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Levetiracetam for neuropathic pain in adults (Review)

Wiffen PJ, Derry S, Moore RA, Lunn MPT

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[Intervention Review]

Levetiracetam for neuropathic pain in adults

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ABSTRACT

Background

Antiepileptic drugs have been used in pain management since the 1960s; some have shown efficacy in treating different neuropathic pain conditions. The efficacy of levetiracetam for relief of neuropathic pain has not previously been reviewed.

Objectives

To assess the analgesic efficacy and adverse events of levetiracetam in chronic neuropathic pain conditions in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6) (via *the Cochrane Library*), MEDLINE, EMBASE, and two clinical trials databases (ClinicalTrials.gov. and the World Health Organisation Clinical Trials Registry Platform) to 3 July 2014, together with reference lists of retrieved papers and reviews.

Selection criteria

We included randomised, double-blind studies of two weeks duration or longer, comparing levetiracetam with placebo or another active treatment in adults with chronic neuropathic pain conditions. Studies had to have a minimum of 10 participants per treatments arm.

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. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction; intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison; 8 to 12 weeks duration; parallel design); second tier evidence from data that failed to meet one or more of these criteria and that we considered at some risk of bias but with at least 200 participants in the comparison; and third tier evidence from data involving fewer than 200 participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both.

Main results

We included six studies: five small, cross-over studies with 174 participants, and one parallel group study with 170 participants. Participants were treated with levetiracetam (2000 mg to 3000 mg daily) or placebo for between four and 14 weeks. Each study included participants with a different type of neuropathic pain; central pain due to multiple sclerosis, pain following spinal cord injury, painful polyneuropathy, central post-stroke pain, postherpetic neuralgia, and post-mastectomy pain.

None of the included studies provided first or second tier evidence. The evidence was very low quality, downgraded because of the small size of the treatment arms, and because studies reported results using last observation carried forward (LOCF) imputation for withdrawals or using only participants who completed the study according to the protocol, where there were greater than 10% withdrawals. There were insufficient data for a pooled efficacy analysis in particular neuropathic pain conditions, but individual studies did not show any analgesic effect of levetiracetam compared with placebo. We did pool results for any outcome considered substantial pain relief (≥ 50% pain intensity reduction or 'complete' or 'good' responses on the verbal rating scale) for four studies with dichotomous data; response rates across different types of neuropathic pain was similar with levetiracetam (10%) and placebo (12%), with no statistical difference (risk ratio 0.9; 95% confidence interval (CI) 0.4 to1.7).

We pooled data across different conditions for adverse events and withdrawals. Based on very limited data, significantly more participants experienced an adverse event with levetiracetam than with placebo (number needed to treat for an additional harmful event (NNH) 8.0 (95% CI 4.6 to 32)). There were significantly more adverse event withdrawals with levetiracetam (NNH 9.7 (6.7 to 18)).

Authors' conclusions

The amount of evidence for levetiracetam in neuropathic pain conditions was very small and potentially biased because of the methods of analysis used in the studies. There was no indication that levetiracetam was effective in reducing neuropathic pain, but it was associated with an increase in participants who experienced adverse events and who withdrew due to adverse events.

PLAIN LANGUAGE SUMMARY

Levetiracetam for neuropathic pain in adults

Neuropathic pain can arise from damage to nerves and injury to the central nervous system. 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 usually effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain.

Levetiracetam is one of a type of medicine normally used to treat epilepsy. Some of these medicines are also useful for treating neuropathic pain. We looked for clinical trials in which levetiracetam was used to treat neuropathic pain. We found six studies in 344 adult participants with six different neuropathic pain conditions published up to July 2014. These studies were randomised and double blind, which usually means we can trust them. But all had one or more problems that could make the results look better than found in practice. There was no benefit from levetiracetam in any of the six conditions. More participants experienced adverse events with levetiracetam (67 in 100) than with placebo (54 in 100), and stopped taking levetiracetam because of adverse events (13 in 100) than stopped taking placebo (2 in 100). Adverse events included tiredness, dizziness, headache, constipation, and nausea.

There was too little information, which was of inadequate quality, to be sure that levetiracetam works as a pain medicine in any of the neuropathic pain conditions investigated. Other medicines have been shown to be effective in some of these conditions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Levetiracetam compared with placebo for neuropathic pain

Patient or population: neuropathic pain (6 studies in central neuropathic pain due to multiple sclerosis, spinal cord injury, polyneuropathy, central post-stroke pain, postherpetic neuralgia, and post-mastectomy pain)
Intervention: levetiracetam 2000 mg to 3000 mg daily
Comparison: placebo

Outcomes	Probable outcome with comparator (placebo)	Probable outcome with intervention	Relative effect (95% CI)	No. of participants and studies	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain	9/57	9/59	Not calculated	2 studies, 59 participants	Very low	Small numbers of studies and participants, cross-over studies, potential bias in analysis
At least 30% reduction in pain	12/57	11/59	Not calculated	2 studies, 59 participants	Very low	Small numbers of studies and participants, cross-over studies, potential bias in analysis
Proportion below 30/100 mm on VAS	No data					
Patient Global Impression of Change very much improved (patient global evaluation of pain relief complete or good)	6/86	4/86	Not calculated	3 studies, 86 participants	Very low	Small numbers of studies and participants, cross-over studies, potential bias in analysis
Patient Global Impression of Change much or very much improved (patient global evaluation of pain relief complete, good or moder-	8/86	13/86	Not calculated	3 studies, 86 participants	Very low	Small numbers of studies and participants, cross-over studies, potential bias in analysis

ate)						
Any measure of 'substantial' pain relief	14/119	12/121	Not calculated	4 studies, 121 participants	Very low	Small numbers of studies and participants, cross-over studies, potential bias in analysis
Adverse event withdrawals	24 in 1000	130 in 1000	RR 4.9 (2.2 to 11) NNH 9.7 (6.7 to 18)	6 studies, 334 participants in total	Very low	Small numbers of studies and participants
Serious adverse events	2/334	2/334	Not calculated	6 studies, 334 participants in total	Very low	Small numbers of studies and participants
Death	No deaths				Very low	Small numbers of studies and participants

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.

CI: confidence interval; NNH: number needed to treat to harm; RR: risk ratio; VAS: visual analogue scale

BACKGROUND

This review is based on a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1). An overview review of antiepileptic drugs for treating neuropathic pain identified that no Cochrane review existed for levetiracetam (Wiffen 2013).

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 a definition agreed at 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). The genesis of neuropathic pain is complex (Apkarian 2011; Baron 2010; Baron 2012; Tracey 2011; von Hehn 2012), and neuropathic pain features can be found in patients with joint pain (Soni 2013). Many people with neuropathic pain conditions are disabled with significant levels of pain for many years. Chronic painful conditions comprise five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased health costs (Moore 2013a).

In primary care in the 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 (95% CI 26 to 29) for trigeminal neuralgia, 0.8 (95% CI 0.6 to 1.1) for phantom limb pain and 21 (95% CI 20 to 22) for painful diabetic neuropathy (Hall 2008). These estimates are in accordance with a systematic review of epidemiological studies from a number of different countries (van Hecke 2014). In other studies the incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while 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). Estimates vary between studies, often because of small numbers of cases. 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) illustrating how common the condition was as well as its chronicity. The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), as high as 8% in the UK (Torrance 2006), about 7% in a systematic review of studies published since 2000 (Moore 2013a), and 7% to 10% in a systematic review of epidemiological studies published between 1966 and 2012 (van Hecke 2014). The prevalence of some types of neuropathic pain, such as diabetic neuropathy and post surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008).

Neuropathic pain is 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 may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Khaliq 2007). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is often by so-called unconventional analgesics, such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Moore 2013d) or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011). While treatment guidelines have general similarities based on the evidence available, they are not always consistent with one another (O'Connor 2009). The proportion of patients who achieve worthwhile,meaningful pain relief (typically at least 50% pain intensity reduction (Moore 2013b)) is small, generally 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNT) usually between 4 and 10 (Moore 2013c).

