;
- CRPS Type I.

Types of interventions

Lamotrigine in any dose, by any route, administered for the relief of neuropathic pain or fibromyalgia, and compared to placebo, no intervention or any other active comparator.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on patient global impression of change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those set out in the earlier review (Wiffen 2007), concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (O'Brien 2010).

We include a 'Summary of findings' table as set out in the Cochrane Pain, Palliative and Supportive Care Group author guide (AUREF 2012). The 'Summary of findings' table includes outcomes of at least 30% and at least 50% pain intensity reduction, PGIC, adverse event withdrawals, serious adverse events and death (Summary of findings for the main comparison).

Primary outcomes

1. Participant-reported pain intensity reduction of 30% or greater.
2. Participant-reported pain intensity reduction of 50% or greater.
3. Participant-reported global impression of clinical change (Patient Global Impression of Change, PGIC) much or very much improved.
4. Participant-reported global impression of clinical change (PGIC) very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.

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

Search methods for identification of studies

Electronic searches

We identified studies by several methods. For the original review we identified RCTs of lamotrigine (and key brand names Lamictal, Lamictin, Neurium) in acute and chronic pain in the Cochrane Central Register of Controlled Trials (CENTRAL, 2010, Issue 12), MEDLINE (via Ovid) from 1966 to January 2011, and EMBASE (via Ovid) from 1994 to January 2011.

For this update we searched for new studies in chronic neuropathic pain and fibromyalgia in:

- Cochrane Central Register of Controlled Trials (CENTRAL, 2013, Issue 11 in *The Cochrane Library*);
- MEDLINE (via Ovid) (January 2010 to 26 November 2013);
- EMBASE (via Ovid) (January 2010 to 26 November 2013);
- PhRMA clinical study results database (clinicaltrials.gov) to 26 November 2013;
- WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch) to 26 November 2013.

Given the limited literature in this area, we undertook a sensitive search strategy. See Appendix 2 for the MEDLINE search strategy, Appendix 3 for the EMBASE search strategy, and Appendix 4 for the CENTRAL search strategy.

Searching other resources

For the original review, we identified additional studies from the reference lists of the retrieved papers and by contacting study authors. We applied no language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently read the titles and abstracts of all studies identified by the search, and the full text of all potentially relevant studies. We reached agreement on eligibility by discussion. We did not anonymise the studies in any way before assessment.

Data extraction and management

Two review authors extracted data using a standard form, and agreed data before entry into Review Manager 5 (RevMan 2012) or any other analysis method. Data extracted included information about the pain condition and number of participants treated, drug and dosing regimen, study design, study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event or a serious adverse event).

Assessment of risk of bias in included studies

We independently scored each study for quality using a three-item scale (Jadad 1996) and agreed a 'consensus' score for each study. Scores of two and below have been associated with greater estimates of efficacy than studies of higher quality (Khan 1996). Quality scores were not used to weight the results in any way.
We used the 'Risk of bias' tool to assess the likely impact on the strength of the evidence of various study characteristics relating to methodological quality (randomisation, allocation concealment, blinding, freedom from selective reporting), study validity (duration, outcome reporting, and handling of missing data), and size (Moore 2010a).
Two review authors independently assessed risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

- 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, eg random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (eg odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before 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 (eg 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 (eg open list).
- 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 states that it was blinded and describes the method used to achieve blinding, eg identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved). We excluded studies that were not double-blind.
- 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 of bias (< 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' (LOCF) analysis); high risk of bias (used 'completer' analysis).
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We used the risk ratio (relative risk, RR) to establish statistical difference. We used numbers needed to treat for an additional beneficial outcome (NNT) or for an additional harmful outcome (NNH) and pooled percentages as absolute measures of benefit or harm.
The following terms are used to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occurred with lamotrigine than with control (placebo or active) we used the term the number needed to treat to prevent one event (NNTp);
- When significantly more adverse outcomes occurred with lamotrigine compared with control (placebo or active) we used the term the number needed to harm or cause one event (NNH).

Unit of analysis issues

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

Dealing with missing data

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

this could be done. We were aware that imputation methods might be problematical and examined trial reports for information about them.

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar painful conditions, and not combining results from dissimilar painful conditions. We assessed statistical heterogeneity visually (L'Abbe 1987) and with the use of the I^2 statistic (Higgins 2003).

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010a). The review did not depend on what authors of the original studies chose to report or not report, though clearly there were difficulties with studies failing to report any dichotomous results. We extracted continuous data, which probably poorly reflected efficacy and utility, and used them only when useful for illustrative purposes.
We undertook no statistical assessment of publication bias.

Data synthesis

We considered individual painful conditions separately because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009a).
We analysed data for each painful condition in three tiers, according to outcome and freedom from known sources of bias.

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

We used dichotomous data to calculate risk ratio for benefit with 95% confidence intervals (CIs), using a fixed-effect model, together with numbers needed to treat for an additional beneficial outcome (NNTs) (Cook 1995). This was done for effectiveness, for adverse effects, and for drug-related study withdrawal. We also undertook meta-analysis when appropriate data were available. We calculated NNTs as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNH (number needed to treat for an additional harmful outcome) is calculated in the same way. In the absence of dichotomous data, we have reported summary continuous data where available and appropriate, but did not carry out any analysis. We undertook meta-analysis using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned no subgroup analyses, beyond separate analysis of different conditions, as we expected that there would be insufficient study data.

Sensitivity analysis

We planned no sensitivity analyses because we knew the evidence base to be too small to allow reliable analysis.

RESULTS

Description of studies

Results of the search

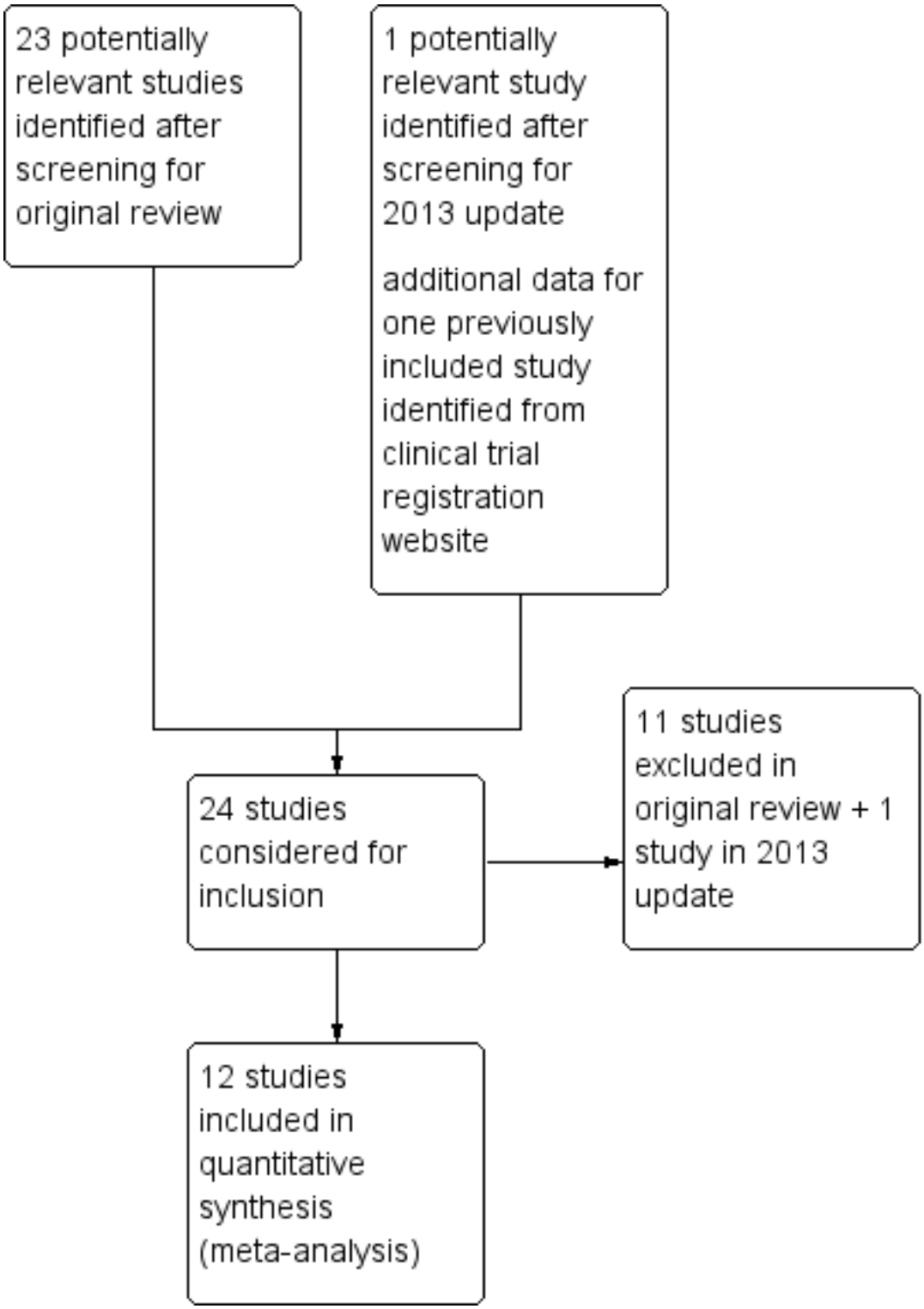
The previous review identified 23 studies, in 23 publications. New searches for this update identified one potentially relevant study.

