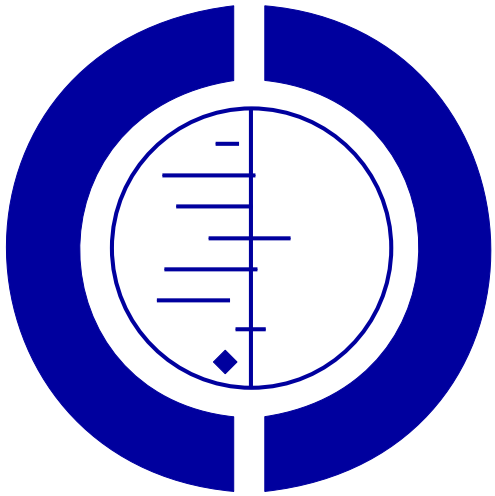
Lamotrigine for acute and chronic pain (Review)

Wiffen PJ, Rees J



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ABSTRACT

Background
Anticonvulsant medicines have a place in the treatment of neuropathic pain (pain due to nerve damage). This review looks at the evidence for the pain relieving properties of lamotrigine.

Objectives
To assess the analgesic efficacy and adverse effects of the anticonvulsant lamotrigine for acute and chronic pain.

Search strategy
Randomised Controlled Trials (RCTs) of lamotrigine (and key brand names Lamictal, Lamictin, Neurium) in acute, chronic or cancer pain were identified from MEDLINE (1966 to August 2006), EMBASE 1994 to August 2006 and the CENTRAL register on *The Cochrane Library* (Issue 3, 2006). Additional reports were sought from the reference list of the retrieved papers.

Selection criteria
RCTs investigating the use of lamotrigine (any dose and by any route) for treatment of acute or chronic pain. Assessment of pain intensity or pain relief, or both, using validated scales. Participants were adults aged 18 and over. Only full journal publication articles were included.

Data collection and analysis
Dichotomous data were used to calculate relative risk with 95% confidence intervals using a fixed effects model unless significant statistical heterogeneity was found. Continuous data was also reported where available. Meta-analysis was undertaken using a fixed effect model unless significant heterogeneity was present (I^2 >50%) in which case a random effects model was used. Numbers-needed-to-treat (NNTs) were calculated as the reciprocal of the absolute risk reduction. For unwanted effects, the NNT becomes the number-needed-to-harm (NNH) and was calculated.

Main results
Sixteen studies were identified. Nine studies were excluded. No studies for acute pain were identified. The seven included studies involved 502 participants, all for neuropathic pain. The studies covered the following conditions: central post stroke pain (1), diabetic neuropathy (1), HIV related neuropathy (2), intractable neuropathic pain (1), spinal cord injury related pain (1) and trigeminal neuralgia (1). The studies included participants in the age range of 26 to 77 years. Only one study for HIV related neuropathy had a statistically significant result for a sub group of patients on anti-retroviral therapy; this result is unlikely to be clinically significant NNT 4.3 (95% CI 2.3 to 37). Approximately 7% of participants taking lamotrigine reported a skin rash.

Authors' conclusions
Given the availability of more effective treatments including anticonvulsants and antidepressant medicines, lamotrigine does not have a significant place in therapy at present. The limited evidence currently available suggests that lamotrigine is unlikely to be of benefit for the treatment of neuropathic pain.

PLAIN LANGUAGE SUMMARY

Lamotrigine is unlikely to be of benefit in chronic pain conditions included in this review, or neuropathic pain (pain due to nerve damage).

Nerves which have been damaged by injury or a disease process, or both, can continue to produce pain. Some anticonvulsant drugs can help in this type of neuropathic pain, but limited evidence shows that lamotrigine is not effective in this type of pain. Serious skin reactions occurred in some patients. No studies were found in acute pain.