Description of the intervention

Levetiracetam is an antiepileptic drug that is related to piracetam - a drug used to treat cortical reflex myoclonus (a type of epilepsy that originates in the cerebral cortex). It is available as oral tablets of 250 mg, 500 mg and 1 g. In addition both an oral solution and an intravenous (IV) infusion are available.

How the intervention might work

The mode of action of levetiracetam has not been fully resolved but is thought to work via gamma-aminobutyric acid (GABA) A receptors. Its mechanism of action is considered to be different from all other antiepileptic drugs (SPC 2013; Wakita 2013). A detailed description of the mode of action and evidence concerning the use of levetiracetam in epilepsy is available in another Cochrane review (Mbzivo 2012). Studies exist that have investigated the potential role of levetiracetam in neuropathic pain treatment.

Why it is important to do this review

Levetiracetam is not commonly prescribed for neuropathic pain and it is not licensed for the treatment of neuropathic pain in the UK or USA, but the potential for benefit from this drug needs to be investigated. This review is one of a series of reviews covering the role of antiepileptics in neuropathic pain, and will be included in an overview review (Wiffen 2013).

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to the number of patients who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the Cochrane Pain, Palliative and Supportive Care Group's Author and Referee Guidance for pain studies (AUREF 2012).

This Cochrane review will assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Moore 2012b). Studies included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc) and size (ideally at least 400 participants in a comparison in which the NNT is four or above (Moore 1998)). This does set high standards and marks a departure from how reviews have been done previously.

OBJECTIVES

1. To assess the analgesic efficacy of levetiracetam for chronic neuropathic pain in adults.

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

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer, although the emphasis of the review was on studies of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised, studies of experimental pain, case reports and clinical observations.

Types of participants

Studies included adults aged 18 years and above. Participants could have one or more of a wide range of chronic neuropathic pain conditions but we specifically searched for and included:

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

If studies had included participants with more than one type of neuropathic pain we would have analysed results according to the primary condition.

Types of interventions

Levetiracetam at any dose, by any route, administered for the relief of neuropathic pain and compared to placebo or any 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 used in most earlier reviews, 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 have included a 'Summary of findings' table as set out in the author guide (AUREF 2012). The 'Summary of findings' table includes outcomes of at least 50% and at least 30% pain intensity reduction, PGIC, adverse event withdrawals, serious adverse events and death.

Primary outcomes

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

4. PGIC very much improved

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6) (via *the Cochrane Library*);
- MEDLINE (via Ovid) from 1946 to 3 July 2014;
- EMBASE (via Ovid) from 1974 to 3 July 2014.

The search strategies for MEDLINE, EMBASE and CENTRAL are in Appendix 2, Appendix 3, and Appendix 4.

Searching other resources

We reviewed the bibliographies of any RCTs identified and review articles, contacted known experts in the field, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators or study sponsors.

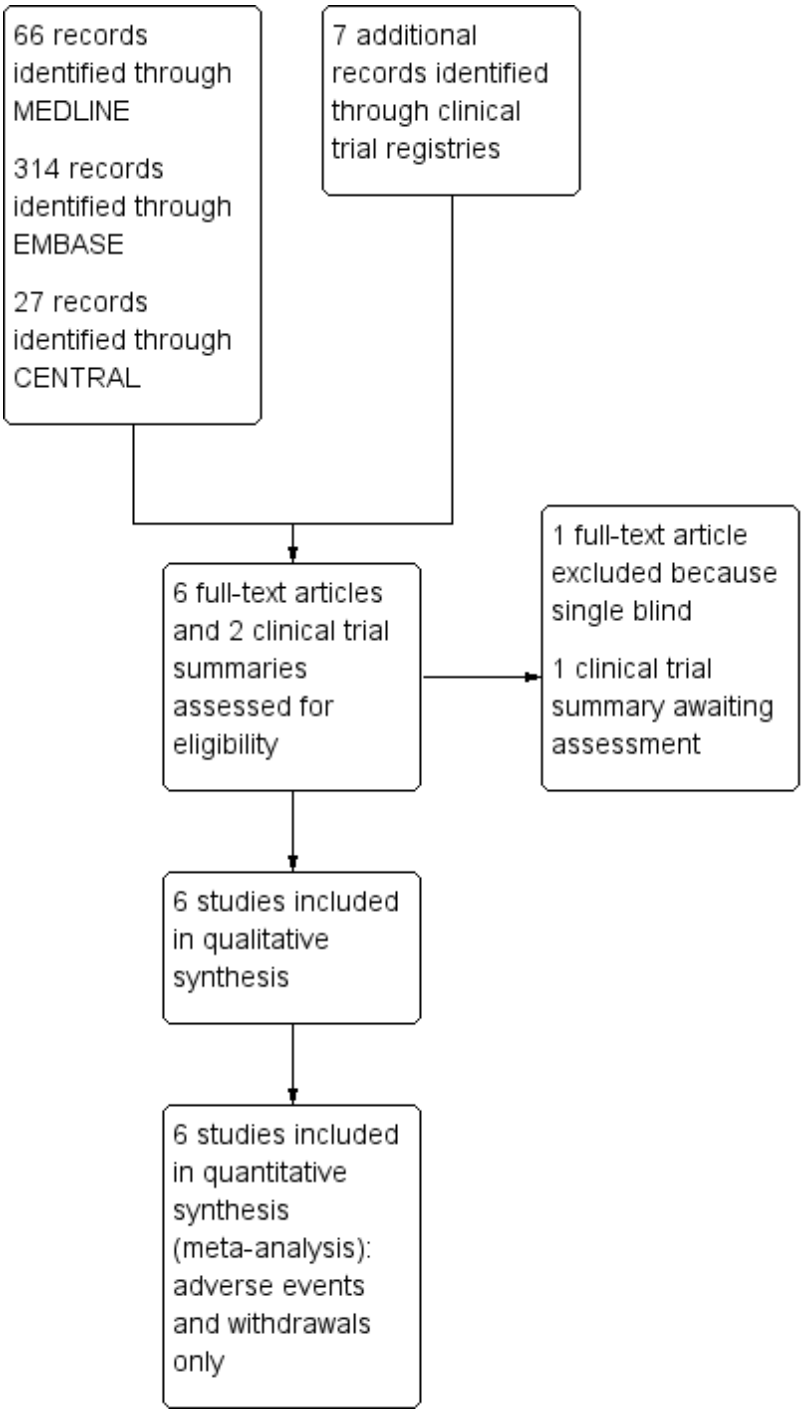
Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions. Analyses combining different neuropathic pain conditions would be done for exploratory purposes only.

Selection of studies

Two authors (PW and SD) independently determined eligibility by reading the abstract of each study identified by the search. Independent authors eliminated studies that clearly did not satisfy inclusion criteria, and we obtained full copies of the remaining studies. Two review authors (PW and SD) read these studies independently and reached agreement by discussion. In the event of disagreement, a third author would adjudicate. We did not anonymise the studies in any way before assessment. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart shows the status of identified studies (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into RevMan (RevMan 2012). We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event, or serious adverse event).

Assessment of risk of bias in included studies

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

Two authors (PW and SD) independently assessed the risk 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:

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, for example 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 (for example, odd or even date of birth; hospital or clinic record number).

2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).

3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and describes the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but does not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants 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 planned to calculate NNTs as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to harm (NNH) and is calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). Continuous data were not used in analyses.

Dealing with missing data

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

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic. If I^2 was greater than 50%, we would consider possible reasons.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010d). The review does not depend on what authors of the original studies chose to report or not. We would extract and use continuous data, which probably poorly reflect efficacy and utility, if useful for illustrative purposes only.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect required

to make any result clinically irrelevant (usually taken to mean NNT values of 10 or higher) (Moore 2008).

Data synthesis

We planned to use a fixed-effect model for meta-analysis. A random-effects model for meta-analysis would have been used if there was significant clinical heterogeneity and it was considered appropriate to combine studies.