Included studies

There were seven studies (400 participants) in the original review (Eisenberg 2001; Finnerup 2002a; McCleane 1999; Simpson 2000; Simpson 2003; Vestergaard 2001; Zakrzewska 1997). In the first update five studies were added (Jose 2007; Rao 2008; Silver 2007; Vinik 2007a; Vinik 2007b), with 1111 participants, almost trebling the number of participants since the previous review. These studies were generally larger in size and of longer duration. We found no new studies for this update that satisfied the inclusion criteria.
Twelve previously identified studies (12 publications), involving 1511 participants are therefore included (Eisenberg 2001; Finnerup 2002a; Jose 2007; McCleane 1999; Rao 2008; Silver 2007; Simpson 2000; Simpson 2003; Vestergaard 2001; Vinik

2007a; Vinik 2007b; Zakrzewska 1997). Two studies were reported in one publication (Vinik 2007a; Vinik 2007b), and an incomplete report of Eisenberg 2001 (Lurie 2000) provided no additional data, but is included and linked to the primary study. Additional data for Silver 2007 (NPP30010) were identified during the latest searches in a results summary posted on the GlaxoSmithKline Clinical Trials Register (Figure 1).

Figure 1. Study flow diagram.



Included studies covered the following conditions: central post-stroke pain (Vestergaard 2001), chemotherapy-induced peripheral neuropathic pain (Rao 2008), diabetic neuropathy (Eisenberg 2001; Jose 2007; Vinik 2007a; Vinik 2007b) HIV-related neuropathy (Simpson 2000; Simpson 2003), mixed neuropathic pain (McCleane 1999; Silver 2007), spinal cord injury-related pain (Finnerup 2002a), and trigeminal neuralgia (Zakrzewska 1997). There were no studies using lamotrigine to treat fibromyalgia.

Eleven studies used a placebo comparator, and one (Jose 2007) used amitriptyline as the comparator. Two studies added lamotrigine or placebo to existing treatments for neuropathic pain (Silver 2007; Zakrzewska 1997). The studies included participants in the age range of 26 to 77 years. One study was for two weeks (Zakrzewska 1997); the remainder were at least six weeks, and eight were of eight-week duration or longer. Four were cross-over studies (Finnerup 2002a; Jose 2007; Vestergaard 2001; Zakrzewska 1997). Details of all eligible studies are given in the Characteristics of included studies table and results for individual studies are in a separate table (Appendix 5).

Excluded studies

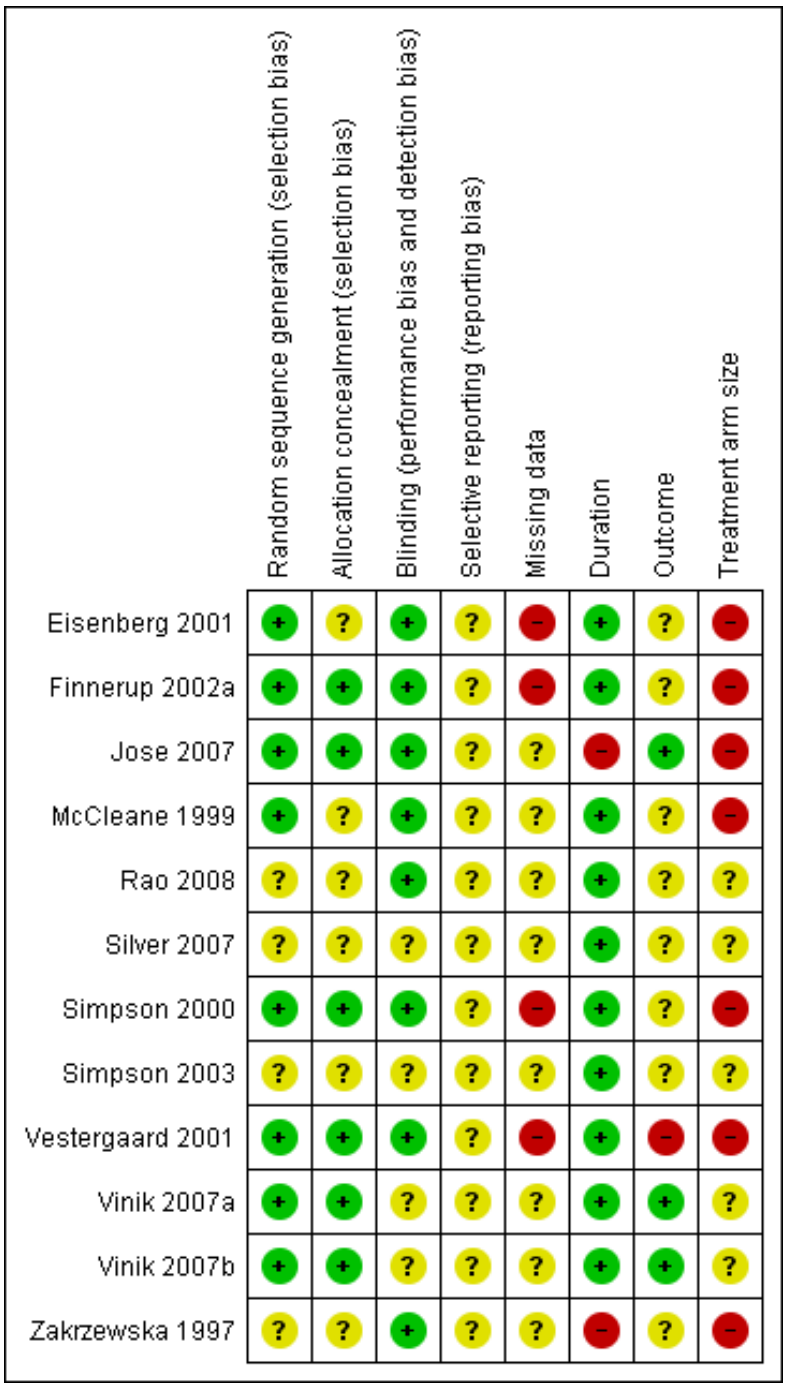
Eleven studies were excluded from the earlier review (Bonicalzi 1997; Breuer 2007; Carrieri 1998; Devulder 2000; Di Vadi 1998; Eisenberg 1998; Eisenberg 2003; Eisenberg 2005; Lunardi 1997; Petersen 2003; Sandner-Kiesling 2002), and one more for this update (Shaikh 2011). Details of the reasons for exclusion are in the Characteristics of excluded studies table.

Risk of bias in included studies

Each study was scored for quality using the three-item Oxford Quality Score scale (Jadad 1996) and agreed by the review authors. All scored 3/5 or greater, with one scoring 3/5, five scoring 4/5, and six scoring 5/5.