BACKGROUND

Pain is complex both in terms of nerve mechanisms but also psychological perceptions. It is usually classified as acute pain which activates normal pain pathways or chronic pain generally considered to be pain lasting for longer than three months. Chronic pain can also be due to nerve damage which is known as neuropathic pain, or to underlying disease including cancer. Chronic pain is a major health problem affecting one in five people in Europe (Pain in Europe 2004; Breivik 2006), though data to determine the incidence of neuropathic pain are more difficult to obtain. Anticonvulsant drugs have been used in pain management since the 1960s, very soon after they were first used in medicine. The clinical impression is that they are useful for neuropathic pain, especially when the pain is lancinating or burning (Jacox 1994). Although neuropathic pain disorders are not common (the incidence of trigeminal neuralgia is four in 100,000 per year (Katusic 1991; Rappaport 1994)), they can be particularly disabling. Recent data suggests a higher incidence of neuropathic pain in the UK of 26 per 100,000 (Hall 2006). There is evidence for the effectiveness of a number of anticonvulsants; these are considered in other reviews published by the Cochrane Pain, Palliative and Supportive Care group through *The Cochrane Database of Systematic Reviews* (Wiffen 2005a; Wiffen 2005b; Wiffen 2005c). Anticonvulsants are sometimes prescribed in combination with antidepressants, as in the treatment of post-herpetic neuralgia (Monks 1994). In the UK carbamazepine and phenytoin are licensed for the treatment of pain associated with trigeminal neuralgia, and gabapentin and pregabalin for the treatment of neuropathic pain. Lamotrigine is also being used for chronic pain but is not licensed in Europe for this condition.

Lamotrigine is a new generation antiepileptic drug exerting its anticonvulsant 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 animal model evidence for lamotrigine use in neuropathic pain and for effect in experimental pain models such as cold induced pain in humans (McCleane 2000). Lamotrigine is chemically unrelated to existing anticonvulsant agents. There has also been discussion of the role of lamotrigine as a pre-emptive analgesic to reduce postsurgical pain (Bonicalzi 1997).

This review is an extension to the published review in the Cochrane Database of Systematic Reviews on Anticonvulsants in acute and chronic pain (Wiffen 2005a).

OBJECTIVES

1. To assess the analgesic efficacy of lamotrigine in acute and chronic pain.
2. To assess the adverse effects associated with the clinical use of lamotrigine for pain.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Reports were included in this review if they were randomised controlled trials (RCTs) which investigated the analgesic effects of lamotrigine in patients, with pain assessment as either the primary or secondary outcome. Full journal publication was required, abstracts were not included. Studies which were non-randomised, studies of experimental pain, case reports, clinical observations or studies of lamotrigine used to treat pain produced by other drugs were also excluded.

Types of participants

Adult participants aged 18 years and above were included. Participants complaining of pain in either the acute pain setting or suffering from a wide range of neuropathic pains including: diabetic neuropathy, HIV neuropathy, post-herpetic neuralgia, phantom limb pain, trigeminal neuralgia, Guillain Barré, and spinal cord injury were included. Trials of participants with more than one type of neuropathic pain were also included.

Types of intervention

Administration of lamotrigine, in any dose, by any route to achieve analgesia.

Types of outcome measures

Data was sought for the following:

- pain condition,

- number of patients studied,
- anticonvulsant drug and dosing regimen,
- study design (placebo or active control),
- study duration and follow-up,
- analgesic outcome measures and results,
- withdrawals,
- adverse effects (minor and major).

A variety of outcome measures were used in the studies, the majority using standard subjective scales for pain intensity or pain relief, or both. A hierarchy of outcome measures was agreed as follows:
1. patient reported pain relief of 50% or greater;
2. patient reported global impression of clinical change;
3. pain on movement, pain on light touch;
4. pain on rest;
5. any other pain related measure;
6. adverse effects with a sub group analysis of the elderly if data were available.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

Reports were identified by several methods. RCTs of lamotrigine (and key brand names Lamictal, Lamictin, Neurium) in acute, chronic or cancer pain were identified using:
MEDLINE from 1966 to August 2006;
EMBASE 1994 to August 2006;
The Cochrane Library (Issue 3, 2006).

Additional reports were identified from the reference list of the retrieved papers, and by contacting investigators. Given the limited literature in this area, a sensitive search strategy was undertaken as follows:
#1 Exp PAIN/
#2 pain*
#3 Exp ANALGESIA/
#4 analges*
#5 neuralgi* or sciatica or headache* or colic* or toothache* OR earache* OR dysmenorrhoea or dysmenorrhoea or arthralgi*
#6 lamotrigine OR lamotrigina OR lamictal* Or lamictin* OR neurium* OR lamictala OR labileno OR crisomet
#7 #1 OR #2 OR #3 OR #4 OR #5
#8 #6 AND #7