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

- The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted eight or more weeks, had a parallel-group design, and had at least 200 participants (preferably at least 400) in the comparison (Moore 1998; Moore 2010a; Moore 2012a). These top-tier results would be reported first.
- The second tier used data from at least 200 participants but where one or more of the above conditions were 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 studies including fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

We pooled adverse event data from different neuropathic pain conditions because there was no reason to believe that adverse responses would differ, and to provide a larger data set for analysis.

Subgroup analysis and investigation of heterogeneity

We planned efficacy analyses to be according to individual painful conditions, because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). Analysis that pooled data from different conditions was carried out where there were insufficient data to analyse conditions separately, and only to give an indication of direction of effect.

Sensitivity analysis

We planned no sensitivity analysis because the evidence base was known to be too small to allow reliable analysis. We would examine details of dose escalation schedules, if available, in the unlikely situation that this could provide some basis for a sensitivity analysis.

RESULTS

Description of studies

Results of the search

We identified 66 potentially relevant records in MEDLINE, 341 in EMBASE, and 27 in CENTRAL. Searches of clinical trials databases identified a further seven potential studies. After reading the abstracts, we read six articles and two clinical trial summaries in full. One of the two clinical trial summaries had insufficient data to determine whether it was randomised study and it was placed in Characteristics of studies awaiting classification (NCT00156689); the principal investigator is unable to provide any data (personal communication). The other clinical trial summary provided little detail (NCT00160511) (Figure 1).

Included studies

We included six studies (344 participants), each enrolling participants with a different type of neuropathic pain: central pain due to multiple sclerosis (Falah 2012), pain following spinal cord injury (Finnerup 2009), painful polyneuropathy (Holbech 2011), central post-stroke pain (Jungehulsing 2013), postherpetic neuralgia (NCT00160511), and post-mastectomy pain (Vilholm 2008).

All participants had experienced their pain for at least three months, and the intensity at study entry was moderate or severe (generally 4/10 to 9/10). The mean age in included studies ranged from 47 to 70 years, and all included both men and women except one in post-mastectomy pain, which included only women (Vilholm 2008). Exclusion criteria for all studies (except NCT00160511, which did not provide information) included causes of pain other than that specified, previous allergic reaction or severe adverse events to levetiracetam or a similar medication, pregnancy or lactation, and severe terminal illness or other condition that would interfere with the study.

All the studies were placebo-controlled. Five used a cross-over design, and one a parallel group design (NCT00160511). Treatment periods were four to eight weeks, with a one- or two-week washout between periods for cross-over studies, and 14 weeks (four-week up titration, eight-week maintenance, two-week taper) for the parallel group study. Previous medication for neuropathic pain was tapered and stopped completely during a pre-study period of one to four weeks in Falah 2012, Holbech 2011, and Vilholm 2008, but some medication was continued (if it was stable and remained unchanged) in Finnerup 2009 and Jungehulsing 2013.

NCT00160511 included a baseline period, but there was no information on washout of existing medication or permitted medication. Levetiracetam was titrated over approximately two weeks in cross-over studies and four weeks in the parallel group study, from 500 mg or 1000 mg daily to a maximum of 3000 mg daily, and taken twice a day. All except two studies (NCT00160511; Vilholm 2008) stated that the dose could be reduced to a minimum of 2000 mg daily or to the previous tolerated dose in the event of intolerable side effects. Rescue medication was specified as 3000 mg or 4000 mg paracetamol daily, sometimes with the addition of tramadol 50 mg, in all but two studies (Jungehulsing 2013; NCT00160511).

Further details are provided in the Characteristics of included studies table. Study drugs were provided in all of the included studies by UCB Pharma, who also provided some financial support.

Excluded studies

We excluded one study because it was single blind (Rossi 2009).

Risk of bias in included studies

Comments on potential biases in individual studies are reported in the Risk of bias section of the Characteristics of included studies table. The findings are displayed in Figure 2 and Figure 3; no sensitivity analysis was undertaken. The greatest risk of bias came from small study size.

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

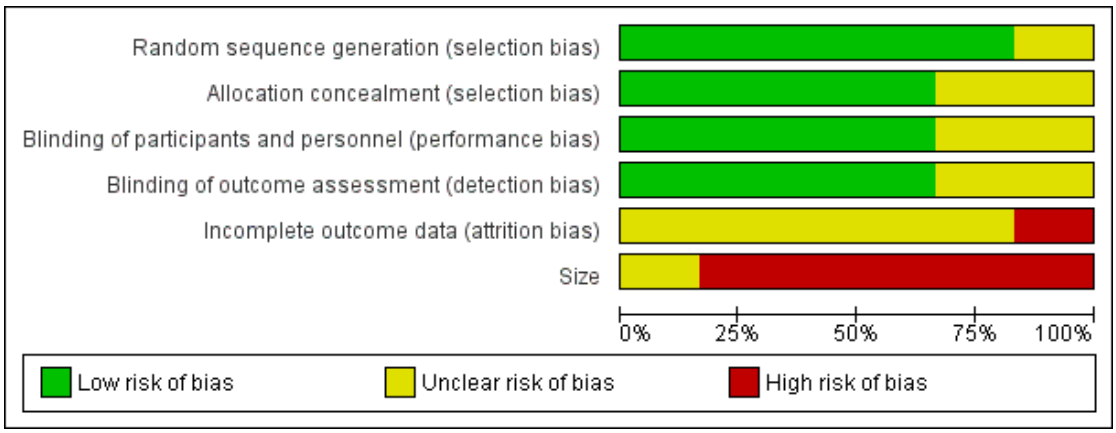
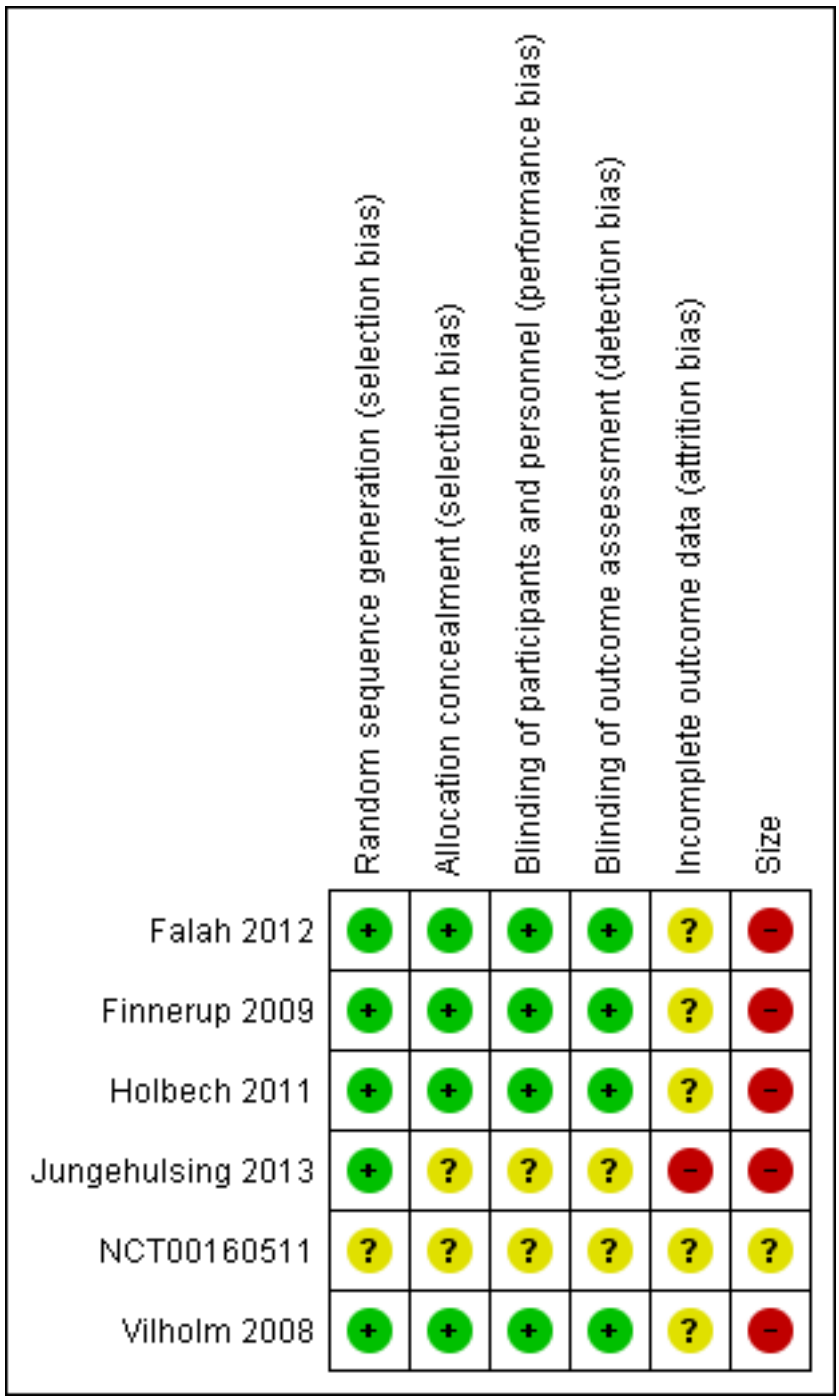