In this update we have used the 'Risk of bias' tool. The comments on individual studies are reported in the Risk of bias section of the Characteristics of included studies table. The findings are displayed in Figure 2; no sensitivity analysis was undertaken. The greatest risks of bias came from imputation after study withdrawal, outcomes used of little relevance, and small study size.

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



Effects of interventions

See: **Summary of findings for the main comparison** Lamotrigine 200 to 400 mg versus placebo for neuropathic pain

For measures of efficacy we considered each condition separately, but for adverse outcomes we combined data across conditions. There were no data for fibromyalgia.

Efficacy

No study provided first-tier evidence for an efficacy outcome. We judged results as second- or third-tier because of use of LOCF imputation or completer analysis, and small size. Details of efficacy outcomes in individual studies are in Appendix 5.

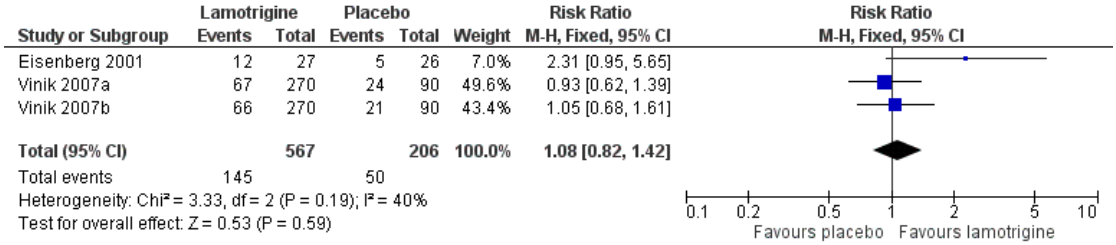
Painful diabetic neuropathy (PDN)

Second tier evidence

Four studies (Eisenberg 2001; Jose 2007; Vinik 2007a; Vinik 2007b) looked at the role of lamotrigine for PDN (758 participants). None of these demonstrated any major benefits.

In one study (Eisenberg 2001), a 50% reduction in pain measured in the last three weeks of treatment was reported by 12/27 on lamotrigine titrated up to 400 mg daily and 5/26 on placebo. In two large randomised studies of lamotrigine 200 mg to 400 mg daily, with a 12-week maintenance phase, there was no difference between lamotrigine and placebo for the outcome of at least 50% pain relief (Vinik 2007a; Vinik 2007b). Combining these studies, 145/567 (26%) of participants experienced at least 50% pain relief with lamotrigine 200 mg to 400 mg daily, and 50/206 (24%) with placebo. There was no overall significant difference between lamotrigine and placebo (RR 1.1 (95% CI 0.8 to 1.4)) (Figure 3). A similar non-significant difference was found for participants reporting "marked improvement".

Figure 3. Forest plot of comparison: 1 Painful diabetic neuropathy, outcome: 1.1 50% pain relief.



In the fourth study, a 20% reduction in pain after six weeks of treatment was reported by 19/46 taking lamotrigine 200 mg daily and 13/46 taking 50 mg amitriptyline at night (Jose 2007). There were insufficient data for analysis.

Mixed neuropathic pain

Third tier evidence

One study of 100 participants examined the use of lamotrigine 200 mg daily in participants with intractable neuropathic pain diagnosed by symptoms of shooting/lancinating pain, burning, numbness, allodynia and paraesthesia/dysaesthesia (McCleane 1999). At least three of these symptoms were required for participation. Participants already taking an antiepileptic were excluded. No useful analgesic benefit was demonstrated. There was a reduction in the overall pain score of 1/100 mm.

A second study used an 'add-on' design for lamotrigine titrated up to 400 mg daily on top of gabapentin, tricyclic antidepressant, or non-opioid analgesic where pain was inadequately controlled (Silver 2007). No additional analgesic benefit could be demonstrated over 14 weeks using responder definitions of $\geq$ 50% and $\geq$ 30% pain reduction or PGIC outcomes of much or very much improved.

Central post-stroke pain

Third tier evidence

Thirty participants took part in a single cross-over study, and only 20 completed both arms (Vestergaard 2001). The difference between lamotrigine 200 mg and placebo for clinical response was significant when assessed at eight weeks. Lower pain scores (reduction of 2/10 or more) were reported by 12 participants with lamotrigine and three with placebo.

Chemotherapy-induced peripheral neuropathic pain

Third tier evidence

In a study of 125 participants (Rao 2008), average pain scores decreased in both the active and placebo groups with no significant difference between the groups. The study authors concluded that lamotrigine was not effective in this condition.

HIV-related neuropathy

Third tier evidence

There were two studies involving participants with HIV-related neuropathy. The first study of 42 participants (Simpson 2000) claimed effectiveness for lamotrigine 300 mg/day, but over 50% of the treatment group dropped out, making results difficult to interpret. The second study (Simpson 2003) analysed the results according to whether participants were receiving antiretroviral therapy (ART) or not. For those who were receiving antiretroviral therapy there did appear to be some benefits in terms of attainment of moderate or better pain relief with lamotrigine (35/62, 57%) than with placebo (7/30, 23%); for PGIC, marked improvement was recorded by 29/62 (47%) of participants with lamotrigine and 4/30 (13%) with placebo.

Spinal cord injury related pain

Third tier evidence

Thirty participants with neuropathic pain following traumatic spinal cord injury were included (Finnerup 2002a). Doses of up to 400 mg daily for lamotrigine were used but the study authors reported no significant difference from placebo for the outcomes of $\geq$ 50% or $\geq$ 30% pain relief.

Trigeminal neuralgia

Third tier evidence

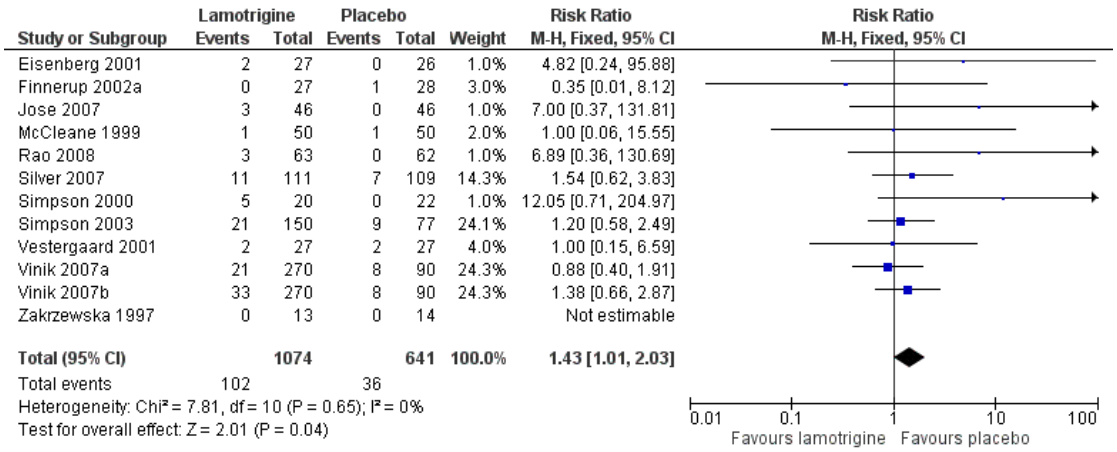
Fourteen participants participated in a cross-over 'add-on' study comparing lamotrigine with placebo in a cross-over study of two two-week phases separated by a three-day long washout (Zakrzewska 1997). All participants continued on carbamazepine or phenytoin throughout the study period. Lamotrigine was not significantly more effective than placebo in this small study; 10/13 participants stated that lamotrigine was better or much better, compared with 8/14 on placebo, using a global evaluation.

Adverse events

Adverse events were not consistently reported across studies. Seven studies, with 1121 participants (Eisenberg 2001; Finnerup 2002a; Silver 2007; Vestergaard 2001; Vinik 2007a; Vinik 2007b; Zakrzewska 1997) reported the number of participants who experienced at least one adverse event. Combining the studies across conditions, 531/740 (72%) of participants had an adverse event with lamotrigine and 237/381 (62%) with placebo. The RR just reached statistical significance at 1.1 (1.01 to 1.2) (Analysis 2.1) and the NNH was 10 (6.5 to 27).