METHODS OF THE REVIEW

- Eligibility was determined by reading each report identified by the search. All reports were read by both review authors and agreement was reached by discussion. Only reports of randomised trials were included. The reports were not anonymised in any way prior to assessment. Intention-to-treat analysis was carried out. Studies were not pre-selected using abstracts as the number of studies was low.
- Numbers-needed-to-treat (NNTs) were calculated as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNT becomes the number-needed-to-harm (NNH), and is calculated in the same way.
- Dichotomous data were used to calculate relative risk with 95% confidence intervals using a fixed effects model unless significant statistical heterogeneity was found (see below). Continuous data (if available) was also entered into RevMan using the appropriate statistic.
- Meta-analysis was undertaken using a fixed effect model unless significant heterogeneity was present (I^2 >50%) in which case a random effects model was used.
- Studies were assessed for quality using the Oxford Quality Scale (Jadad 1996). Sub group analysis was undertaken for adverse effects in the elderly where data were available .

DESCRIPTION OF STUDIES

Sixteen studies were identified. Nine studies were excluded (see 'Characteristics of excluded studies') (Bonicalzi 1997b; Carrieri 1998; Devulder 2000; di Vadi 1998; Eisenberg 1998; Eisenberg 2003; Lunardi 1997; Petersen 2003; and Sandner-Kiesling2002). There were seven included studies which involved 502 participants ((Eisenberg 2001; Finnerup 2002; McCleane 1999; Simpson 2000; Simpson 2003; Vestergaard 2001; Zakrzewska 1997).

The included studies covered the following conditions: central post stroke pain (Vestergaard 2001), diabetic neuropathy (Eisenberg 2001), HIV related neuropathy (Simpson 2000; Simpson 2003), intractable neuropathic pain (McCleane 1999), spinal cord injury related pain (Finnerup 2002) and trigeminal neuralgia (Zakrzewska 1997). The studies included participants in the age range of 26 to 77 years. Details of all eligible reports are given in the 'Characteristics of included studies'.

METHODOLOGICAL QUALITY

Each report was scored for quality using the three-item Oxford Quality Score scale and agreed by the review authors (Jadad 1996). The quality scores for individual trials are reported in the notes section of 'Characteristics of Included Studies' table. These scores were not used to weight the results in any way. Five studies scored five, one scored four and one scored three. Most of the studies were small and only one study (Simpson 2003) had more than 100 participants. This together with the fact that generally there is only one study for each condition means that results at best show weak evidence to support the effect of lamotrigine.

RESULTS

One study (Bonicalzi 1997b) examined the use of Lamotrigine for acute pain but this was excluded as all patients were given buprenorphine, a potent analgesic.

The seven included studies covered the following conditions: central post stroke pain (Vestergaard 2001), diabetic neuropathy (Eisenberg 2001), HIV related neuropathy (Simpson 2000; Simpson 2003), intractable neuropathic pain (McCleane 1999), spinal cord injury related pain (Finnerup 2002) and trigeminal neuralgia (Zakrzewska 1997).

Central post stroke pain
Thirty participants took part in this crossover study (Vestergaard 2001). The difference between lamotrigine 200 mg and placebo for clinical response was significant when assessed at eight weeks. Relative risk (RR) was 4 (1.3 to 12.6); NNT was 3 (1.8 to 9). The definition of clinical response was at least two points improvement on an 11 point Likert scale, a modest level of improvement.

Diabetic neuropathy
Fifty nine participants with at least six months pain due to diabetic neuropathy were included (Eisenberg 2001). The authors reported a positive result, but the confidence intervals are wide and the NNT for a global impression of 'highly effective' was not significant. A 50% reduction in pain intensity was achieved by 12/27 lamotrigine and 5/26 placebo patients (RR not significant), for global impression of moderate or better improvement; RR 1.7 (0.97 to 3 (not significant)) NNT 3 (2 to 59 (not significant)). These results indicate that lamotrigine is not effective.

HIV related neuropathy (Simpson 2000; Simpson 2003)
The first study of 42 participants (Simpson 2000) claimed effectiveness for lamotrigine 300 mg/day but over 50% of the group dropped out making results difficult to interpret. The second study (Simpson 2003) analysed the results by sub groups of either receiving antiretroviral therapy (ART) or not. However, only one group demonstrated a significant result for moderate or better pain relief; the ART group had an RR of 2.0 (1.1 to 3.6 (statistically significant)); an NNT of 4.3 (2.3 to 37). The non-ART RR was 1.3 (0.94 to 1.9 (not significant)) and the NNT was not significant.

Intractable neuropathic pain (McCleane 1999)
This study of 100 participants examined the use of lamotrigine 200 mg in patients with intractable neuropathic pain diagnosed by symptoms of shooting/lancinating pain, burning, numbness, allodynia and paraesthesia/dysaesthesia. At least three of these symptoms were required for participation. Patients already taking an anticonvulsant were excluded. No useful analgesic benefit was demonstrated. There was a reduction in the overall pain score of 1 mm. A calculated NNT was not statistically significant.

Spinal cord injury related pain (Finnerup 2002)
Thirty patients with neuropathic pain following traumatic spinal cord injury were included. Doses of up to 400 mg daily for lamotrigine were used but the study authors reported no significant effects on pain intensity.

Trigeminal neuralgia (Zakrzewska 1997)
Fourteen patients participated in a crossover study comparing Lamotrigine or placebo in a crossover study of two two-week phases with a three day long washout. All participants continued on carbamazepine or phenytoin throughout the study period. Lamotrigine was slightly more effective than placebo in this small study (RR not significant). 10/13 stated that Lamotrigine was better or much better, 8/14 on placebo claimed their treatment was better, or much better, using a global evaluation

Adverse effects
These were not consistently reported across studies. It was not possible to determine the incidence of mild and severe adverse effects. Rash can be problematic with lamotrigine and in the seven included studies 35 cases of rash due to lamotrigine were reported, an incidence of approximately 7%. The incidence of rash may be related to the rate of dose escalation but this cannot be determined in these studies. Some studies were of short duration and so there may have been insufficient time for a rash to develop. Other important symptoms included drowsiness, headache and insomnia, these were not greater in the lamotrigine group compared to placebo.

DISCUSSION

Anticonvulsant drugs have demonstrated a role in the treatment of neuropathic pain since carbamazepine was first used for trigeminal neuralgia in the 1960s. Subsequently other drugs in the class have been used so that gabapentin is now widely used and other drugs such as valproate and pregabalin are considered to have a role in neuropathic pain (Wiffen 2005a; Wiffen 2005b; Wiffen 2005c). It was therefore inevitable that lamotrigine should also be investigated.

There is some evidence for effect of lamotrigine in central post stroke pain and in a subgroup of HIV related neuropathy who also received antiretroviral therapy. No benefit was demonstrated for diabetic neuropathy in intractable neuropathic pain, spinal cord injury or trigeminal neuralgia. The small number of studies and the small number of participants is insufficient to provide robust evidence for effect. This together with the difficulties of dose titration and adverse effects are likely to dissuade many clinicians from choosing lamotrigine to treat neuropathic pain. It is possible that those running the study trials have chosen to include the more difficult patients in terms of severity and duration of pain, nevertheless, while neuropathic pain is difficult to manage there are more effective and safer medicines available (Wiffen 2005c).

Adverse effects
Safety is an important aspect of the choice of treatment even in difficult conditions. In this review, approximately 7% of partici-

pants 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 one in 1000 (SPC 2007).

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. 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 anticonvulsant drugs and antidepressants in the treatment of acute and chronic pain and therefore there is probably no justification for further research given the lack of evidence and the potential for harm due to skin rash which can occasionally be serious.

POTENTIAL CONFLICT OF INTEREST

No identified conflicts of interest

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Pain Research Oxford UK

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TABLES

Characteristics of included studies

Study	**Eisenberg 2001**
Methods	Randomised DB, placebo controlled study for 11 weeks. Seven day screening phase, eight week treatment phase, two week post treatment phase
Participants	59 participants with painful diabetic neuropathy (Age 50 to 60 years). Participants who had received anticonvulsants or antidepressants for reasons other than pain and those who had received opioids were excluded
Interventions	Lamotrigine 25 mg dispersible tablets or matching placebo. 25 mg daily for two weeks, 50 mg daily for two weeks then 100 mg, 200 mg, 300 mg and 400 mg - one week at each dose level. Rescue analgesia as paracetamol, dipyrone or NSAIDs
Outcomes	Daily pain intensity, McGill, Beck depression, Pain disability index, Global assessment. Results. 50% reduction in pain measured in last three weeks of treatment; lamotrigine 12/27, placebo 5/26. Global assessment: a) highly effective lamotrigine 7/22, placebo 2/21; moderate or better lamotrigine 16/22 placebo 9/21
Notes	2/27 withdrew on lamotrigine (rash), 2/26 withdrew on placebo (one impotence, one diarrhoea) 17 participants reported AEs in lamotrigine group, 21 in placebo QS = 5
Allocation concealment	D – Not used

Study	**Finnerup 2002**
Methods	Randomised DB placebo controlled crossover study. One week baseline assessment, two nine week treatment periods separated by two week washout
Participants	30 participants with neuropathic pain after traumatic spinal cord injury (SCI). Age 27 to 63 years
Interventions	Dose escalation to 400 mg a day. Weeks one and two 25 mg daily, weeks two and four 50 mg, one week each at 100 mg, 200 mg, and 300 mg then 2/52 at 400 mg. Treatment with spasmolytics, sedatives and simple analgesics allowed. Paracetamol up to 3G per day as rescue
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 Results. No significant effect on PI. Median change in pain score on placebo was 0 and on lamotrigine 1. Authors claim some response among pts with incomplete spinal lesions. Very few patients obtained >50% pain relief and NNT was not statistically significant
Notes	Eight dropped out after randomisation. Four discontinued treatment early (two after eight weeks on placebo and two after seven weeks on lamotrigine). Data missing for one participant.

	13/27 reported AEs on lamotrigine, 14/28 on placebo One dropout (placebo phase) due to rash. QS = 5
Allocation concealment	D – Not used

Study	**McCleane 1999**
Methods	Randomised DB, placebo controlled study for 56 days
Participants	100 participants with intractable neuropathic pain. Mean age placebo group 4.7 years, treatment group 47.1 years. All had failed on codeine or NSAID based analgesics. Those on anticonvulsants excluded. Mean age 45 years
Interventions	Lamotrigine 25 mg dispersible tablets or matching placebo. One tab daily for 14 days, then two daily for 14 days then four daily for seven days, then six daily for seven days then eight daily until day 56
Outcomes	Daily patient recorded VAS for PI, shooting pain, burning pain, paraesthesia, numbness, QOL, mobility, sleep and mood. Daily analgesic consumption Results: Scores aggregated at 56 days. No useful analgesic benefit demonstrated by lamotrigine in doses up to 200 mg. From a baseline of 6.76 (on 10 cm VAS) overall pain on lamotrigine reduced by 0.01 and on placebo increased by 0.03
Notes	Eighteen withdrew: eight nausea (five placebo, three lamotrigine); two skin rash (one lamotrigine); two bad taste of tablets (one lamotrigine); six due to lack of analgesia two placebo four lamotrigine). Eight failed to attend final assessment QS = 5
Allocation concealment	D – Not used

Study	**Simpson 2000**
Methods	Multicentre randomised DB placebo controlled study over 14 weeks
Participants	42 participants with painful HIV associated polyneuropathy. Mean age 44 years. Participants on valproate excluded
Interventions	Lamotrigine or placebo. Week one and two 25 mg/day; weeks three and four 50 mg/day; week five 100 mg/day, week six 100 mg twice daily; weeks seven to 14 150 mg twice a day
Outcomes	Average and peak neuropathic pain using Gracely Pain Scale. Difference in weekly mean pain scores. Pain assessed in weeks one and 14, also slope of change in pain scores Results: Significantly greater fall in pain scores in lamotrigine group but over half of this group dropped out. Mean difference (baseline and week 14) in pain score (SE) Placebo - 0.18 (0.09),lamotrigine -0.55 (0.14) (placebo 20 reported, lamotrigine nine reported)
Notes	Withdrawals: lamotrigine 5/20 due to rash, 1/20 GI infection, 5/20 lost to follow up; placebo 2/22 personal reasons, 1/22 lost to follow up QS = 5
Allocation concealment	D – Not used

Study	**Simpson 2003**
Methods	Randomised DB placebo controlled parallel multicentre trial over 12 weeks. Randomisation stratified according to use of neurotoxic antiretroviral therapy (ART)
Participants	HIV associated sensory neuropathy. Age 32 to 67 years. 227 participants. Participants with previous or current use of lamotrigine were excluded

Characteristics of included studies (*Continued*)

Interventions	Lamotrigine or placebo 25 mg alternate days for two weeks then dose escalation over seven weeks to a target dose of 400 mg/day. (Up to 600 mg/day allowed for those on enzyme inducing drugs). Four week maintenance phase
Outcomes	Daily pain rating of average pain and worst pain on Gracely Pain Scale. VASPI and short form McGill at end of baseline and beginning and end of maintenance phase Results: 60% 53/88 lamotrigine had moderate or better pain relief 30% 21/47 placebo had moderate or better pain relief For ART group 53% 33/62 lamotrigine had moderate or better pain relief 30% 9/30 placebo had moderate or better pain relief
Notes	Withdrawals: 34/150 withdrew on lamotrigine, 21/77 withdrew on placebo. Adverse events; 21/150 rash on lamotrigine; 9/77 rash on placebo. 4/150 withdrew due to AEs on lamotrigine, 3/77 withdrew due to AEs on placebo QS = 3 (R1, DB1, W1)
Allocation concealment	D – Not used

Study	**Vestergaard 2001**
Methods	Randomised DB placebo controlled crossover study. Two by eight week treatment periods
Participants	Central post stroke pain with score of >4 on an 11 point scale. Age 37 to 77 years 30 participants
Interventions	Lamotrigine 25 mg/day increased every 2nd week to 200 mg/day. Soluble tablets or matching placebo. No concomitant use of antidepressants, antiepileptics or analgesics allowed. Paracetamol as rescue medication
Outcomes	Average daily pain score during last week of treatment. (11 point Likert scale). Cat PR and cat PI. Use of rescue medication Results. Significant difference in mean pain scores between lamotrigine 200 mg and placebo. 12/16 lamotrigine and 3/13 placebo considered as clinical responders. Pain scores on doses up to 100 mg lamotrigine no different from placebo
Notes	Claim lamotrigine 200 mg dose is well tolerated. Withdrawals - 3/16 lamotrigine due to AEs. Five patients had skin related side effects during lamotrigine and two developed a rash, two patients on placebo also developed a rash. 17 pts reported AEs on lamotrigine and 18 on placebo QS = 5
Allocation concealment	D – Not used

Study	**Zakrzewska 1997**
Methods	Randomised DB placebo crossover study of five weeks. Two by two week treatment periods with three day washout. Lamotrigine added to existing anticonvulsant treatment
Participants	Refractory trigeminal neuralgia. Fourteen participants aged 44 to 75 (mean 60 years)
Interventions	All participants on carbamazepine or phenytoin, or both. Lamotrigine of placebo added. Doses: day one 50 mg, day two 100 mg, day three 200 mg then 400 mg days four to 14. Increased dose of carbamazepine or phenytoin used for rescue for uncontrollable pain
Outcomes	No of pain paroxysms. CAT PI, CATPR and global assessment at the end of each treatment period Results. 10/13 improved on lamotrigine, 8/14 improved on placebo. (defined as better or much better)
Notes	Withdrawals. One on placebo for uncontrolled pain. 7/13 reported AEs on lamotrigine and 7/14 on placebo QS = 4 (R1, DB2, W1)

Allocation concealment D – Not used

AEs = adverse effects, DB = double blind, CatPI categorical scale of pain intensity, CATPR categorical scale of pain relief, NNT = number needed to treat, PI = pain intensity, QOL = quality of life, VAS = visual analogue scale. QS- quality scale (R-randomisation, DB - double blind, W withdrawals)

Characteristics of excluded studies

Study	Reason for exclusion
Bonicalzi 1997b	Pre emptive study but all participants also received a known analgesic-buprenorphine
Carrieri 1998	Case study
Devulder 2000	Survey not RCT
Eisenberg 1998	Not randomised
Eisenberg 2003	Not randomised
Lunardi 1997	Case series
Petersen 2003	RCT but healthy volunteers
Sandner-Kiesling2002	Case report
di Vadi 1998	Case report only

ANALYSES

Comparison 01. Central stroke pain

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Improvement (better) lamotrigine 200mg vs placebo			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. Diabetic Neuropathy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Moderate or better Lamotrigine 400mg vs placebo			Relative Risk (Fixed) 95% CI	Totals not selected
02 Highly effective Lamotrigine 400mg vs Placebo			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 03. HIV neuropathy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Moderate or better pain relief (ART group) Lamotrigine 400mg vs placebo			Relative Risk (Fixed) 95% CI	Totals not selected
02 Moderate or better pain relief (No ART group) Lamotrigine 400mg vs placebo			Relative Risk (Fixed) 95% CI	Totals not selected