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All except one of the studies (NCT00160511) adequately described the method used to generate the random number sequence, and all but two also described how the allocation was concealed (Jungehulsing 2013; NCT00160511).

Blinding

All the studies were double blind, and all but two adequately described how the blinding was achieved (Jungehulsing 2013; NCT00160511).

Incomplete outcome data

Four cross-over studies stated that they used last observation carried forward (LOCF) imputation for participants who withdrew from the study, and we judged them at unknown risk of bias (Falah 2012; Finnerup 2009; Holbech 2011; Vilholm 2008). One cross-over study reported a per protocol analysis and had more than 10% withdrawals, so we judged it at high risk of bias (Jungehulsing 2013). For some outcomes, analyses included only those participants who provided data for both phases of the cross-over. None of the cross-over studies reported efficacy results separately for the first treatment phase.

The parallel group study had high withdrawal rates (33% with levetiracetam and 22% with placebo) and did not report how these withdrawals were handled in the analysis of mean data (NCT00160511). All participants were included in analyses of adverse events and withdrawals.

Other potential sources of bias

Five of the studies were small, with fewer than 50 participants per treatment arm, and we judged them at high risk of bias. The remaining study, with 84 and 86 participants in the treatment arms, was judged at unclear risk of bias.

Effects of interventions

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

None of the included studies provided first or second tier evidence. We downgraded the evidence was because of the small size of the treatment arms and because studies reported results using LOCF imputation for withdrawals or reported a per protocol analysis where there were greater than 10% withdrawals.

NCT00160511 did not report any dichotomous data and did not contribute to any efficacy analysis.

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

Third tier evidence

Participant-reported pain relief of 30% or greater, and 50% or greater

Two studies reported these outcomes.

In Finnerup 2009, 3/34 participants treated with levetiracetam, and 4/32 with placebo experienced at least 33% reduction in pain at the end of the five-week treatment periods; 1/34 with levetiracetam and 1/32 with placebo experienced at least 50% pain reduction over five weeks.

In Vilholm 2008, 8/25 participants experienced at least 50% pain reduction over the four-week treatment period with both levetiracetam and placebo.

Patient Global Impression of Change (PGIC) 'much or very much improved' and 'very much improved'

No studies reported these outcomes using the standard 5-point scale. However, three studies used a 6-point verbal rating scale to measure participants' pain relief at the end of the treatment periods (Falah 2012; Finnerup 2009; Holbech 2011): 'complete' (6), 'good' (5), 'moderate' (4), 'slight' (3), 'none' (2) or 'worse' (1). While this was not a predefined outcome we considered it equivalent to PGIC very much improved when the result reported was 'complete' or 'good', and PGIC much or very much improved when the result reported was 'moderate', 'complete' or 'good' (Moore 2013b).

In Falah 2012, no participants experienced complete relief, 1/27 reported 'good' relief with both levetiracetam and placebo, and 4/27 reported 'moderate' relief with levetiracetam compared to 1/27 with placebo.

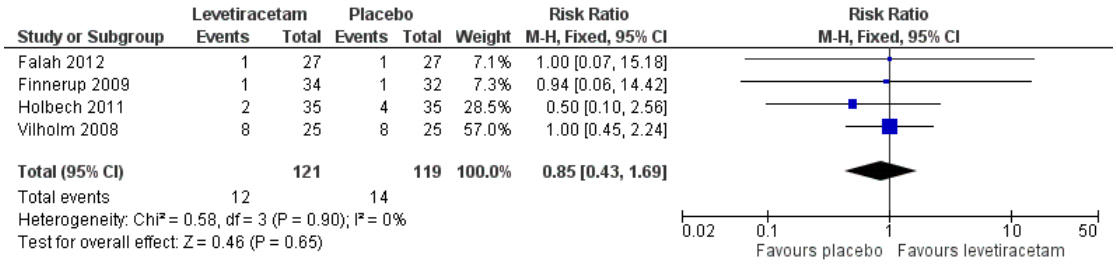
In Finnerup 2009, no participants experienced complete relief, 1/24 reported 'good' relief with both levetiracetam and placebo, and 2/24 reported 'moderate' relief with levetiracetam compared to 0/24 with placebo.

In Holbech 2011, 1/35 participants experienced complete relief with levetiracetam and none with placebo, 1/35 reported 'good' relief with levetiracetam and 4/35 with placebo, and 3/35 reported 'moderate' relief with levetiracetam compared to 1/35 with placebo.

Analysis 1.1 shows the results for outcomes measuring substantial pain relief (≥ 50% pain intensity reduction or 'complete' or 'good' responses on the verbal rating scale) for the four studies with dichotomous data. Where studies reported both outcomes, we have used ≥ 50% pain intensity reduction preferentially. The overall response rate across these different types of neuropathic pain was similar with levetiracetam (10%) and placebo (12%), with no individual study significantly different from placebo (Figure 4). There

was no statistical difference between levetiracetam and placebo (RR 0.9; 95% CI 0.4 to1.7).

Figure 4. Forest plot of comparison: 1 Levetiriacetam versus placebo, outcome: 1.1 Participants with substantial pain relief (≥50% pain intensity reduction, or complete or good pain relief).



Any pain-related outcome indicating some improvement

All the studies reported that the mean or median pain scores at the end of each treatment period did not differ between levetiracetam and placebo.

There was no evidence that levetiracetam provided better pain relief than placebo.

Use of rescue medication

Use of rescue medication was not a prespecified outcome in the protocol, but was reported in four studies. These data are analysed for completeness.

In the four studies that specified use of rescue medication, there was no difference in the mean number of tablets of paracetamol and tramadol (where allowed) consumed per week (Falah 2012; Finnerup 2009; Holbech 2011; Vilholm 2008), and usage was unchanged from the baseline period. During the baseline period and in both treatment arms, there was a very wide range in the number of tablets used.

Adverse events

We combined data from different neuropathic pain conditions for adverse events.

Participants experiencing any adverse event

Five studies reported the number of participants who experienced at least one adverse event during the treatment period (Falah 2012; Finnerup 2009; Holbech 2011; NCT00160511; Vilholm 2008). Combining the studies across conditions, 136/204 (67%) of participants experienced an adverse event with levetiracetam, and 111/205 (54%) with placebo. The risk ratio (RR) was 1.2 (95% confidence interval (CI) 1.1 to 1.5), and the number needed to treat for an additional harmful event (NNH) was 8.0 (4.6 to 32) (Analysis 1.2).

Where reported, the intensity of adverse events was mostly moderate or severe with levetiracetam, and mild or moderate with placebo. With levetiracetam the most common events were fatigue or tiredness, dizziness, headache, constipation, and nausea. With placebo the most common events were tiredness, headache, nausea, and constipation or abdominal discomfort.