Rash can be problematic with lamotrigine. It was mentioned as an adverse event or adverse event withdrawal in 11 studies, and omitted from a long list of adverse events in the other (Zakrzewska 1997). Combining studies, the overall incidence of rash was 9.5% with lamotrigine and 5.6% with placebo, barely achieving statistical significance (RR 1.4 (1.01 to 2.0)) (Figure 4). This would indicate that rash with lamotrigine would affect about one person in 27 who would not have been affected with placebo.

Figure 4. Forest plot of comparison: 2 All conditions: lamotrigine versus placebo, outcome: 2.2 Rash.



DISCUSSION

Antiepileptic drugs have been used in the treatment of neuropathic pain since lamotrigine was first used for trigeminal neuralgia in the 1960s. Other antiepileptic drugs have been examined, with good evidence of efficacy for gabapentin (Moore 2011a) and pregabalin (Moore 2009a), and these two are now widely used. Although various drugs may be useful in controlling seizures, they have different mechanisms of action. There is no reason why a drug effective at seizure control should necessarily be effective in treating neuropathic pain. Lamotrigine, a relatively new antiepileptic drug, has therefore been investigated in neuropathic painful conditions.

Summary of main results

Large, high-quality, long-duration studies reporting clinically useful levels of pain relief for individual participants provide no convincing evidence that lamotrigine is effective in treating neuropathic pain and fibromyalgia at doses of about 200 mg to 400 mg daily. There is very limited evidence for a possible effect of lamotrigine in central post-stroke pain and in a subgroup of patients with HIV-related neuropathy receiving antiretroviral therapy. No benefit was demonstrated for diabetic neuropathy, in intractable neuropathic pain, spinal cord injury, or trigeminal neuralgia. We found no studies testing lamotrigine in fibromyalgia. The small number of studies and the small number of participants are insufficient to provide robust evidence for effect.

Safety is an important aspect of the choice of treatment even in difficult conditions. In this review, about 10% of participants developed a rash; this fits with wider epidemiological work (Hirsch 2006). The results are consistent with reports in the manufacturer's summary of product characteristics. Serious potentially life-threatening rashes such as Stevens Johnson Syndrome are estimated to occur at an incidence of 1 in 1000 (SPC 2013).

Overall completeness and applicability of evidence

The difficulties of dose titration and adverse effects are likely to dissuade many clinicians from choosing lamotrigine to treat neuropathic pain, and it is possible that those conducting the studies have chosen to include the more difficult participants in terms of severity and duration of pain.

Efficacy and adverse event outcomes were not consistently reported across the studies, and this limited the analyses to some extent.

Quality of the evidence

The studies included in this review covered a number of different painful conditions. For some, like HIV neuropathy for instance, it is unclear whether antiepileptic drugs are effective in the condition, and any indication of benefit is welcome. The main quality issues involve reporting of outcomes of interest, particularly dichotomous outcomes equivalent to Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), as well as better reporting of adverse events. The earliest study was published in 1997, and there have been major changes in clinical trial reporting since then. The studies themselves appear to be largely well-conducted, and individual patient analysis could overcome some of the shortcomings of reporting, though not the paucity of participants studied in each neuropathic pain condition.

Potential biases in the review process

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

- Duration - NNT estimates of efficacy in chronic pain studies tend to increase (get worse) with increasing duration (Moore 2010d). However, all studies were six weeks or longer, and most longer than eight weeks.
- Outcomes may affect estimates of efficacy, but the efficacy outcomes chosen were of participants achieving the equivalent of IMMPACT-defined moderate or substantial improvement, and it is likely that lesser benefits, such as 'any benefit' or 'any improvement', are potentially related to inferior outcomes, though this remains to be clarified. Most authors attempted to report dichotomous outcomes of interest, especially in the larger, more recent studies.
- The question of whether cross-over trials exaggerate treatment effects in comparison with parallel-group designs, as has been seen in some circumstances (Khan 1996), is unclear but unlikely to be the source of major bias (Elbourne 2002). Withdrawals meant that any results were more likely to be per protocol for completers than for a true ITT analysis. Parallel group studies were larger than cross-over studies, and predominated analyses in terms of number of participants, with only about 100 participants in cross-over studies.
- The absence of publication bias (unpublished trials showing no benefit of lamotrigine over placebo) can never be proven. However, publication bias is irrelevant where the published studies show no effect of treatment.
- Imputation methods used when participants withdrew were typically either last observation carried forward (LOCF) or were not stated; no study reported clearly that participants achieving acceptable levels of pain relief were unequivocally on treatment at the end of the study. Use of LOCF imputation can overestimate efficacy, particularly where adverse event withdrawals are high with active treatment (Moore 2012b).

Agreements and disagreements with other studies or reviews

This update does not substantially change the results of the 2011 update, which itself was broadly in agreement with the previous Cochrane review (Wiffen 2007).

A systematic review of pharmacological treatment of painful HIV-associated sensory neuropathy (Phillips 2010) did not find lamotrigine 600 mg/day to be better than placebo. A non-systematic review considered lamotrigine to be effective, but based on only a fraction of the results presented in this updated review (Jensen 2002), and Finnerup 2002b suggested that lamotrigine is as good as amitriptyline and is a first-line agent in central neuropathic pain. Guidelines from Europe (Attal 2010) and the International Association for the Study of Pain (Dworkin 2010) reported that there were few data for lamotrigine in any neuropathic pain condition, and recommended its use only as a third line medication, and probably only in a specialist setting. Guidelines from NICE in the UK do not recommend lamotrigine for neuropathic pain (NICE 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Based on current evidence, the routine use of lamotrigine is unlikely to be of benefit in the treatment of neuropathic pain, and there are more effective and safer medicines available (Moore 2009a; Moore 2011a). There may be a role for experimental use or in patients who have failed to obtain pain relief from other treatments. The incidence of skin rash is not trivial and must be considered before initiating therapy.

Implications for research

Reasonable levels of evidence exist for the benefit of other antiepileptic drugs and antidepressants in the treatment of chronic neuropathic pain. There is therefore probably no justification for further research given the lack of evidence for benefit from lamotrigine and the potential for harm due to skin rash, which can occasionally be serious.

ACKNOWLEDGEMENTS

Jayne Edwards (Rees) contributed as an author to the original review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Eisenberg 2001

Methods	Randomised DB placebo controlled, parallel group study for 11 weeks. One-week screening phase, 8-week treatment phase, 2-week post-treatment phase
Participants	59 participants with painful diabetic neuropathy. Age 50 to 60 years Excluded: participants who had received antiepileptics or antidepressants for reasons other than pain and those who had received opioids
Interventions	Lamotrigine 25 mg dispersible tablets or matching placebo 25 mg daily for 2 weeks, 50 mg daily for 2 weeks, then 100 mg, 200 mg, 300 mg and 400 mg for 1 week at each dose level Rescue analgesia as paracetamol, dipyrone or NSAIDs
Outcomes	Daily pain intensity, McGill, Beck depression, Pain disability index, Global assessment. Responder: 50% reduction in pain measured in final 3 weeks of treatment
Notes	Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done in blocks of four according to a computer generated random code"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Assessors	Low risk	"Patients in the placebo group received equal numbers of identical looking placebo tablets"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	High risk	Completer analysis - data from withdrawals not carried forward
Duration	Low risk	"Eight weeks treatment phase"
Outcome	Unclear risk	Looked for reduction in pain intensity but reports numbers with 50% reduction. No mention of imputation method
Treatment arm size	High risk	59 participants: 29 active, 30 placebo