03 Change data for pain scores. Lamotrigine vs placebo	Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 04. Trigeminal neuralgia

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain relief			Relative Risk (Fixed) 95% CI	Totals not selected

COVER SHEET

Title	Lamotrigine for acute and chronic pain
Authors	Wiffen PJ, Rees J
Contribution of author(s)	PW: wrote the protocol, ran the search strategy, collected relevant papers, extracted data and wrote review. JR: agreed the included studies, independently checked the data extraction and data analysis. Approved final version.
Issue protocol first published	2006/2
Review first published	2007/2
Date of most recent amendment	21 February 2007
Date of most recent SUBSTANTIVE amendment	07 February 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Mr Philip Wiffen Co-ordinating Editor, Cochrane Pain, Palliative and Supportive Care Group Pain Research Unit The Churchill Hospital Old Road Headington Oxford OX3 7LJ UK E-mail: phil.wiffen@pru.ox.ac.uk Tel: +44 1865 225762 Fax: +44 1865 225400
DOI	10.1002/14651858.CD006044.pub2
Cochrane Library number	CD006044

Editorial group	Cochrane Pain, Palliative and Supportive Care Group
Editorial group code	HM-SYMPT

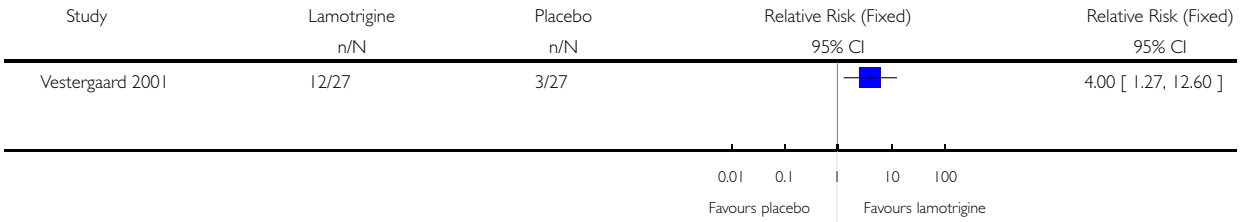
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Central stroke pain, Outcome 01 Improvement (better) lamotrigine 200mg vs placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 01 Central stroke pain

Outcome: 01 Improvement (better) lamotrigine 200mg vs placebo

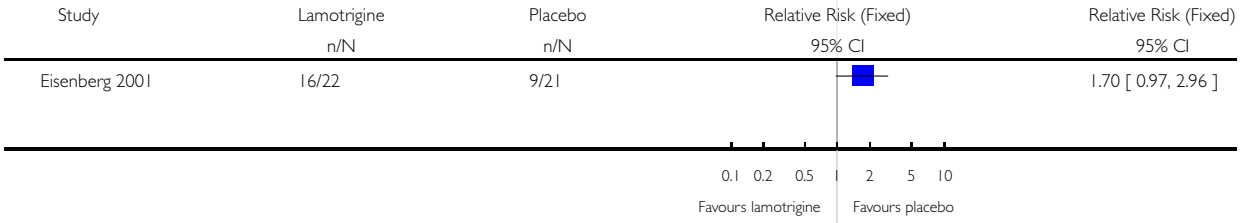


Analysis 02.01. Comparison 02 Diabetic Neuropathy, Outcome 01 Moderate or better Lamotrigine 400mg vs placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 02 Diabetic Neuropathy

Outcome: 01 Moderate or better Lamotrigine 400mg vs placebo

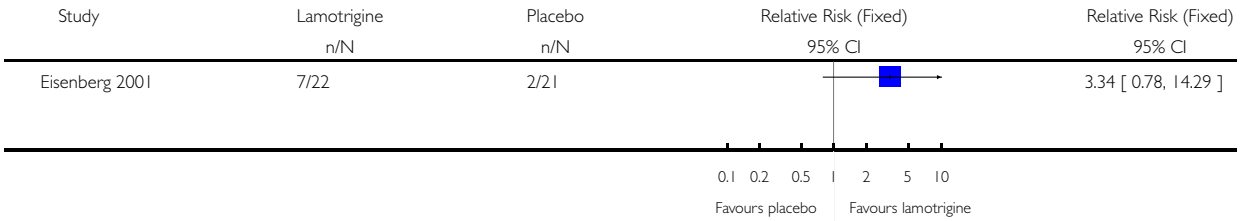


Analysis 02.02. Comparison 02 Diabetic Neuropathy, Outcome 02 Highly effective Lamotrigine 400mg vs Placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 02 Diabetic Neuropathy

Outcome: 02 Highly effective Lamotrigine 400mg vs Placebo

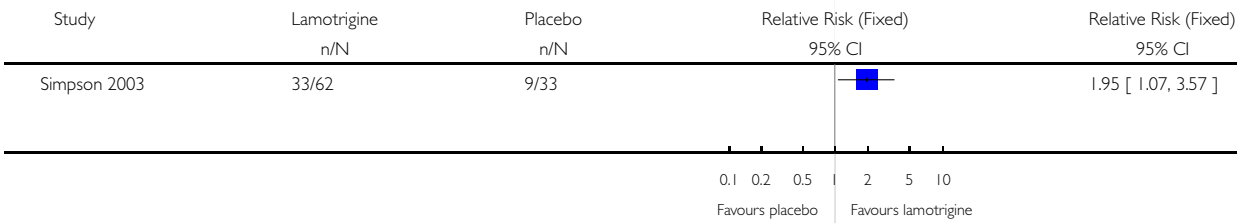


Analysis 03.01. Comparison 03 HIV neuropathy, Outcome 01 Moderate or better pain relief (ART group) Lamotrigine 400mg vs placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 03 HIV neuropathy

Outcome: 01 Moderate or better pain relief (ART group) Lamotrigine 400mg vs placebo

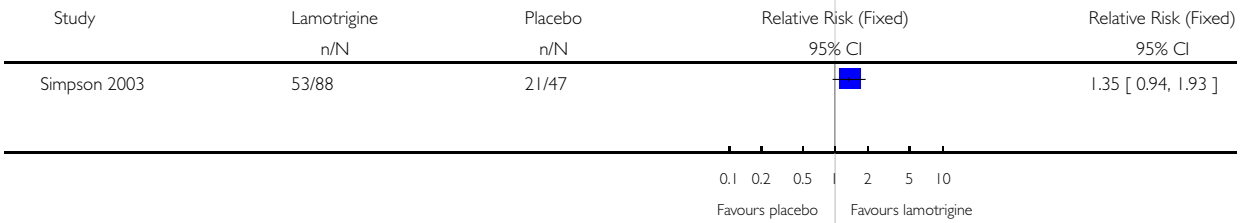


Analysis 03.02. Comparison 03 HIV neuropathy, Outcome 02 Moderate or better pain relief (No ART group) Lamotrigine 400mg vs placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 03 HIV neuropathy

Outcome: 02 Moderate or better pain relief (No ART group) Lamotrigine 400mg vs placebo

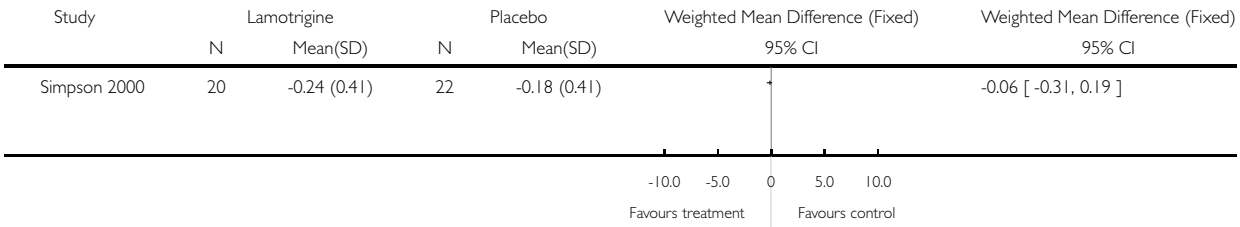


Analysis 03.03. Comparison 03 HIV neuropathy, Outcome 03 Change data for pain scores. Lamotrigine vs placebo

Review: Lamotrigine for acute and chronic pain

Comparison: 03 HIV neuropathy

Outcome: 03 Change data for pain scores. Lamotrigine vs placebo



Analysis 04.01. Comparison 04 Trigeminal neuralgia, Outcome 01 Pain relief

Review: Lamotrigine for acute and chronic pain

Comparison: 04 Trigeminal neuralgia

Outcome: 01 Pain relief