Serious adverse events

Two serious adverse events were reported in both treatment arms of the parallel group study; none were judged related to study medication by the study investigators.

Deaths

There were no deaths reported in the studies.

Withdrawals

All studies reported on withdrawals for both treatment arms in participants who took at least one dose of study medication.

All cause withdrawals

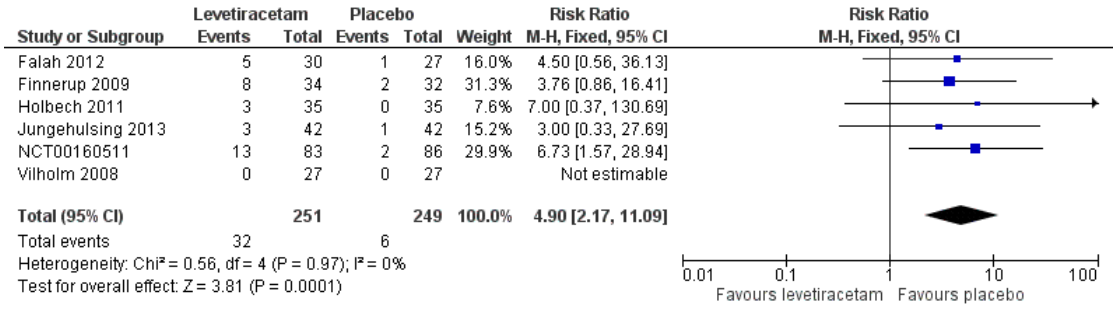
Combining studies across conditions, a total of 59/251 (23%) of participants withdrew from treatment with levetiracetam, and 31/

249 (12%) from treatment with placebo. The RR was 1.9 (95% CI 1.3 to 2.8), and the NNH was 9.1 (5.7 to 23) (Analysis 1.3).

Adverse events withdrawals

Combining studies across conditions, 32/251 (13%) of participants withdrew from treatment with levetiracetam, and 6/249 (2%) from treatment with placebo because of adverse events. The RR was 4.9 (95% CI 2.2 to 11), and the NNH was 9.7 (6.7 to 18) (Analysis 1.4; Figure 5).

Figure 5. Forest plot of comparison: 1 Levetiriacetam versus placebo, outcome: 1.4 Adverse event withdrawal.



Lack of efficacy withdrawals

Combining studies across conditions, 16/251 (6%) of participants withdrew from treatment with levetiracetam, and 12/249 (5%) from treatment with placebo because of lack of efficacy. The RR was 1.3 (95% CI 0.66 to 2.5). The NNH was not calculated (Analysis 1.5).

DISCUSSION

Summary of main results

We found six studies enrolling 344 participants with chronic neuropathic pain of different origins: central pain due to multiple sclerosis, spinal cord injury, polyneuropathy, central post-stroke pain, postherpetic neuralgia, and post-mastectomy pain. All studies compared levetiracetam with placebo; five used a cross-over design, and one a parallel group design.

No first or second tier evidence was available. No pooling of efficacy data was possible, but third tier evidence in individual studies did not indicate any improvement in pain relief with levetiracetam compared with placebo. Combining studies across pain conditions, participants taking levetiracetam were more likely to experience any adverse event during treatment (NNH 8.0), and the intensity of adverse events was reported as moderate or severe with levetiracetam, and mild to moderate with placebo. There were significantly more adverse event withdrawals with levetiracetam. Two serious adverse events were reported with both levetiracetam and placebo, all of which were judged unrelated to study medication by the investigators. There were no deaths in the studies. See Summary of findings for the main comparison.

Overall completeness and applicability of evidence

Levetiracetam was tested in small numbers of people with six different types of neuropathic pain that did not include some of the most common types, such as painful diabetic neuropathy. The results here cannot reliably be extrapolated to other neuropathic pain conditions.

Treatment duration in most of the included studies was four to six weeks, and although short-term studies (less than six weeks) may not accurately predict longer term efficacy in chronic conditions, it is very likely that some analgesic effect would be seen by four weeks

if the intervention was effective in the conditions investigated. The single study of longer duration in postherpetic neuralgia also failed to show any benefit of levetiracetam based on group mean data.

The included studies were underpowered to provide reliable information relating to tolerability and safety.

Quality of the evidence

Reporting quality in the studies was generally poor by current standards. While all the studies were randomised and double-blind, none provided data that met predefined criteria for first or second tier analysis. The studies were small, with only one having more than 50 participants in any treatment arm. Five used a cross-over design without separate reporting of first period data, and reported only on participants who provided data for both phases of treatment. The single, larger parallel group study had a high rate of withdrawals and did not report how these were handled in the efficacy analysis of group mean data.

Potential biases in the review process

We carried out a broad search for studies, and think it is unlikely that significant amounts of data remain unknown to us.

Five of the included studies used a cross-over design. The degree of exaggeration of treatment effects in cross-over trials compared to parallel-group designs, as has been seen in some circumstances (Khan 1996), is unclear but in itself is unlikely to be the source of major bias (Elbourne 2002). However, these studies reported results for both treatment periods combined, and only for participants who completed at least part of each treatment period, with last observation carried forward imputation for withdrawals, which is likely to overestimate efficacy.

Agreements and disagreements with other studies or reviews

We are not aware of any other reviews of levetiracetam for relief of neuropathic pain. Levetiracetam has been identified as a drug that should not been used for treating neuropathic pain because of a lack of evidence (NICE 2013).

AUTHORS' CONCLUSIONS

Implications for practice

This review found no evidence to suggest that levetiracetam provides pain relief in any neuropathic pain condition. Studies were small, mostly of relatively short duration for a chronic condition, and were potentially subject to major bias. There are more effective medicines available for the more common neuropathic pain conditions (Kalso 2013;Lunn 2014; Moore 2013c; Wiffen 2013).

Implications for research

Reasonable levels of evidence exist for the benefit of other antiepileptic and antidepressant drugs in the treatment of chronic neuropathic pain (for example, 14 studies of pregabalin in 3680 participants (Moore 2009); nine studies of duloxetine in 2776 participants (Lunn 2014)). Although the evidence for levetiracetam was of very low quality, there does not appear to be any justification for continued research with the drug in neuropathic pain given the poor results for efficacy, and because other treatments with evidence of significant efficacy are available.

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Wakita M, Kotani N, Kogure K, Akaike N. Inhibition of excitatory synaptic transmission in hippocampal neurons by levetiracetam involves Zn2+-dependentGABAA receptor-mediated presynaptic modulation. *Journal of Pharmacology and Experimental Therapeutics* 2013;**Nov 20**:Epub ahead of print. [PUBMED: 24259680]

Wiffen 2013

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2013, Issue 11. DOI: 10.1002/14651858.CD010567.pub2

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Falah 2012

Methods	Randomised, double-blind, placebo-controlled, cross-over study (2 x 6 weeks of treatment with 1 week washout) Pain medication tapered and stopped during pre-study period of ≥ 1 week Medication taken twice daily, titrated slowly over 15 days to maximum tolerated dose; target 3000 mg daily, reduction to minimum 2000 mg daily allowed for intolerable side effects
Participants	Central neuropathic pain due to multiple sclerosis (specialist confirmed). Median total pain rating ≥ 4/10 during week off pain medication N = 30 M 2, F 22 Median age 47 years (31 to 63) Median baseline pain 5.8/10 (4 to 9)
Interventions	Levetiracetam 2000 to 3000 mg daily (maximum tolerated) Placebo Rescue medication: up to 6 x 500 mg paracetamol + 50 mg tramadol daily
Outcomes	PR at end of treatment period: 6 point scale PI: NRS (0 to 10) for total pain and specific pain symptoms, daily Sleep disturbance: NRS (0 to 10), daily Phasic spacticity: NRS (0 to 4), daily Rescue medication Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5 Study drugs provided by UCB Pharma, who also provided some financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Remote allocation. Packaged and numbered by pharmacy, allocated consecutively. Sealed opaque envelopes with treatment details for emergencies
Blinding of participants and personnel (performance bias) All outcomes	Low risk	placebo tablets "identical in appearance, dosed similarly"