Finnerup 2002a

Methods	Randomised DB placebo controlled, cross-over study. One-week baseline assessment, two 9-week treatment periods separated by 2-week washout
Participants	30 participants with neuropathic pain after traumatic spinal cord injury (SCI). Age 27 to 63 years
Interventions	Lamotrigine tablets or identical placebo. Dose escalation to 400 mg a day. Weeks 1 and 2 at 25 mg daily, weeks 3 and 4 at 50 mg, 1 week each at 100 mg, 200 mg, and 300 mg then 2 weeks at 400 mg. Concomitant treatment with spasmolytics, sedatives for insomnia, and simple analgesics for other pain allowed in constant unchanged dose Rescue analgesia: paracetamol up to 3 g daily
Outcomes	Average daily pain on 11-point numeric scale. Change in median weekly pain score from baseline to final week. Participant preference, other measures included details of types of pain, impact on sleep, and use of rescue medication
Notes	Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"assignment to treatment was random via a computer generated randomisation list with blocks of four"
Allocation concealment (selection bias)	Low risk	"The primary investigator was provided with sealed code envelopes- one for each patient- containing information on the treatment given . . . and envelopes were returned unopened to the monitor after the study termination."
Blinding (performance bias and detection bias) Assessors	Low risk	"lamotrigine and identical placebo"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	High risk	completer
Duration	Low risk	Nine week per arm treatment period
Outcome	Unclear risk	Looked for reduction in pain intensity but reports numbers with 50% reduction
Treatment arm size	High risk	30 participants total, 22 completers

Jose 2007

Methods	Randomised DB active controlled, cross-over study. Two 6-week treatment periods separated by 2-week washout
Participants	53 participants, of whom 46 received both treatments, with Type 2 Diabetes and painful diabetic neuropathy for at least 1 month Excluded: participants taking antidepressants, antiepileptics, opioids and local anaesthetic agents
Interventions	Lamotrigine dose escalation to 100 mg twice daily over 6 weeks or amitriptyline to 50 mg at night with matching placebo in the morning. Two-week washout using placebo between treatment periods Rescue analgesia: paracetamol up to 3 g daily
Outcomes	Patient global assessment (> 50% pain relief = good, > 25% pain relief), VAS PI, short form McGill, 5-point categorical scale for pain and Hamilton depression scale
Notes	CONSORT flow chart indicated 23 patients randomised to lamotrigine and 30 to amitriptyline on first cross-over arm, 23 each on second. 46 participants included in ITT analysis. Outcomes reported for both arms of cross-over, with 46 as denominator for efficacy Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"numbers generated using random number tables by block randomisation"
Allocation concealment (selection bias)	Low risk	"blinding and randomisation carried out by independent person unrelated to the study", "drug codes were maintained under lock and key"
Blinding (performance bias and detection bias) Assessors	Low risk	"drugs were blinded, packed and numbered serially"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	LOCF used
Duration	High risk	6 weeks dose escalation then cross over
Outcome	Low risk	"VAS score showing improvement of > 50%, > 25% and < 25%" used

Jose 2007 (*Continued*)

Treatment arm size	High risk	53 participants; 23 per treatment arm, with 46 completers

McCleane 1999

Methods	Randomised DB placebo controlled, parallel group study. Eight-week treatment period
Participants	100 participants with intractable neuropathic pain. Mean age placebo group 44.7 years, lamotrigine group 47.1 years. All had failed response to codeine or NSAID-based analgesics Excluded: participants taking antiepileptics
Interventions	Lamotrigine 25 mg dispersible tablets or matching placebo 25 mg daily for 1 week, then 50 mg daily for 2 weeks, then 100 mg daily for 1 week, then 150 mg daily for 1 week, then 200 mg daily for 3 weeks Rescue analgesia not reported
Outcomes	Daily participant-recorded VAS for PI, shooting pain, burning pain, paraesthesia, numbness, QOL, mobility, sleep and mood. Daily analgesic consumption
Notes	18 withdrew: 8 nausea (5 placebo, 3 lamotrigine); 2 skin rash (1 lamotrigine); 2 bad taste of tablets (1 lamotrigine); 6 due to lack of analgesia (2 placebo, 4 lamotrigine). Eight failed to attend final assessment Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients randomly assigned in equal numbers to one of two groups using computer generated random number lists"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Assessors	Low risk	"patients received either lamotrigine.. . . . or identical looking dispersible placebo tablets"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	Not stated
Duration	Low risk	8-week study
Outcome	Unclear risk	VAS recorded

McCleane 1999 (*Continued*)

Treatment arm size	High risk	74 participants; placebo 38, lamotrigine 36

Rao 2008

Methods	Randomised DB placebo controlled, parallel group study. Ten-week treatment period, followed by 4-week tapered withdrawal
Participants	125 participants (63 received lamotrigine) with diagnosis of symptomatic chemotherapy-induced peripheral neuropathy > 1 month due to neurotoxic agents. Age 29 to 84 years. Average pain > 4 on NRS Excluded: participants taking drugs for treating neuropathic pain, including antiepileptics, opioids or topical analgesics at study entry; NSAIDs were permitted
Interventions	Lamotrigine or matching placebo. 25 mg once daily for 2 weeks, then 25 mg, 50 mg, 100 mg, 150 mg twice daily for 2 weeks at each dose, then 4 weeks taper down
Outcomes	Average daily pain score using NRS and ENS (Eastern Cooperative Oncology neuropathy scale)
Notes	Oxford Quality Score: R1, DB2, W1 = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	stated to be randomised
Allocation concealment (selection bias)	Unclear risk	Not statement
Blinding (performance bias and detection bias) Assessors	Low risk	"an identical appearing placebo"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	Not stated
Duration	Low risk	10 weeks
Outcome	Unclear risk	Average daily pain scores
Treatment arm size	Unclear risk	125 participants; lamotrigine 63, placebo 62

Silver 2007

Methods	Randomised DB placebo controlled, parallel group, 'add on study'. Fourteen-week treatment period consisting of 8 weeks dose escalation and 6 weeks at fixed dose, followed by 1 week tapered withdrawal
Participants	Neuropathic pain defined as DN, PHN, nerve injury, spinal cord injury, MS or HIV neuropathy. Mean age 60 years (SD 12). Mean weekly pain score > 4 on 11-point scale. Participants on stable (≥ 4 weeks) treatment with gabapentin, tricyclics or non-opioid analgesics Excluded: back and neck pain
Interventions	Lamotrigine 200 to 400 mg daily or placebo in addition to other (inadequate) treatments as above Rescue analgesia: paracetamol up to 3 g daily
Outcomes	Numerical PR (11-point), sleep interference, short form McGill, neuropathic pain scale, Patient Global Impression of Change
Notes	Oxford Quality Score: R1, DB2, W1 = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Assessors	Unclear risk	Placebo tablets were "identical in appearance"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	LOCF
Duration	Low risk	14 week treatment
Outcome	Unclear risk	Change in daily pain intensity
Treatment arm size	Unclear risk	111 participants lamotrigine, 109 placebo

Simpson 2000

Methods	Multicentre randomised DB placebo controlled, parallel study. Fourteen-week treatment period
Participants	42 participants with painful HIV associated polyneuropathy. Mean age 44 years Excluded: participants taking valproate
Interventions	Lamotrigine or placebo. Week 1 and 2 at 25 mg daily, weeks 3 and 4 at 50 mg daily, week 5 at 100 mg daily, week 6 at 100 mg twice daily, then weeks 7 to 14 at 150 mg twice daily
Outcomes	Average and peak neuropathic pain using Gracely Pain Scale. Difference in weekly mean pain scores. Pain assessed in weeks 1 and 14, also slope of change in pain scores
Notes	Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The biostatistician generated a list of treatment assignments in random order using a program written in SAS"
Allocation concealment (selection bias)	Low risk	"The biostatistician had no contact with patients nor did he communicate these to anyone other than the pharmacists' (to supply the medicines)"
Blinding (performance bias and detection bias) Assessors	Low risk	"Lamotrigine and matching placebo"
Selective reporting (reporting bias)	Unclear risk	LOCF used for part of the analysis
Missing data	High risk	Combination of LOCF and completer
Duration	Low risk	14 weeks including dose escalation
Outcome	Unclear risk	Difference in weekly mean pain scores between baseline and final week
Treatment arm size	High risk	42 participants in total at start