Falah 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	placebo tablets "identical in appearance, dosed similarly"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for withdrawals
Size	High risk	< 50 participants per treatment arm (n ≤ 30)

Finnerup 2009

Methods	Randomised, double-blind, placebo-controlled, cross-over study (1 week baseline then 2 x 5 weeks of treatment with 1 week washout) Medication taken twice daily, increased over 2 weeks to maximum tolerated dose; target 3000 mg daily, reduction to minimum of 2000 mg daily allowed for intolerable side effects
Participants	SCI with resulting at- or below-level of injury (or both) neuropathic pain for ≥ 3 months and median pain intensity ≥ 4/10 during baseline period N = 36 M 29, F 7 Mean age 53 years (SD ± 11)
Interventions	Levetiracetam 2000 to 3000 mg daily (maximum tolerated) Placebo Antidepressant medication tapered off during pre-study period, other spasmolytics, antiepileptics, opioids, simple analgesics continued if constant and unchanged Rescue medication: up to 6 x 500 mg paracetamol daily
Outcomes	PI: NRS (0 to 10), daily Sleep interference: NRS (0 to 10), daily Change in median pain score from baseline week to end of study PR: 6 point scale (overall, at-level, below-level pain) ≥ 33% pain relief Change in specific pain symptoms Spasm intensity and severity: NRS (0 to 10) PGIC: 5-point scale Rescue medication Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5 Study drugs provided by UCB Pharma, who also provided some financial support

Risk of bias

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

Finnerup 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	"computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Remote allocation. Packaged and numbered by pharmacy, allocated consecutively. Sealed opaque envelopes with treatment details for emergencies
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical placebo tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical placebo tablets"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for withdrawals
Size	High risk	< 50 participants per treatment arm (n ≤ 36)

Holbech 2011

Methods	Randomised, double-blind, placebo-controlled, cross-over study (1 week baseline then 2 x 6 weeks of treatment with 1 week washout) All pain medication tapered and stopped during pre-study period of ≥ 1 week Medication taken twice daily, titrated slowly over 15 days to maximum tolerated dose; target 3000 mg daily, reduction to minimum 2000 mg daily allowed for intolerable side effects
Participants	Polyneuropathy with pain ≥ 6 months and sensory disturbance in area of pain. Median total pain rating ≥ 4/10 during week off pain medication N = 39 M 22, F 13 (participants with sufficient data from both periods) Median age 57 years (21 to 74) Median total pain at baseline 5.7 (4 to 9)
Interventions	Levetiracetam 2000 mg to 3000 mg daily (maximum tolerated) Placebo Rescue medication: up to 6 x 500 mg paracetamol + 50 mg tramadol daily
Outcomes	PR: 6-point scale at end of each week PI:NRS (0 to 10) for total pain and specific pain symptoms, daily Sleep disturbance: NRS (0 to 10), daily Quality of life: SF-36 at end of each treatment period Rescue medication Adverse events

Holbech 2011 (*Continued*)

Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5 Study drugs provided by UCB Pharma, who also provided some financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Remote allocation. Packaged and numbered by pharmacy, allocated consecutively. Sealed opaque envelopes with treatment details for emergencies
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo tablets with identical appearance were dosed similarly"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Placebo tablets with identical appearance were dosed similarly"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for withdrawals
Size	High risk	< 50 participants per treatment arm (n ≤ 39)

Jungehulsing 2013

Methods	Randomised, double-blind, placebo-controlled, cross-over study (4-week baseline then 2 x 8 weeks of treatment with 2 week washout after each) Medication taken twice daily, starting at 1000 mg daily and increased every second week to target 3000 mg daily, reduction to previous tolerated dose allowed for intolerable side effects
Participants	Central spot-stroke pain for > 3 months with pain intensity ≥ 4/10 at baseline N = 42 M 26, F 16 Mean age 62 years (40 - 76) Median baseline pain 7/10
Interventions	Levetiracetam to 3000 mg daily (maximum tolerated) Placebo Antidepressants, antipsychotics, antiepileptics and analgesics allowed if stable and unchanged

Jungehulsing 2013 (*Continued*)

Outcomes	PI: NRS (0 to 10) three times daily Responder = PI reduction of ≥ 2/10 in final week compared to end of baseline Pain assessment: McGill Pain Questionnaire Depression: Beck Depression Inventory Quality of life: SF-12 Adverse events
Notes	Oxford Quality Score: R = 2, DB = 1, W = 1. Total = 4/5 Study drugs provided by UCB Pharma, who also provided some financial support

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Independent generation of list. Sequential allocation of numbers. Sealed envelopes with treatment details for emergencies
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals > 10%. Per protocol data reported. Imputation method not described
Size	High risk	< 50 participants per treatment arm (n ≤ 42)

NCT00160511

Methods	Randomised, double-blind, placebo-controlled, parallel group. Multicentre 16 week duration: 1-week baseline, 4-week up titration, 8-week maintenance, taper blinded period, 1-week drug-free Medication taken twice daily
Participants	Post herpetic neuralgia for ≥ 3 months and PI ≥ 40/100 at baseline with average daily score ≥ 4/10 for ≥ 4 days/week N = 170 M 90, F 77 (ITT) Mean age 70 years (± 12)

NCT00160511 (*Continued*)

Interventions	Levetiracetam 1000 mg to 3000 mg daily Placebo
Outcomes	Change in PI from baseline to final week of treatment Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5 Completed 2005. Study sponsor: UCB, Inc. Unpublished study; methods from clinicaltrials.gov, results from clinical study summary

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals > 20%. Mean data for efficacy with no mention of imputation method
Size	Unclear risk	50 to 200 participants per treatment arm (n = 83 to 86)

Vilholm 2008

Methods	Randomised, double-blind, placebo-controlled, cross-over study (2 x 4 weeks of treatment with 1 week washout) All pain medication tapered during pre-study period of ≥ 1 week Medication taken twice daily, titrated over 11 days to 3000 mg daily
Participants	Post-mastectomy pain (in breast, axilla, arm) ≥ 6 months after surgery for breast cancer. Pain duration ≥ 3 months, present ≥ 4 days/week, with median rating ≥ 4/10 during week off pain medication N = 27 All F Median age 60 years (38 to 80) Mean baseline pain 5.9/10 (4 to 9.6)

Vilholm 2008 (*Continued*)

Interventions	Levetiracetam 3000 mg daily Placebo Rescue medication: up to 8 x 500 mg paracetamol + 50 mg tramadol daily
Outcomes	PR: NRS (0 to 10) at end of treatment period PI: NRS (0 to 10) for total pain and specific pain symptoms, daily Rescue medication Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5 Study drugs provided by UCB Pharma, who also provided some financial support

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	Remote allocation. Packaged and numbered by pharmacy, allocated consecutively
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"placebo tablets with identical appearance were dosed similarly"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"placebo tablets with identical appearance were dosed similarly"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for withdrawals
Size	High risk	< 50 participants per treatment arm (n ≤ 27)

DB: double-blinding
F: female
ITT: intention-to-treat
LOCF: last observation carried forward
M: male
NRS: numerical rating scale
PGIC: Patient Global Impression of Change
PI: pain intensity
PR: pain relief
R: randomisation
SCI: spinal cord injury
SD: standard deviation

W: withdrawals

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

Study	Reason for exclusion
Rossi 2009	Single blind

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

NCT00156689

Methods	None provided. Probably not randomised, controlled, double-blind
Participants	Chronic idiopathic axonal polyneuropathy. Pain for ≥ 3 months, with intensity ≥ 40/100 at baseline (average daily score ≥ 4/10 for ≥ 4 days/week) M and F Age ≥ 18 years
Interventions	Levetiracetam (no dose or duration of treatment provided, implies 6 weeks) No comparator provided
Outcomes	Change in PI from baseline to last week of evaluation 30% responder 50% responder PGIC at final visit
Notes	Completed 2007. Study sponsor: Vanderbilt University. Principle investigator: Gary W Duncan, MD, Vanderbilt University

F: female
M: male
PGIC: Patient Global Impression of Change
PI: pain intensity

DATA AND ANALYSES

Comparison 1. Levetiriacetam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with substantial pain relief (≥50% pain intensity reduction, or complete or good pain relief)	4	240	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.43, 1.69]
2 Participants with at least one adverse event	5	409	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.06, 1.45]
3 All cause withdrawal	6	501	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.28, 2.81]
4 Adverse event withdrawal	6	500	Risk Ratio (M-H, Fixed, 95% CI)	4.90 [2.17, 11.09]
5 Lack of efficacy withdrawal	6	500	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.66, 2.52]

Analysis 1.1. Comparison 1 Levetiriacetam versus placebo, Outcome 1 Participants with substantial pain relief (≥50% pain intensity reduction, or complete or good pain relief).