Simpson 2003

Methods	Randomised DB placebo controlled parallel multicentre trial. One-week screening phase, then 11-week treatment period. Randomisation stratified according to use of neurotoxic antiretroviral therapy (ART)
Participants	227 participants with HIV-associated sensory neuropathy. Age 32 to 67 years Excluded: participants with previous or current use of lamotrigine
Interventions	Lamotrigine or placebo. Weeks 1 and 2 at 25 mg on alternate days (daily if taking enzyme-inducing drugs), then dose escalation over 5 weeks to a target dose of 400 mg daily (up to 600 mg daily allowed if taking enzyme-inducing drugs), followed by 4-week maintenance phase. Concomitant medication allowed if stable (≥ 4 weeks) and unchanged Rescue analgesia: opioid and non-opioid analgesics as needed
Outcomes	Daily pain rating of average pain and worst pain on Gracely Pain Scale. VAS PI and short form McGill at end of baseline and beginning and end of maintenance phase, PGIC
Notes	Oxford Quality Score: R1, DB1, W1 = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Assessors	Unclear risk	"double blind placebo controlled"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	observed scores used - meaning unclear
Duration	Low risk	13 weeks including dose escalation
Outcome	Unclear risk	"average pain and worse pain" recorded
Treatment arm size	Unclear risk	227 participants; 150 lamotrigine, 77 placebo

Vestergaard 2001

Methods	Randomised DB placebo controlled, cross-over study. Two 8-week treatment periods, separated by 2-week washout
Participants	30 participants with central post-stroke pain with score of > 4 on an 11-point scale. Age 37 to 77 years
Interventions	Lamotrigine soluble tablets or matching placebo. Initial dose of 25 mg daily increased every 2nd week to 200 mg daily. No concomitant use of antidepressants, antiepileptics or analgesics allowed Rescue analgesia: paracetamol 500 mg as needed
Outcomes	Average daily pain score during last week of treatment (11-point Likert scale). Clinical responders defined as 2/10 reduction on lamotrigine compared with placebo period. CAT PR and CAT PI. Use of rescue medication
Notes	Oxford Quality Score: R2, DB2, W1 = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were randomised to treatment according to a computer generated randomisation list with a cluster size of six"
Allocation concealment (selection bias)	Low risk	"code envelopes were kept by the investigator during the trial and returned unopened to the monitor at the termination of the study. The blinding was maintained throughout"
Blinding (performance bias and detection bias) Assessors	Low risk	"soluble lamotrigine and identical placebo"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	High risk	Completer analysis
Duration	Low risk	Two 8-week cross-over periods
Outcome	High risk	Clinical response stated to be 2 or more points lower for lamotrigine compared to placebo
Treatment arm size	High risk	30 participants; 16 lamotrigine, 13 placebo at initial randomisation, with 20 completers

Vinik 2007a

Methods	Randomised DB placebo controlled parallel group. Nineteen-week treatment period comprising 7-week dose escalation and 12-week fixed dose maintenance phase. Study no NPP30004
Participants	360 participants with diabetic neuropathy (type1 or type 2 diabetics). Pain > 6 months and pain score > 4 on 11-point Likert scale. Mean age 59 years (SD 11)
Interventions	Lamotrigine at daily dose of 200 mg, 300 mg, 400 mg, or placebo. Dose doubled initially every 2nd week, then weekly to target dose. Concomitant gabapentin and TCAs allowed Rescue analgesia: paracetamol up to 4 g daily 91/360 received gabapentin, 17/360 received TCAs
Outcomes	Average pain intensity (11 point pain NRS). Sleep disturbance. Short form McGill
Notes	Oxford Qulaity Score: R2, DB1, W1 = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'in accordance with a computer generated randomisation schedule. A central randomisation procedure was used'
Allocation concealment (selection bias)	Low risk	'the study center called into a central system'
Blinding (performance bias and detection bias) Assessors	Unclear risk	stated to be double blind
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	LOCF
Duration	Low risk	Seven week dose escalation and 12 weeks fixed dose
Outcome	Low risk	50% reduction in pain intensity
Treatment arm size	Unclear risk	360 participants; 90 patients randomised per group

Vinik 2007b

Methods	Randomised DB placebo controlled parallel group. Nineteen week treatment period comprising 7 week dose escalation and 12 week fixed dose maintenance phase. Study no NPP30005
Participants	360 participants with diabetic neuropathy (type 1 or type 2 diabetics). Pain > 6 months and pain score > 4 on 11 point Likert scale. Mean age 60 years (SD 11). Gabapentin and TCAs allowed. Paracetamol as rescue
Interventions	Lamotrigine at daily dose of 200 mg, 300 mg, 400 mg, or placebo. Dose doubled initially every 2nd week, then weekly to target dose. Concomitant gabapentin and TCAs allowed Rescue analgesia: paracetamol up to 4 g daily 76/360 received gabapentin, 23/360 received TCAs
Outcomes	Average pain intensity (11-point pain NRS). Sleep disturbance. Short form McGill Greater than 50% reduction in average pain intensity
Notes	Oxford Quality Score: R2, DB1, W1 = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"in accordance with a computer generated randomisation schedule. A central randomisation procedure was used"
Allocation concealment (selection bias)	Low risk	"the study center called into a central system"
Blinding (performance bias and detection bias) Assessors	Unclear risk	stated to be double blind
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	LOCF
Duration	Low risk	7-week dose escalation and 12 weeks fixed dose
Outcome	Low risk	50% reduction in pain intensity
Treatment arm size	Unclear risk	360 participants; 90 randomised per group

Zakrzewska 1997

Methods	Randomised DB placebo controlled, cross-over, 'add on study'. Two 2-week treatment periods separated by 3-day washout. Lamotrigine added to existing antiepileptic treatment
Participants	14 participants with refractory trigeminal neuralgia. Age 44 to 75 (mean 60 years)
Interventions	Lamotrigine or placebo added to existing stable regimen of carbamazepine or phenytoin, or both. Day 1 at 50 mg, day 2 at 100 mg, day 3 at 200 mg, then days 4 to 14 at 400 mg Rescue analgesia: increased dose of carbamazepine or phenytoin used for uncontrollable pain
Outcomes	No of pain paroxysms. CAT PI, CAT PR and global assessment at the end of each treatment period
Notes	Oxford Quality Score: R1, DB2, W1 = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Assessors	Low risk	"dispersible lamotrigine and identical placebo"
Selective reporting (reporting bias)	Unclear risk	Not stated
Missing data	Unclear risk	unclear
Duration	High risk	2 weeks per arm
Outcome	Unclear risk	composite efficacy index
Treatment arm size	High risk	14 participants

AEs = adverse effects, DB = double blind, CAT PI = categorical scale of pain intensity, CAT PR = categorical scale of pain relief, LOCF = last observation carried forward, NNTB = number needed to treat for an additional beneficial outcome, NRS = numerical rating scale, NSAID = non-steroidal anti-inflammatory drug, PI = pain intensity, QOL = quality of life, R = randomisation, TCA = tricyclic antidepressant, VAS = visual analogue scale, W = withdrawals

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

Study	Reason for exclusion
Bonicalzi 1997	Pre-emptive study but all participants also received a known analgesic-buprenorphine
Breuer 2007	RCT of multiple sclerosis pain. Not neuropathic pain
Carrieri 1998	Case study
Devulder 2000	Survey not RCT
Di Vadi 1998	Case report only
Eisenberg 1998	Not randomised
Eisenberg 2003	Not randomised
Eisenberg 2005	Review article
Lunardi 1997	Case series
Petersen 2003	RCT but healthy volunteers
Sandner-Kiesling 2002	Case report
Shaikh 2011	Not randomised or double blind

DATA AND ANALYSES

Comparison 1. Painful diabetic neuropathy: lamotrigine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% pain relief	3	773	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.42]

Comparison 2. All conditions: lamotrigine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least one adverse event	7	1121	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.01, 1.22]
2 Rash	12	1715	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.01, 2.03]

Analysis 1.1. Comparison 1 Painful diabetic neuropathy: lamotrigine versus placebo, Outcome 1 50% pain relief.

Review: Lamotrigine for chronic neuropathic pain and fibromyalgia in adults

Comparison: 1 Painful diabetic neuropathy: lamotrigine versus placebo

Outcome: 1 50% pain relief

Study or subgroup	Lamotrigine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Eisenberg 2001	12/27	5/26		7.0 %	2.31 [0.95, 5.65]
Vinik 2007a	67/270	24/90		49.6 %	0.93 [0.62, 1.39]
Vinik 2007b	66/270	21/90		43.4 %	1.05 [0.68, 1.61]
Total (95% CI)	**567**	**206**		**100.0 %**	**1.08 [0.82, 1.42]**

Total events: 145 (Lamotrigine), 50 (Placebo)

Heterogeneity: $Chi^2 = 3.33$, df = 2 (P = 0.19); $I^2 = 40\%$

Test for overall effect: Z = 0.53 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 All conditions: lamotrigine versus placebo, Outcome 1 At least one adverse event.

Review: Lamotrigine for chronic neuropathic pain and fibromyalgia in adults

Comparison: 2 All conditions: lamotrigine versus placebo

Outcome: 1 At least one adverse event

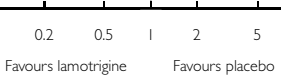
Study or subgroup	Lamotrigine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Eisenberg 2001	17/27	21/26		7.2 %	0.78 [0.55, 1.10]
Finnerup 2002a	13/27	14/28		4.6 %	0.96 [0.56, 1.65]
Silver 2007	79/111	61/109		20.8 %	1.27 [1.04, 1.56]
Vestergaard 2001	17/30	18/30		6.1 %	0.94 [0.62, 1.45]
Vinik 2007a	206/267	62/88		31.5 %	1.10 [0.94, 1.27]
Vinik 2007b	192/265	54/86		27.5 %	1.15 [0.96, 1.38]
Zakrzewska 1997	7/13	7/14		2.3 %	1.08 [0.52, 2.23]
Total (95% CI)	**740**	**381**		**100.0 %**	**1.11 [1.01, 1.22]**

Total events: 531 (Lamotrigine), 237 (Placebo)

Heterogeneity: $Chi^2 = 6.77$, df = 6 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 All conditions: lamotrigine versus placebo, Outcome 2 Rash.

Review: Lamotrigine for chronic neuropathic pain and fibromyalgia in adults

Comparison: 2 All conditions: lamotrigine versus placebo

Outcome: 2 Rash

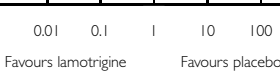
Study or subgroup	Lamotrigine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Eisenberg 2001	2/27	0/26		1.0 %	4.82 [0.24, 95.88]
Finnerup 2002a	0/27	1/28		3.0 %	0.35 [0.01, 8.12]
Jose 2007	3/46	0/46		1.0 %	7.00 [0.37, 131.81]
McCleane 1999	1/50	1/50		2.0 %	1.00 [0.06, 15.55]
Rao 2008	3/63	0/62		1.0 %	6.89 [0.36, 130.69]
Silver 2007	11/111	7/109		14.3 %	1.54 [0.62, 3.83]
Simpson 2000	5/20	0/22		1.0 %	12.05 [0.71, 204.97]
Simpson 2003	21/150	9/77		24.1 %	1.20 [0.58, 2.49]
Vestergaard 2001	2/27	2/27		4.0 %	1.00 [0.15, 6.59]
Vinik 2007a	21/270	8/90		24.3 %	0.88 [0.40, 1.91]
Vinik 2007b	33/270	8/90		24.3 %	1.38 [0.66, 2.87]
Zakrzewska 1997	0/13	0/14			Not estimable
Total (95% CI)	**1074**	**641**		**100.0 %**	**1.43 [1.01, 2.03]**

Total events: 102 (Lamotrigine), 36 (Placebo)

Heterogeneity: Chi^2 = 7.81, df = 10 (P = 0.65); I^2 =0.0%

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

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Methodological considerations in chronic pain

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

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

Appendix 2. MEDLINE search strategy

1. (pain* or analgesi* or neuralgi* or headache* or toothache* or earache* or sciatica or causalgi* or arthralgi* or colic* or dysmenorrhoea or dysmenorrhea).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. (lamotrigin* or lamictal* or lamictin* or neurium* or labileno or crisomet).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. *lamotrigine/
4. 3 or 2
5. 4 and 1
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. drug therapy.fs.
11. randomly.ab.
12. trial.ab.
13. groups.ab.
14. or/6-13
15. (animals not (humans and animals)).sh.
16. 14 not 15
17. 16 and 5

Appendix 3. EMBASE (via OVID) search strategy

1. (pain* or analgesi* or neuralgi* or headache* or toothache* or earache* or sciatica or causalgi* or arthralgi* or colic* or dysmenorrhoea or dysmenorrhea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2. (lamotrigin* or lamictal* or lamictin* or neurium* or labileno or crisomet).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. *lamotrigine/
4. 2 or 3
5. 1 and 4
6. 4 and 5
7. random$.tw.
8. factorial$.tw.
9. crossover$.tw.
10. cross over$.tw.
11. cross-over$.tw.
12. placebo$.tw.
13. (doubl$ adj blind$).tw.
14. (singl$ adj blind$).tw.
15. assign$.tw.
16. allocat$.tw.
17. volunteer$.tw.
18. Crossover Procedure/
19. double-blind procedure.tw.
20. Randomized Controlled Trial/
21. Single Blind Procedure/
22. 1or/7-15
23. (animal/ or nonhuman/) not human/
24. 16 not 17
25. 6 and 18

Appendix 4. CENTRAL search strategy

1. (lamotrigin* OR lamictal* Or lamictin* OR neurium* OR labileno OR crisomet):ti,ab,kw
2. (pain* OR analgesi* OR neuralgi* or headache* OR toothache* OR earache* OR sciatica OR causalgi* OR arthralgi* OR colic* OR dysmenorrhoea or dysmenorrhea):ti,ab,kw
3. (#1 AND #2)
4. (#3 AND CENTRAL)

Appendix 5. Results in individual studies

Study ID	Maximum daily dose of lamotrigine Titration/fixed	Comparator Numbers in trial	Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
Central post-stroke pain						

(*Continued*)

Vestergaard 2001	Lamotrigine titrated from 25 mg daily to 200 mg daily. Cross-over at 8 weeks. 2-week washout	Placebo N = 30	lamotrigine 4 (3 due to AEs, 1 lack of efficacy); placebo 4 (3 lack of efficacy, 1 protocol violation)	'Responders' on lamotrigine 200 mg 12/27 No difference 12/27 Lower pain scores on placebo 3/27 lamotrigine up to 100 mg no different from placebo	Any AE: lamotrigine 17/30 placebo 18/30 10 participants reported AEs during washout period	3 participants on lamotrigine withdrew (rash, headache and severe pain) . 5 participants had skin-related AEs with lamotrigine and 2 with placebo
Chemotherapy-induced peripheral neuropathy						
Rao 2008	Lamotrigine titrated up to 150 mg twice daily over 10 weeks then 4 weeks taper down	Placebo N = 125	lamotrigine 29 withdrew (13 refusals, 7 due to AEs, 9 other); placebo 16 withdrew (10 refusals, 1 AE, 5 other)	Small reduction in 11-point Likert pain scale of less than one point in both groups. No difference between groups	AEs "occurred at relatively equivalent rates in both groups"	Mainly dizziness and fatigue. 3 on lamotrigine reported skin rash of ≥ grade 2 severity; none with placebo
Diabetic Neuropathy						
Eisenberg 2001	Dose titrated from 25 mg daily up to 400 mg daily	Placebo N = 59 (46 completed)	lamotrigine 5/29 (2 rash, 3 other); placebo 8/30 (2 AE, 6 other)	50% reduction in pain measured in final 3 weeks of treatment: lamotrigine 12/27, placebo 5/26 (not ITT); Global assessment: 'highly effective' lamotrigine 7/22, placebo 2/21 'moderate or better' lamotrigine 16/22, placebo 9/21	Any AE: lamotrigine 17/27 placebo 21/26	Most common: nausea, drowsiness and dizziness Withdrew: lamotrigine 2/27 (rash) placebo 2/26 (1 impotence, 1 diarrhoea)
Jose 2007	Dose titration up to 100 mg twice daily over 6 weeks. Cross-over with	Amitriptyline up to 50 mg at night N = 53	6 did not attend for 1st visit and 1 for 2nd visit	≥ 50% reduction on VAS global assessment (good improvement)	11 events in participants with lamotrigine, 33 with amitriptyline	3 participants developed rash with lamotrigine

(*Continued*)

	2 weeks washout			: lamotrigine 19/46, amitriptyline 13/46; Increased sleep: lamotrigine 0/46, amitriptyline 19/46		
Vinik 2007a	Dose titration over 7 weeks to max in assigned group (200 mg, 300 mg, 400 mg)	Placebo N = 360	All: lamotrigine 200 mg 10/90, 300 mg 10/90, 400 mg 15/90, placebo 5/90; AE withdrawals: lamotrigine 200 mg 2/90, 300 mg 5/90, 400 mg 9/90, placebo 2/90	50% or greater reduction in pain intensity: lamotrigine 200 mg 21/90, 300 mg 30/90, 400 mg 16/90, placebo 24/90 Not significant	Any AE: lamotrigine (all doses) 206/267 placebo 62/88	Most common: Headache: lamotrigine 40/267 placebo 3/88; Rash: lamotrigine 31/267 placebo 8/88
Vinik 2007b	Dose titration over 7 weeks to max in assigned group (200 mg, 300 mg, 400 mg)	Placebo N = 360	All: lamotrigine 200 mg 10/90, 300 mg 9/90, 400 15/90, placebo 9/90; AE withdrawals: lamotrigine 200 mg 10/90, 300 mg 9/90, 400 15/90, placebo 9/90	50% or greater reduction in pain intensity: lamotrigine 200 mg 22/90, 300 mg 22/90, 400 mg 22/90, placebo 21/90 Not significant	Any AE: lamotrigine (all doses) 192/265 placebo 54/86	Most common: Headache: lamotrigine 47/265 placebo 6/86; Rash: lamotrigine 33/265 placebo 8/86
HIV-related neuropathy						
Simpson 2000	Lamotrigine titrated by 25 mg doses to 300 mg at 7 weeks	Placebo N = 42	lamotrigine 11/20 (6 AE, 5 lost to follow-up); placebo 3/22 (2 personal reason, 1 lost to follow-up)	Large dropout- only 9 completed in lamotrigine group. Higher falls in pain scores in lamotrigine group	Not reported	lamotrigine 6/20 (5 rash, 1 GI infection)
Simpson 2003	Lamotrigine titrated by 25 mg every other day to a target of 400 mg/day	Placebo N = 227	lamotrigine 34/150 (10 AE, 6 withdrew consent, 8 lost to follow-up, 8 protocol violations, 2 other);	Moderate or better pain relief (> 30%): Participants receiving ART: lamotrigine 35/62 (57%)	87 events with lamotrigine (150 participants) 39 with placebo (77 participants)	Most common: lamotrigine events (causing withdrawal): rash 21 (2), infection 17, nausea 17 (1)

(*Continued*)

			placebo 21/77 (7 AE, 1 withdrew consent, 4 lost to follow-up, 5 protocol violations, 4 other)	, placebo 7/30 (23%); Participants not receiving ART: lamotrigine 46/88 (52%) (> 30%), placebo 21/47 (45%); For PGIC (marked improvement) : lamotrigine 76/150, placebo 34/77 (29/62 vs 4/30 ART group)		, diarrhoea 16, headache 16 (1); placebo events (causing withdrawal): rash 9 (1), infection 7, nausea 8 (1), diarrhoea 7 (1), headache 8
Mixed neuropathic pain						
McCleane 1999	Lamotrigine titrated to 200 mg daily. Study duration 8 weeks	Placebo N = 100	lamotrigine 14 (10 AE, 4 lack of efficacy); placebo 8 (6 AE, 2 lack of efficacy) . 8 participants refused to attend the end of study review	No participants achieved 50% pain relief	No further data available	Withdrawals: lamotrigine (3 nausea, 2 skin rash, 1 bad taste) ; placebo (5 nausea, 1 bad taste)
Silver 2007	Lamotrigine 200 - 400 mg daily titrated over 8 weeks then 6 week fixed dose. Add-on study to existing (inadequate) treatment	Placebo N = 220	lamotrigine 47/111 (28 due to AEs); placebo 31/109 (11 due to AEs)	No statistically significant difference between lamotrigine or placebo in mean change in pain intensity between baseline and week 14	Any AE: lamotrigine 79/111 placebo 61/109	Most common: Rash: lamotrigine 20/111 placebo 14/109; Dizziness: lamotrigine 10/111 placebo 11/109; Somnolence: lamotrigine 7/111 placebo 2/109
Spinal cord injury						
Finnerup 2002a	Lamotrigine 400 mg titrated over 8 weeks. Cross-over study with 2	Placebo N = 30	lamotrigine 3/15 (1 AE, 1 new trauma, 1 left country);	No significant difference between groups for 50%	Any AE: lamotrigine 13/27 placebo 14/28	Most common (events): CNS: lamotrigine 12/

(*Continued*)

	weeks washout		placebo 5/15 (2 AE, 1 consent withdrawn, 1 protocol violation, 1 escape medication)	or 30% pain relief, though authors claim benefit in subgroup who had incomplete SCI. ? post hoc analysis		27 placebo 9/28; Skin: lamotrigine 4/27 placebo 4/28; GI: lamotrigine 4/27 placebo 3/8; 1 placebo patient withdrew due to rash
Trigeminal neuralgia						
Zakrzewska 1997	Lamotrigine 400 mg titrated up over 4 days. Cross-over. 2 weeks treatment, 1 week washout then 2 weeks treatment. Add-on study in participants also receiving either carbamazepine or phenytoin	Placebo N = 14	One placebo participant on day 14 (uncontrolled pain)	7/14 claimed to be 'much better' with lamotrigine, 1/14 with placebo ; 10/13 'better or much better' with lamotrigine, 8/14 with placebo	Any AE: lamotrigine 7/13 placebo 7/14	Most common (events): Dizziness: lamotrigine 5 placebo 1; GI: lamotrigine 8 placebo 3; No skin rash reported

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

Protocol first published: Issue 2, 2006

Review first published: Issue 2, 2007

Date	Event	Description
31 May 2016	Review declared as stable	See Published notes.
27 August 2013	New search has been performed	New searches run in November 2013 identified no new studies for inclusion, but did find a small amount of additional data for one study that was already included (Silver 2007), and one additional excluded study (Shaikh 2011). We have updated the Background section and made minor changes to the Methods, in line with a standard protocol for antiepileptic drugs for neuropathic pain and fibromyalgia. A new analysis of participants experiencing any adverse event has been added. We have also included a PRISMA flow chart and 'Summary of findings' table Title changed from 'Lamotrigine for acute and chronic pain' in order to conform with other reviews in the series on neuropathic pain and fibromyalgia, since there is little or no use or intended use of lamotrigine and similar drugs in acute pain, or other forms of chronic pain
27 August 2013	New citation required but conclusions have not changed	The conclusions of the review are unchanged.
18 January 2011	New search has been performed	Five new studies (Jose 2007; Rao 2008; Silver 2007; Vinik 2007a; Vinik 2007b) were added with 1111 additional participants, increasing substantially the amount of information on this drug and further confirming its conclusions
18 January 2011	New citation required but conclusions have not changed	This review update involves new authors and up to date methodology to confirm the conclusions. It is unlikely that the conclusions of this review will change in the foreseeable future
30 October 2008	Amended	Dates section corrected
7 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All authors contributed equally to updating this review.

DECLARATIONS OF INTEREST

SD and PW have received research support from charities, government and industry sources at various times, but none relate to this review.

RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions, including (in the past five years) AstraZeneca, Eli Lilly, Flynn Pharma, Furtura Medical, Grünenthal, GSK, Horizon Pharma, Lundbeck, Menarini, MSD, Pfizer, Reckitt Benckiser, Sanofi Aventis, Urgo, Astellas, and Vifor Pharma.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support for the original review and updates

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The updated review conforms to more stringent evidence standards than those pertaining at the time of the original protocol.

NOTES

A restricted search in May 2016 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Analgesics [*therapeutic use]; Anticonvulsants [therapeutic use]; Chronic Disease; Fibromyalgia [*drug therapy]; Lamotrigine; Neuralgia [*drug therapy]; Randomized Controlled Trials as Topic; Triazines [*therapeutic use]

MeSH check words

Adult; Humans