Review: Levetiracetam for neuropathic pain in adults

Comparison: 1 Levetiriacetam versus placebo

Outcome: 1 Participants with substantial pain relief (≥50% pain intensity reduction, or complete or good pain relief)

Study or subgroup	Levetiracetam n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Falah 2012	1/27	1/27		7.1 %	1.00 [0.07, 15.18]
Finnerup 2009	1/34	1/32		7.3 %	0.94 [0.06, 14.42]
Holbech 2011	2/35	4/35		28.5 %	0.50 [0.10, 2.56]
Vilholm 2008	8/25	8/25		57.0 %	1.00 [0.45, 2.24]
Total (95% CI)	**121**	**119**		**100.0 %**	**0.85 [0.43, 1.69]**

Total events: 12 (Levetiracetam), 14 (Placebo)

Heterogeneity: Chi^2 = 0.58, df = 3 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Levetiriacetam versus placebo, Outcome 2 Participants with at least one adverse event.

Review: Levetiracetam for neuropathic pain in adults

Comparison: 1 Levetiriacetam versus placebo

Outcome: 2 Participants with at least one adverse event

Study or subgroup	Levetiracetam n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Falah 2012	22/27	15/27		13.6 %	1.47 [1.00, 2.15]
Finnerup 2009	14/34	11/32		10.3 %	1.20 [0.64, 2.24]
Holbech 2011	22/35	17/35		15.4 %	1.29 [0.85, 1.98]
NCT00160511	64/83	53/86		47.2 %	1.25 [1.02, 1.53]
Vilholm 2008	14/25	15/25		13.6 %	0.93 [0.58, 1.50]
Total (95% CI)	**204**	**205**		**100.0 %**	**1.24 [1.06, 1.45]**

Total events: 136 (Levetiracetam), 111 (Placebo)

Heterogeneity: Chi^2 = 2.19, df = 4 (P = 0.70); I^2 =0.0%

Test for overall effect: Z = 2.70 (P = 0.0069)

Test for subgroup differences: Not applicable

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

Review: Levetiracetam for neuropathic pain in adults

Comparison: 1 Levetiriacetam versus placebo

Outcome: 3 All cause withdrawal

Study or subgroup	Levetiracetam n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Falah 2012	6/30	1/27		3.4 %	5.40 [0.69, 42.04]
Finnerup 2009	9/34	3/32		10.0 %	2.82 [0.84, 9.51]
Holbech 2011	8/35	5/35		16.2 %	1.60 [0.58, 4.41]
Jungehulsing 2013	7/42	2/42		6.5 %	3.50 [0.77, 15.88]
NCT00160511	28/84	19/86		60.7 %	1.51 [0.92, 2.48]
Vilholm 2008	1/27	1/27		3.2 %	1.00 [0.07, 15.18]
Total (95% CI)	**252**	**249**		**100.0 %**	**1.90 [1.28, 2.81]**

Total events: 59 (Levetiracetam), 31 (Placebo)

Heterogeneity: Chi^2 = 3.18, df = 5 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 3.22 (P = 0.0013)

Test for subgroup differences: Not applicable

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

Review: Levetiracetam for neuropathic pain in adults

Comparison: 1 Levetiriacetam versus placebo

Outcome: 4 Adverse event withdrawal

Study or subgroup	Levetiracetam n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Falah 2012	5/30	1/27		16.0 %	4.50 [0.56, 36.13]
Finnerup 2009	8/34	2/32		31.3 %	3.76 [0.86, 16.41]
Holbech 2011	3/35	0/35		7.6 %	7.00 [0.37, 130.69]
Jungehulsing 2013	3/42	1/42		15.2 %	3.00 [0.33, 27.69]
NCT00160511	13/83	2/86		29.9 %	6.73 [1.57, 28.94]
Vilholm 2008	0/27	0/27			Not estimable
Total (95% CI)	**251**	**249**		**100.0 %**	**4.90 [2.17, 11.09]**

Total events: 32 (Levetiracetam), 6 (Placebo)

Heterogeneity: $Chi^2 = 0.56$, df = 4 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 3.81 (P = 0.00014)

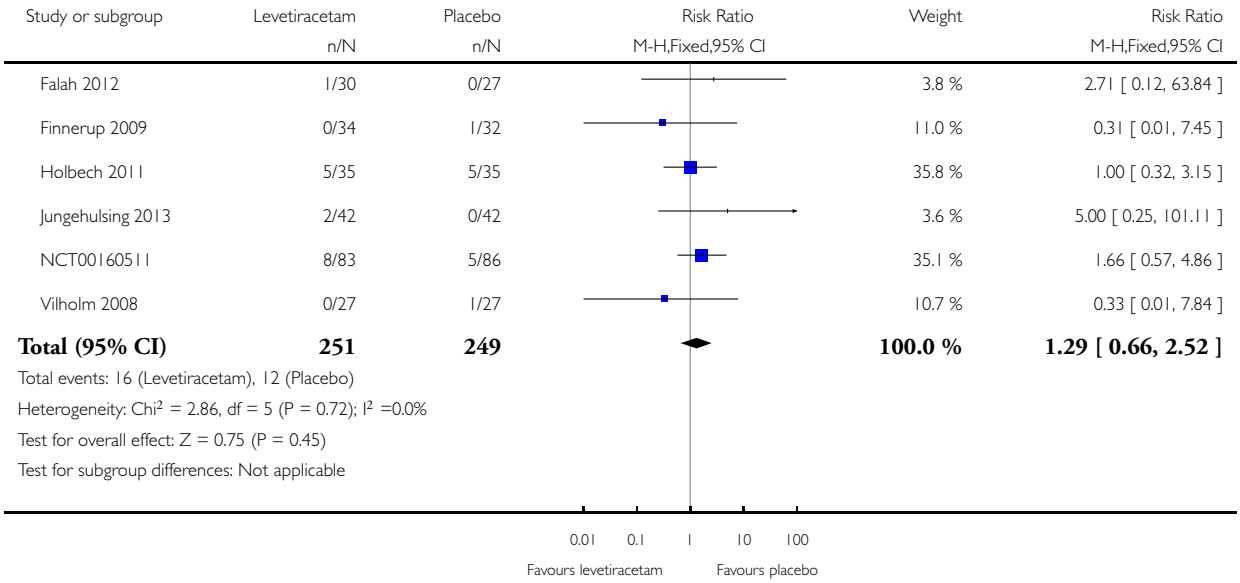
Test for subgroup differences: Not applicable

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

Review: Levetiracetam for neuropathic pain in adults

Comparison: 1 Levetiriacetam versus placebo

Outcome: 5 Lack of efficacy withdrawal



APPENDICES

Appendix 1. Methodological considerations for 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; Moore 2010e), arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010), and generally in chronic pain (Moore 2013d); 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 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013d; Straube 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good reasons for doing so.

4. Individual patient analyses and other evidence 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 2010d; Moore 2013a).

Appendix 2. Search strategy for MEDLINE via OVID

1. (Levetiracetam or etiracetam or keppra or kopodex or matever or lo 59 OR lo59).mp. (1809)
2. exp Pain/ (298354)
3. (pain* or analges*).mp. (540557)
4. 2 or 3 (613221)
5. randomized controlled trial.pt. (362550)
6. controlled clinical trial.pt. (87486)
7. randomized.ab. (262961)
8. placebo.ab. (142353)
9. drug therapy.fs. (1663512)
10. randomly.ab. (187682)
11. trial.ab. (270707)
12. or/5-11 (2211133)
13. 1 and 4 and 12 (66)

Appendix 3. Search strategy for EMBASE (via Ovid)

1. (Levetiracetam or etiracetam or keppra or kopodex or matever or lo 59 or lo59).mp. (9642)
2. exp Pain/ (816579)
3. (pain* or analges*).mp. (940753)
4. 2 or 3 (1160760)
5. randomized controlled trial/ (370534)
6. double-blind procedure/ (123176)
7. crossover-procedure/ (40022)
8. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1224329)
9. 5 or 6 or 7 or 8 (1309212)
10. 1 and 4 and 9 (341)

Appendix 4. Search strategy for CENTRAL

1. (Levetiracetam or etiracetam or keppra or kopodex or matever or lo 59 OR lo59):it,ab,kw (325)
2. pain or painful:it,ab,kw (71733)
3. analgesi*:it,ab,kw (28077)
4. MeSH descriptor: [Pain] explode all trees (31406)
5. #2 or #3 or #4 (84869)
6. #1 and #5 (33)
7. Limit to CENTRAL (27)

Appendix 5. Summary of outcomes in individual studies: efficacy

Study ID	Treatment	Pain outcome	Other efficacy outcome	Rescue medication
Falah 2012	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**PR** at end of treatment period (6-point scale) **Complete or good**: Levet 1/27 Placebo 1/27 **Complete, good or moderate**: Levet 5/27 Placebo 2/27	Group mean (SD) for final week of treatment **PI** (0-10): Levet 5.3 (2.0) Placebo 5.7 (1.8) No change from baseline **PR** (1-6): Levet 2.4 (1.0) Placebo 2.1 (0.9)	Mean (SD) tablets/week Levet: paracetamol 17.6 (17.7), tramadol 0.9 (2.4) Placebo: paracetamol 18.3 (17.6), tramadol 1.3 (2.5) Unchanged from baseline period
Finnerup 2009	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**PR** at end of treatment period (6 point scale) **Complete or good**: Levet 1/24 Placebo 1/24 **Complete, good or moderate**: Levet 3/27 Placebo 1/27 **≥50% PR**: Levet 1/34 Placebo 1/32 **≥33% PR**: Levet 3/34 Placebo 4/32	Group median (range) for final week of treatment **PI** (0-10, baseline 6): Levet 6 (3-9.5) Placebo 7 (3-9)	Median (range) tablets/week Levet: paracetamol 0 (0-56) Placebo: 0 (0-56) Unchanged from baseline period
Holbech 2011	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**PR** at end of treatment period (6 point scale) **Complete or good**: Levet 2/35 Placebo 4/35 **Complete, good or moderate**: Levet 5/35 Placebo 5/35	Group mean (SD) for final week of treatment **PI** (total pain, 0-10, baseline 5.7): Levet 5.5 (2.5) Placebo 5.3 (2.3)	Mean (SD) tablets/week Levet: paracetamol 14.3 (13.9), tramadol 2.0 (2.6) Placebo: paracetamol 12.9 (12.7), tramadol 1.8 (2.9) Unchanged from baseline period

(*Continued*)

Jungehulsing 2013	(1) Levet to max 3000 mg daily (2) Placebo	No dichotomous data reported	Median **PI** in treatment groups did not differ: 7/10 No change in any secondary outcomes	Not reported
NCT00160511	(1) Levet to max 3000 mg daily (2) Placebo	No dichotomous data reported	Mean change in **PI** score: Levet -1.50 Placebo -1.84	Not reported
Vilholm 2008	(1) Levet 3000 mg daily (2) Placebo	≥**50% PR**: Levet 8/25 Placebo 8/25	Mean **PI** (0-10, range) in treatment group did not differ: Levet 4 (2-6) Placebo 4 (1.5-6.5)	Mean (range) tablets/week Levet: paracetamol 14.9 (0-54), tramadol 0.4 (0-4) Placebo: paracetamol 13.9 (0-42), tramadol 0.3 (0-5) Unchanged from baseline period

Levet: levetiracetam; PI: pain intensity; PR: pain relief; SD: standard deviation

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

Study	Treatment	Adverse events	Withdrawals
Falah 2012	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**Any**: Levet 22/27 Placebo 15/27	**All cause**: Levet 6/30 Placebo 1/27 **Adverse event**: Levet 5/30 (fatigue, tiredness, dizziness, MS attack) Placebo 1/27 ('flu, tiredness) **Lack of efficacy**: Levet 1/30 Placebo 0/27
Finnerup 2009	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**Any**: Levet 14/34 Placebo 11/32	**All cause**: Levet 9/34 Placebo 3/32 **Adverse event**: Levet 8/34 Placebo 2/32 **Lack of efficacy**: Levet 0/34

(*Continued*)

			Placebo 1/32 1 participant with Levet had major protocol violation
Holbech 2011	(1) Levet 2000 mg to 3000 mg daily (2) Placebo	**Any**: Levet 22/35 Placebo17/35	**All cause**: Levet 8/35 Placebo 5/35 **Adverse event**: Levet 3/35 (fatigue, sleep disturbance) Placebo 0/35 **Lack of efficacy**: Levet 5/35 Placebo 5/35 1 participant on Levet withdrew due to lack of efficacy and adverse event 1 participant on Levet withdrew due to logistic problem
Jungehulsing 2013	(1) Levet to max 3000 mg daily (2) Placebo	**Any**: not reported **Serious**: none	**All cause**: Levet 7/42 Placebo 2/42 **Adverse event**: Levet 3/42 (fatigue) Placebo 1/42 (fatigue) **Lack of efficacy**: Levet 2/42 Placebo 0/42 2 participants in Levet and 1 in placebo groups excluded due to incomplete pain diary
NCT00160511	(1) Levet to max 3000 mg daily (2) Placebo	**Any**: Levet 64/83* Placebo 53/86 **Serious**: Levet 2/83 Placebo 2/86 * 1 participant did not take any medication	**All cause**: Levet 28/84 Placebo 19/86 **Adverse event**: Levet 13/83 Placebo 2/86 **Lack of efficacy**: Levet 8/83 Placebo 5/86
Vilholm 2008	(1) Levet 3000 mg daily (2) Placebo	**Any**: Levet 14/25 Placebo 15/25	**All cause**: Levet 1/27 Placebo 1/27

(*Continued*)

			Adverse event: none **Lack of efficacy**: Levet 0/27 Placebo 1/27

Levet: levetiracetam

WHAT'S NEW

Date	Event	Description
29 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 1, 2014

Review first published: Issue 7, 2014

Date	Event	Description
1 July 2016	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

Protocol: PW and SD wrote the protocol, based on a PaPaS template for antiepileptic drugs for neuropathic pain.

Review: PW and SD searched for studies, selected studies for inclusion, and carried out data extraction. RAM acted as arbitrator. All authors were involved in writing the 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 and Company, Flynn Pharma, Futura Medical, Grünenthal, GlaxoSmithKline (GSK), Horizon Pharma, Lundbeck, Menarini, MSD, Pfizer, Reckitt Benckiser, Sanofi Aventis, Urgo, Astellas, and Vifor Pharma. He has no interests to declare related to this review.

MPL has received honoraria for consultation from Baxter Pharmaceuticals, CSL Behring, and LfB, and he has received a travel support grant from Grifols. He has no interests to declare related to this review.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support

External sources

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

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Use of rescue medication was reported in four studies but was not a prespecified outcome in the protocol. We added the outcome for completeness.

NOTES

A restricted search in June 2016 did not identify any potentially relevant studies. 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)

Analgesics [*therapeutic use]; Chronic Disease; Levetiracetam; Neuralgia [classification; *drug therapy; etiology]; Piracetam [*analogs & derivatives; therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans