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Lamotrigine add-on therapy for drug-resistant focal epilepsy (Review)

Panebianco M, Bresnahan R, Ramaratnam S, Marson AG

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[Intervention Review]

Lamotrigine add-on therapy for drug-resistant focal epilepsy

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ABSTRACT

Background

This is an updated version of the Cochrane Review previously published in 2016.

Epilepsy is a common neurological disorder, affecting 0.5% to 1% of the population. For nearly 30% of these people, their epilepsy is resistant to currently available drugs. Pharmacological treatment remains the first choice to control epilepsy. Lamotrigine is one of the newer antiepileptic drugs. Lamotrigine, in combination with other antiepileptic drugs (add-on), can reduce seizures, but with some adverse effects.

Objectives

To determine the effects of lamotrigine on (1) seizures, (2) adverse-effect profile, and (3) cognition and quality of life, compared to placebo, when used as an add-on treatment for people with drug-resistant focal epilepsy.

Search methods

For the latest update of the review, we searched the following databases on 9 March 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to March 06, 2020). CRS Web includes randomized or quasi-randomized, controlled trials from PubMed, EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy. No language restrictions were imposed.

Selection criteria

Randomised placebo-controlled trials of people with drug-resistant focal epilepsy of any age, in which an adequate method of concealment of randomisation was used. The studies were double-, single- or unblinded, placebo-controlled. For cross-over studies, the first treatment period was treated as a parallel trial. Eligible participants were adults or children with drug-resistant focal epilepsy.

Data collection and analysis

For this update, two review authors independently assessed the trials for inclusion, and extracted data. Outcomes included 50% or greater reduction in seizure frequency, treatment withdrawal (any reason), adverse effects, effects on cognition and quality of life. Primary analyses were by intention-to-treat. Sensitivity best- and worse-case analyses were undertaken to account for missing outcome data. Pooled risk ratios (RRs) with 95% confidence intervals (95% CIs) were estimated for the primary outcomes of seizure frequency and treatment withdrawal. For adverse effects, we calculated pooled RRs and 99% CIs.

Main results

We did not identify any new studies for this update, therefore, the results and conclusions are unchanged.

In previous updates of this review, the authors found five parallel add-on studies, eight cross-over studies in adults or children with drug-resistant focal epilepsy, and one parallel add-on study with a responder-enriched design in infants. In total, these 14 studies included 1806 eligible participants (38 infants, 199 children, 1569 adults). Baseline phases ranged from four to 12 weeks; treatment phases from eight to 36 weeks. Overall, 11 studies (1243 participants) were rated as having low risk of bias, and three (697 participants) had unclear risk of bias due to lack of reported information around study design. Effective blinding of studies was reported in four studies (563 participants).

The overall risk ratio (RR) for 50% or greater reduction in seizure frequency was 1.80 (95% CI 1.45 to 2.23; 12 trials, 1322 participants (adults and children); moderate-certainty evidence) indicating that lamotrigine was significantly more effective than placebo in reducing seizure frequency. The overall RR for treatment withdrawal (for any reason) was 1.11 (95% CI 0.91 to 1.37; 14 trials; 1806 participants; moderate-certainty evidence). The adverse events significantly associated with lamotrigine were: ataxia, dizziness, diplopia (double vision), and nausea. The RR of these adverse effects were as follows: ataxia 3.34 (99% Cl 2.01 to 5.55; 12 trials; 1525 participants; high-certainty evidence); dizziness 2.00 (99% Cl 1.52 to 2.64;13 trials; 1768 participants; moderate-certainty evidence); diplopia 3.79 (99% Cl 2.15 to 6.68; 3 trials, 944 participants; high-certainty evidence); nausea 1.81 (99% Cl 1.22 to 2.68; 12 studies,1486 participants; moderate-certainty evidence). The limited data available precluded any conclusions about effects on cognition and quality of life. No important heterogeneity between studies was found for any of the outcomes. Overall, we assessed the evidence as high to moderate certainty, due to incomplete data for some outcomes.

Authors' conclusions

Lamotrigine as an add-on treatment for drug-resistant focal seizures appears to be effective in reducing seizure frequency, and seems to be fairly well-tolerated. However, the trials were of relatively short duration and provided no evidence for the long term. Further trials are needed to assess the long-term effects of lamotrigine, and to compare lamotrigine with other add-on drugs.

PLAIN LANGUAGE SUMMARY

Lamotrigine add-on therapy for drug-resistant focal epilepsy

Background

Epilepsy is a disorder in which unexpected electrical discharges from the brain cause seizures. Approximately one-third of patients with epilepsy continue to have seizures, despite treatment with presently used (older) antiepileptic drugs (AEDs). In addition, the older AEDs have a lot of adverse effects. Therefore, the development of effective new therapies for the treatment of drug-resistant seizures is of considerable importance. As a result, a range of new AEDs has been developed as 'add-on' treatments. Lamotrigine is one of these drugs.

Aims of the review

This review aimed to determine the effects of lamotrigine on seizures, adverse effects, cognition (ability to learn and understand) and quality of life compared to placebo controls, when used as an add-on treatment for people with focal epilepsy that would not respond to existing AEDs. For this update, we did not identify any new studies to add, and thus, the conclusions remain unchanged. The review included 14 randomised controlled trials with a total number of 1806 participants.

Results

Lamotrigine, used in combination with other AEDs in patients who have drug-resistant focal epilepsy can decrease the frequency of seizures further. However, adding lamotrigine to the usual treatment is more often associated with an increase in adverse effects such as unsteadiness (ataxia), dizziness, double vision (diplopia), and nausea.

Certainty of the evidence

We assessed the trials with regards to risk of bias and overall we judged them as low to unclear. We rated the certainty of the evidence as high to moderate.

Conclusions

Further high-quality research is needed to fully evaluate the efficacy and tolerability of lamotrigine and compare it with other newer AEDs.

The evidence is current to 9 March 2020.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Lamotrigine versus placebo for drug-resistant focal epilepsy

Patient or population: participants with drug-resistant focal epilepsy

Settings: outpatient setting

Intervention: add-on lamotrigine

Control: add-on placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Lamotrigine				
50% or greater reduction in seizure frequency - ITT analysis	**157 per 1000**	**283 per 1000** (223 to 350)	**RR 1.80** (95% CI 1.45 to 2.23)	1322 (12 studies)	⊕⊕⊕⊖ moderate[1]	RR > 1 indicates outcome is more likely in lamotrigine group
Treatment withdrawal	**159 per 1000**	**176 per 1000** (144 to 217)	**RR 1.11** (95% CI 0.91 to 1.37)	1806 (14 studies)	⊕⊕⊕⊖ moderate[1]	RR > 1 indicates outcome is more likely in lamotrigine group
Ataxia	**45 per 1000**	**150 per 1000** (90 to 250)	**RR 3.34** (99% CI 2.01 to 5.55)	1525 (12 studies)	⊕⊕⊕⊕ high[1,3]	RR > 1 indicates outcome is more likely in lamotrigine group
Diplopia	**61 per 1000**	**233 per 1000** (132 to 410)	**RR 3.79** (2.15 TO 6.68)	944 (3 studies)	⊕⊕⊕⊕high[1,3]	RR > 1 indicates outcome is more likely in lamotrigine group
Dizziness	**128 per 1000**	**255 per 1000** (194 to 337)	**RR 2.00** (99% CI 1.52 to 2.64)	1768 (13 studies)	⊕⊕⊕⊖ moderate[2]	RR > 1 indicates outcome is more likely in lamotrigine group
Fatigue	**113 per 1000**	**93 per 1000** (62 to 138)	**RR 0.82**	1552	⊕⊕⊕⊖ moderate[1]	RR < 1 indicates outcome is less likely in lamotrigine group

			(99% CI 0.55 to 1.22)	(12 studies)		
Nausea	**83 per 1000**	**150 per 1000** (101 to 222)	**RR 1.81** (99% CI 1.22 to 2.68)	1486 (12 studies)	⊕⊕⊕⊖ moderate[1]	RR > 1 indicates outcome is more likely in lamotrigine group

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes[4]. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once for imprecision: Number of events (< 400) did not suffice the optimal information size.
[2] Downgraded once for inconsistency: Significant statistical heterogeneity was detected (P < 0.10).
[3] Upgraded once for large effect size: Risk ratio greater than 2.00.

BACKGROUND

This review is an update of the Cochrane Review previously published in 2016, Issue 6 of the *Cochrane Database of Systematic Reviews* (Ramaratnam 2016).

Description of the condition

Epilepsy is characterised by recurrent and unprovoked seizures, constituting a transient sign and symptom of abnormal, excessive electrical activity in the cerebral cortex (Fisher 2005). Epilepsy is one of the most common serious neurological conditions worldwide, with significant psychosocial and physical morbidity. Its management requires expertise and good pharmacological knowledge of the available options (Lyer 2014). The condition affects approximately 50 million people worldwide. The total annual cost in Europe is approximately 15.5 billion Euros (Mula 2013). Between 2% and 3% of the population will be given a diagnosis of epilepsy at some time in their lives (Hauser 1993), the majority of whom will become seizure free. However, up to 30% will continue to have seizures, refractory to treatment with adequate doses of antiepileptic drugs (AEDs), which are often given in combination (Cockerell 1995). There is no internationally accepted definition of "drug-resistant". For the purposes of this review, people will be considered to be drug-resistant if they have failed to respond to a minimum of two AEDs, given as monotherapy. The majority of drug-resistant people have focal onset (also called focal or localisation-related) seizures. In other words, seizures start in one part of the brain and during the course of the seizure, the abnormal electrical activity remains localised or spreads to other parts of the brain. Focal seizures can be divided into three types: simple focal; complex focal, and secondarily generalised tonic-clonic seizures (Commission 1989).

Description of the intervention

Although more than a dozen new AEDs have entered the market since 1993, up to 30% of patients remain refractory to current treatments. Thus, a concerted effort continues to identify and develop new therapies that will help these patients (Barker-Haliski 2014). Pharmacological treatment remains the first choice for controlling epilepsy (Loscher 2002), although recent decades have seen advances in vagal stimulation (Panebianco 2015), and surgery (West 2019). Given that our standard drugs (e.g. carbamazepine, phenytoin, valproate, gabapentin) do not leave all people seizure free and are not without adverse effects (Panebianco 2018), over the past 20 to 25 years, there has been renewed interest in the development of newer AEDs. Lamotrigine is a relatively more recent AED, widely used in the treatment of epilepsy as adjunctive treatment for focal, secondarily generalised, and tonic-clonic seizures in patients with drug-resistant epilepsy, and bipolar disorder (Yamamoto 2012).

How the intervention might work

Lamotrigine was approved by the Food and Drug Administration in the USA in 1994 for use in focal-onset seizures. It was ultimately approved for monotherapy in 1998. Lamotrigine is effective against a broad spectrum of seizure types and has a favourable metabolic profile. It has gained widespread use in the USA as both an immediate and an extended-release agent (Moore 2012). Lamictal (GlaxoSmithKline) is considered the reference drug (Girolineto 2012). In vitro pharmacological studies suggest that the main mechanism of action of lamotrigine is to inhibit voltage-sensitive sodium channels, thereby stabilising neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids, e.g. glutamate and aspartate (Leach 1995). Lamotrigine has been demonstrated to be effective as both an antiepileptic drug and a mood stabiliser (Vajda 2013).

Why it is important to do this review

In this review, we summarise evidence from randomised controlled trials where the efficacy and tolerability of lamotrigine for people with drug-resistant focal epilepsy have been investigated, in order to aid clinical decision-making when considering lamotrigine as add-on treatment within this population. Antiepileptic drugs may impair people's cognitive abilities, and in this review, we include outcomes that assess cognitive effects. In addition, we have chosen to include quality of life (QOL) outcomes, to assess the global impact of this drug on people's well-being.

OBJECTIVES

To determine the effects of lamotrigine on (1) seizures, (2) adverse-effect profile, and (3) cognition and quality of life, compared to placebo, when used as an add-on treatment for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included trials that met all the following criteria.

1. Randomised controlled trials, in which an adequate method of concealment of randomisation was used (e.g. allocation of sequentially sealed packages of medication, sealed opaque envelopes, telephone randomisation).
2. Double-blind, single-blind trials and unblinded trials.
3. Placebo-controlled trials.
4. Parallel group and cross-over studies. For cross-over studies, the first treatment period was treated as a parallel trial, for the purposes of analysis of efficacy and safety data (i.e. only data from the first treatment period was used).

Types of participants

Individuals of any age with focal epilepsy (i.e. experiencing simple focal, complex focal, or secondarily generalised tonic-clonic seizures) who had failed to respond to at least two antiepileptic drugs ((AEDs) (drug-resistant epilepsy).

Types of interventions

1. The treatment group received lamotrigine in addition to conventional AEDs treatment.
2. The control group received conventional AED treatment plus a matched placebo, or 'no treatment' control.

Types of outcome measures

Primary outcome

Fifty per cent or greater reduction in seizure frequency

The primary outcome was the proportion of participants with a 50% or greater reduction in seizure frequency during the treatment

period, compared to the pre-randomisation baseline frequency. We chose this outcome as it is commonly reported in this type of study and can be calculated for studies that do not report this outcome, provided that baseline seizure data were recorded.

Secondary outcomes

Treatment withdrawal

The proportion of participants who had treatment withdrawn during the course of the treatment period was chosen as a measure of global effectiveness. Treatment may be withdrawn due to adverse effects, lack of efficacy, or a combination, and this is an outcome to which the individual makes a direct contribution. However, in studies of relatively short duration, such as studies that would be included in this review, adverse effects were likely to be the main reason for treatment withdrawal.

Adverse effects

1. The proportion of participants experiencing any of the following adverse effects, which we considered to be the most common and important adverse effects of AEDs:
   a. ataxia;
   b. dizziness
   c. fatigue;
   d. nausea.
2. The proportion of participants who experienced the five most common adverse effects in a study, if different from those stated above.

Cognitive effects

The difference between intervention and control group(s) means for cognitive assessments used in the individual studies.

Quality of life (QOL)

The difference between intervention and control group(s) means for QOL assessments used in the individual studies.

Search methods for identification of studies

Electronic searches

Searches were run for the original review in 1999 and subsequent searches were run in 2001, 2002, 2003, 2005, 2007, 2010, 2011, 2012, 2015, 2017 and 2018. For the latest update, we searched the following databases on 9 March 2020.

1. Cochrane Register of Studies (CRS Web), using the strategy outlined in Appendix 1.
2. MEDLINE (Ovid, 1946 to March 06, 2020), using the strategy outlined in Appendix 2.

CRS Web includes randomized or quasi-randomized, controlled trials from PubMed, EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy. We imposed no language restrictions.

Searching other resources

For the original review and this update, we checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials, and authors and manufacturers of lamotrigine (GlaxoSmithKline) for additional information.

Data collection and analysis

Selection of studies

For this update, two review authors (SR and MP) independently assessed trials for inclusion. Any disagreements were resolved by discussion with a third review author (AM). Two review authors (SR and MP) independently extracted data and assessed the risk of bias for included trials; again, disagreements were resolved by mutual discussion.

Data extraction and management

We extracted the following data for each trial, using a data extraction form.

1. Methods and trial design:
   a. method of randomisation;
   b. method of allocation concealment;
   c. method of blinding;
   d. whether any participants had been excluded from reported analyses;
   e. duration of baseline period;
   f. duration of treatment period;
   g. dose(s) of lamotrigine tested;
   h. information on sponsorship and funding.
2. Participant and demographic information:
   a. total number of participants allocated to each treatment group;
   b. age and sex;
   c. number with focal and generalised epilepsy;
   d. seizure types;
   e. seizure frequency during the baseline period;
   f. number of background drugs.
3. Outcomes:
   a. we recorded the number of participants who experienced each outcome (*see*Types of outcome measures) per randomised group, and contacted authors of trials for any missing information.

Assessment of risk of bias in included studies

Two review authors (SR and MP) independently assessed the risk of bias for each trial, using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We discussed and resolved disagreements. We completed a 'Risk of bias' table for each included study in RevMan (RevMan 2014). We rated all included studies as having a low, high or unclear risk of bias on six domains applicable to randomised controlled trials: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

We analysed the primary outcome of seizure reduction as a binary outcome and presented it as a risk ratio. We also analysed secondary outcomes, including treatment withdrawal

and adverse effects as binary outcomes and presented risk ratio. We had also planned to present cognitive effects and quality of life as continuous outcomes via mean differences if the same measurement scales were used or via standardised mean differences if different measurement scales were used to measure the same outcome. However, due to the limited amount of data available for these outcomes, we have presented these outcomes in a narrative discussion

Unit of analysis issues

We included eight cross-over studies in the review. We analysed data for the first treatment period from these studies only; we analysed parallel and cross-over design studies in separate subgroups.

Dealing with missing data

We sought missing data by contacting the study authors. We carried out intention-to-treat (ITT), best-case and worst-case analysis on the primary outcome to account for any missing data (see Data synthesis). We presented all analyses in the main report.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials (e.g. age, seizure type, duration of epilepsy, number of AEDs taken at time of randomisation), and trial factors (e.g. randomisation concealment, blinding, losses to follow-up). We examined statistical heterogeneity using a Chi^2 test and I^2 statistic. When we found no significant heterogeneity ($P < 0.10$), we used a fixed-effect model. Had we found heterogeneity (> 50%), we had planned to use a random-effects model for the analysis.

Assessment of reporting biases

We requested protocols for all included studies to enable a comparison of outcomes of interest. If outcome reporting bias was suspected for any included study, we had planned to further investigate using the ORBIT matrix system (Kirkham 2010). We had planned an examination of asymmetry funnel plots to establish publication bias, but such an assessment was not possible due to the small number of studies included in the review.

Data synthesis

We used a fixed-effect model meta-analysis to synthesise the data. We measured the effect of each comparison on our preset primary and secondary outcomes, if data were available. Comparisons we expected to carry out included:

1. usual treatment plus lamotrigine versus usual treatment plus placebo;
2. usual treatment plus lamotrigine versus no treatment;
3. usual treatment plus lamotrigine versus usual treatment.

Our preferred estimator for all binary outcomes was the Mantel-Haenzsel risk ratio (RR). For the outcomes 50% or greater reduction in seizure frequency and treatment withdrawal, we used 95% confidence intervals (CIs). For individual adverse effects, we used 99% CIs to make an allowance for multiple testing.

Our analyses included all participants in the treatment groups to which they had been allocated following randomisation.

For the efficacy outcome (50% or greater reduction in seizure frequency), we undertook three analyses.

(a) Primary (ITT) analysis
Participants not completing follow-up or with inadequate seizure data were assumed to be non-responders. To test the effect of this assumption, we undertook the following sensitivity analyses. Analysis by ITT was done where this was reported by the included studies.

(b) Worst-case analysis
Participants not completing follow-up or with inadequate seizure data were assumed to be non-responders in the lamotrigine group, and responders in the placebo group.

(c) Best-case analysis
Participants not completing follow-up or with inadequate seizure data were assumed to be responders in the lamotrigine group, and non-responders in the placebo group.

Subgroup analysis and investigation of heterogeneity

We considered adults and children and doses in our subgroup analyses. We performed a subgroup analysis for adverse events.

Sensitivity analysis

We intended to carry out sensitivity analyses if peculiarities were found between study quality, characteristics of participants, interventions and outcomes.

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables, using GRADEpro and the GRADE approach for assessing the certainty of evidence (GRADEpro 2014). We GRADE-assessed the evidence for six of the outcomes: 50% or greater reduction in seizure frequency; treatment withdrawal; ataxia; dizziness; fatigue; and nausea.

RESULTS

Description of studies

Results of the search

The search carried out on 13 December 2018 identified 27 records from the databases outlined above. We screened 23 records after duplicates were removed for inclusion in the review. We excluded 16 studies at this point, and requested seven full-text articles to assess for eligibility. We contacted authors of these trials for more information, providing their contact details were available. Following this, we excluded all seven studies (please see Figure 1 and Characteristics of excluded studies for reasons of exclusion). The latest search (9 March 2020) identified no new, relevant studies. Thus, no new studies were included in this review.

Figure 1. Study flow diagram for 2018 update.

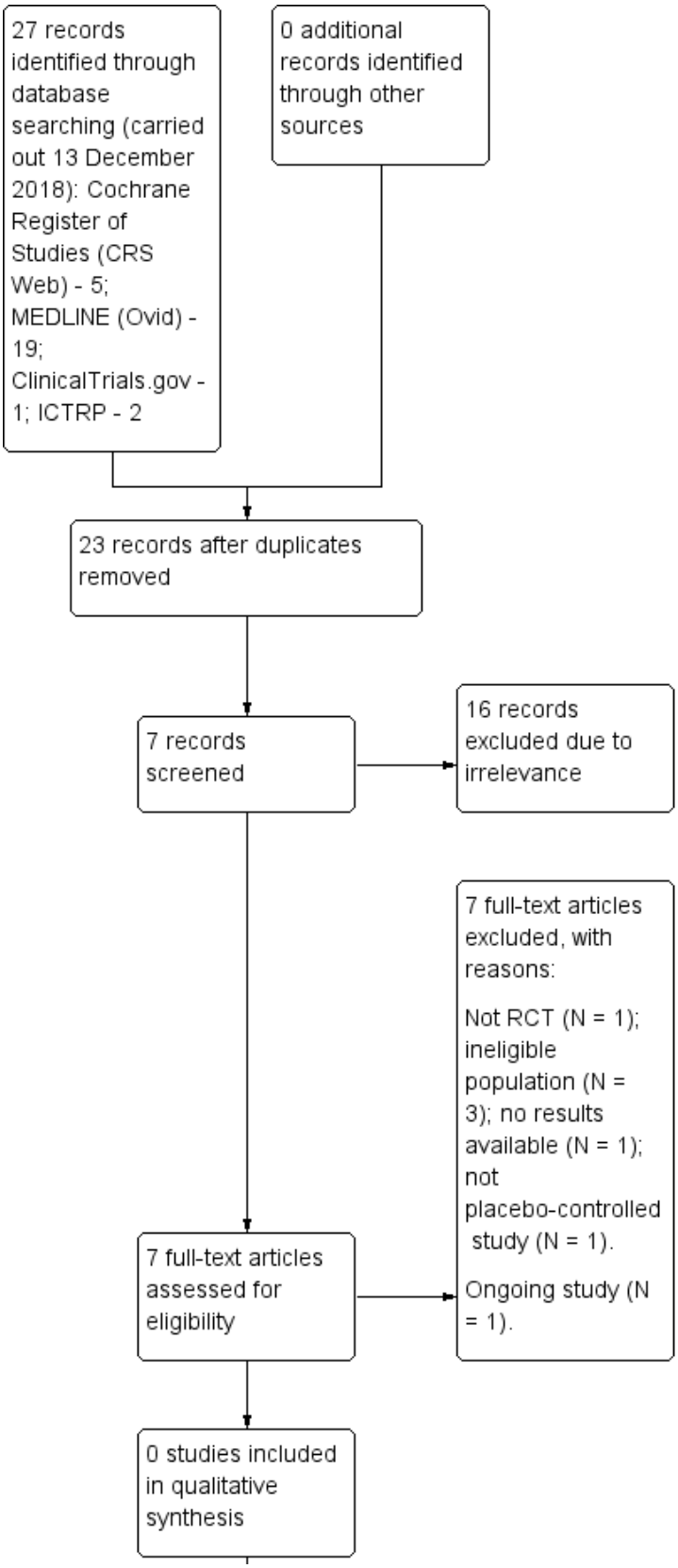
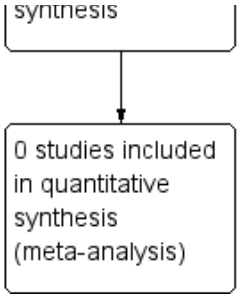


Figure 1. (Continued)



Included studies

We did not find any new studies for this update.

In a previous version of this review, the review authors included 14 randomised controlled trials that investigated the use of add-on lamotrigine compared to placebo, in 1806 participants with uncontrolled focal seizures (38 infants, 199 children, 1569 adults). Trial characteristics are summarised below. For further information on each trial, please see Characteristics of included studies.

The 14 studies included five parallel group studies (Baulac 2010; Duchowny 1999; Matsuo 1993; Naritoku 2007; Schachter 1995); one parallel group study in infants with a responder-enriched design, in which all patients received adjunctive lamotrigine during an open-label phase and those who had a 40% or greater reduction in the frequency of focal seizures during the last four weeks were randomly assigned to double-blind treatment for up to eight weeks with continued lamotrigine or placebo (Piña-Garza 2008); and eight cross-over studies (Binnie 1989; Boas 1996; Jawad 1989; Loiseau 1990; Messenheimer 1994; Schapel 1993; Schmidt 1993; Smith 1993). All but two studies recruited adults; Duchowny 1999 recruited only children, and Piña-Garza 2008 enrolled only infants aged one to 24 months of age. One trial used extended-release formulation of lamotrigine (Naritoku 2007), while the other trials used immediate-release formulations. In general, the individuals included in these studies had at least three to four focal seizures a month, despite therapy with a stable antiepileptic drug (AED) regimen consisting of two or three AEDs, which were appropriate for the type of epilepsy, and were given in adequate doses.

Almost all studies excluded people with: intellectual disabilities, progressive neurological disease, major psychiatric problems, associated pseudo seizures, newly-diagnosed epilepsy, status epilepticus in the 24 weeks preceding the trial, associated systemic diseases, abnormal laboratory investigations not explained by enzyme induction by AEDs, a history of non-compliance, failure to keep reliable records of seizures or adverse effects, irregular clinic visits, recent use of any other investigational AED, abuse of alcohol or other prescription or non-prescription drugs; people receiving chronic medication, especially antipsychotic drugs, women who were pregnant or at risk of pregnancy, lactating women. For the cross-over studies, participants were not randomised to a single dose, but took a range of doses, depending on their clinical response and the concurrent administration of other AEDs. Use of valproate was not permitted in three studies (Matsuo 1993; Messenheimer 1994; Schachter 1995), two excluded people on valproate monotherapy (Schapel 1993; Smith 1993), while others used lower dosages of lamotrigine for people on valproate. One parallel study tested doses of 300 mg and 500 mg of lamotrigine per day (Matsuo 1993), whereas the others tested a range of doses between 75 mg and 600 mg per day (median between 200 mg and 400 mg/day). The length of the treatment period varied from eight to 24 weeks.

All studies were published as full articles, except Schmidt 1993, which was only published as an abstract. All studies, except Baulac 2010 (which was sponsored by Pfizer Inc), were sponsored by GlaxoSmithKline, manufacturers of lamotrigine, as part of their pre-licensing programme.

Excluded studies

In the 2018 update, we excluded seven studies for the following reasons: one study was not a randomised trial; three studies did not investigate an eligible population; study results were not available for one study; and one study was not a placebo-controlled trial. One study was an ongoing study. The details of these studies are given in the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of the risk of bias in each included study. Each study was allocated an overall rating for risk of bias: low, high, or unclear. See below for specific domain ratings.

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

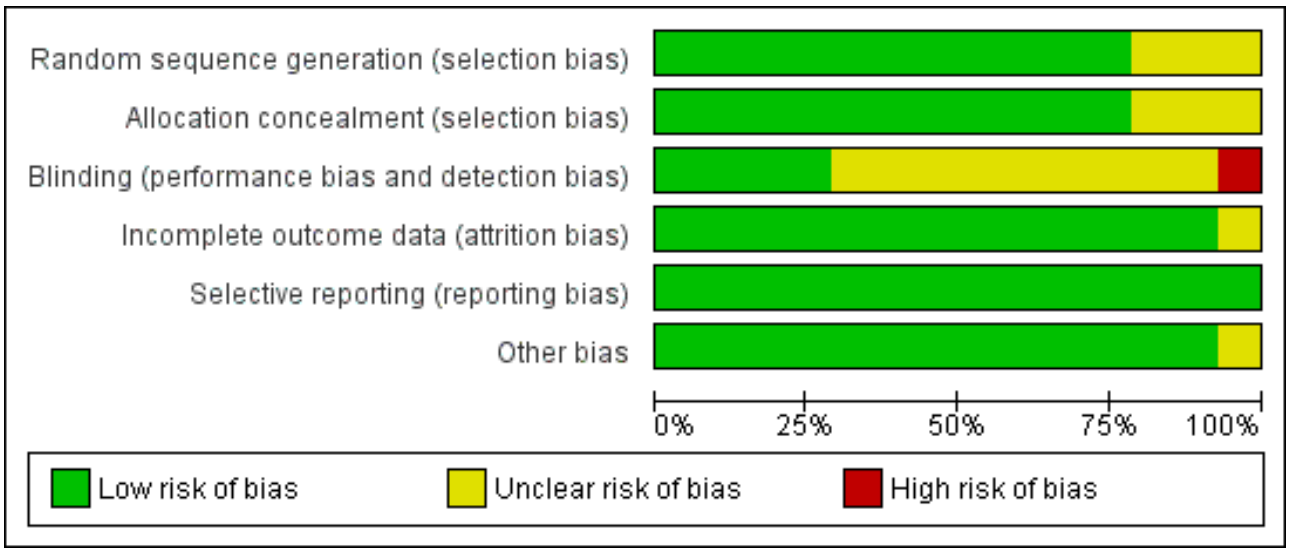
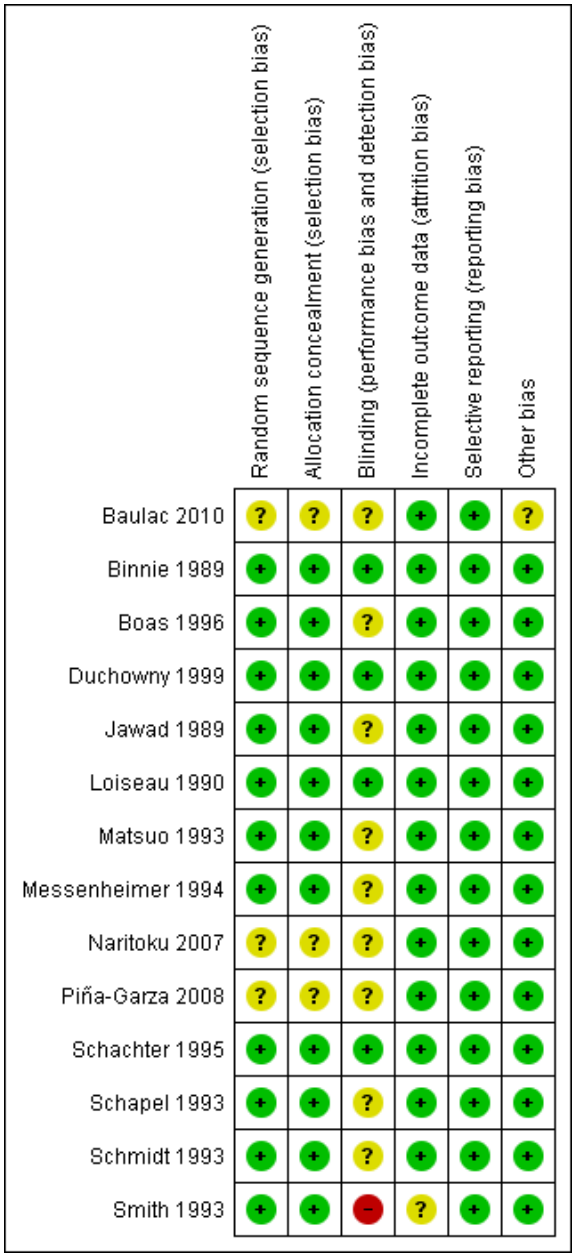


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

We rated the method by which allocation was randomised as having low risk of bias in 11 trials (1243 participants), because they used a computer-generated randomisation schedule or random number tables (Binnie 1989; Boas 1996; Duchowny 1999; Jawad 1989; Loiseau 1990; Matsuo 1993; Messenheimer 1994; Schachter 1995; Schapel 1993; Schmidt 1993; Smith 1993). The investigators did not provide clear methods In three trials (563 participants), which were rated as unclear (Baulac 2010; Naritoku 2007; Piña-Garza 2008). For sequence generation, we rated the same 11 studies as having low risk of bias because they dispensed sequentially numbered packages to each participant, and random permuted blocks were used to generate the allocation sequence. We rated three studies (563 participants) as having unclear risk of bias due to a lack of details on the methods used (Baulac 2010; Naritoku 2007; Piña-Garza 2008).

Blinding

We rated four studies (704 participants) as having low risk of bias for this particular domain because participants, parents and investigators were blinded (Binnie 1989; Duchowny 1999 ; Loiseau 1990; Schachter 1995). We judged blinding of participants as unclear in 9 papers (1021 participants) because no details of the method of blinding were provided (Baulac 2010; Boas 1996; Jawad 1989; Matsuo 1993; Messenheimer 1994; Naritoku 2007; Piña-Garza 2008; Schapel 1993; Schmidt 1993). One study (81 participants) was rated as high risk of bias because patients and investigators were able to identify the lamotrigine treatment (Smith 1993).

Incomplete outcome data

We rated all the included studies (13 studies, 1725 participants), except one (Smith 1993) , as having low risk of bias for this domain as there were minimal missing data. Additionally, either ITT analysis was employed, or there were no concerns of missing data having an effect on the overall outcome estimate. Smith 1993 (81 participants) was rated as unclear risk of bias because participants who discontinued prematurely did not complete the health-related quality of life (HRQOL) measure at the time of discontinuation.

Selective reporting

We requested the protocols for all included studies to compare a priori methods and outcomes to the published report, but none of the protocols for the included studies were available. We rated all included studies as low risk of bias for this domain as there was no suspicion of selective outcome reporting bias. All expected outcomes were reported in each of the publications.

Other potential sources of bias

We did not detect any other sources of bias across the included studies, except one (Baulac 2010), because responder rates were mentioned as percentages and actual numbers were not given.

Effects of interventions

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

For the cross-over trials, we analysed data from the first treatment phase for the efficacy, treatment, withdrawal, and adverse effects. These data were unpublished and obtained from Glaxo Wellcome, the sponsors of all but one study (Baulac 2010).

Primary Outcome

Fifty per cent or greater reduction in seizure frequency

A Chi^2 test for responses to lamotrigine indicated no significant heterogeneity between trials ($Chi^2 = 11.02$; df = 11; P = 0.44; $I^2 = 0\%$), so a fixed-effect model was used to measure efficacy.

For 12 studies (1322 participants (adults and children)), the risk ratio (RR) was 1.80; 95% confidence interval (CI) 1.45 to 2.23 for any dose of lamotrigine added to regular antiepileptic drug therapy versus placebo. The RR from eight cross-over studies (382 participants) was 2.58; 95% CI 1.44 to 4.61 (Analysis 1.1).

The RR for the worst-case and best-case scenarios were RR 0.97 (95% CI 0.82 to 1.15; Analysis 1.2) and RR 2.88 (95% CI 2.36 to 3.50; Analysis 1.3), respectively fixed.

The RR for a daily dose of 300 mg of lamotrigine was 1.23; 95% CI 0.57 to 2.67; the RR was 2.13; 95% CI 1.08 to 4.20 for lamotrigine 500 mg per day, compared to placebo (Matsuo 1993). For children, the RR was 2.64; 95% CI 1.59 to 4.38 (Duchowny 1999) (Analysis 1.1).

We could not calculate responder rates for Schachter 1995 because baseline seizure counts were not obtained, or for the infants in Piña-Garza 2008, where the primary end point was exit due to treatment failure.

Secondary Outcomes

Treatment withdrawal

Fourteen studies (1806 participants) were included in this analysis. The overall RR for treatment withdrawal for any reason was RR 1.11 (95% CI 0.91 to 1.37); thus there was insufficient evidence to conclude that participants were more likely to discontinue lamotrigine than placebo (Analysis 2.1).

We obtained the following data: 136 participants withdrew from treatment and 77 participants withdrew from control groups in parallel studies in adults (Baulac 2010, Matsuo 1993, Naritoku 2007, Schachter 1995); 14 participants withdrew from treatment and 18 from control groups in a parallel study in children (Duchowny 1999); 19 participants withdrew from treatment and 10 participants withdrew from control groups in cross-over studies in adults (Binnie 1989, Boas 1996, Jawad 1989, Loiseau 1990, Messenheimer 1994, Schapel 1993, Schmidt 1993, Smith 1993); 11 participants withdrew from treatment and 16 withdrew from control groups in a parallel study in infants (Piña-Garza 2008) (Analysis 2.1).

Insufficient data were available to undertake the planned dose-response subgroup analyses.

Adverse effects

In addition to reports of ataxia, dizziness, fatigue, and nausea, some studies reported somnolence, diplopia and headache among the five most common adverse effects and are included in the analysis. Ataxia, dizziness, diplopia, and nausea were significantly more likely with lamotrigine. The RR for individual adverse effects were:

1. ataxia - RR 3.34; (99% CI 2.01 to 5.55) (12 studies, 1525 participants, Analysis 3.1);
2. dizziness - RR 2.00 (99% CI 1.52 to 2.64) (13 studies, 1768 participants, Analysis 3.2);
3. fatigue - RR 0.82 (99% CI 0.55 to 1.22) (12 studies, 1552 participants, Analysis 3.3);
4. nausea - RR 1.81(99% CI 1.22 to 2.68) (12 studies, 1486 participants, Analysis 3.4);
5. somnolence - RR 1.39 (99% CI 0.96 to 2.00) (13 studies, 1768 participants, Analysis 3.5);
6. diplopia - RR 3.79 (99% CI 2.15 to 6.68) (3 studies, 944 participants, Analysis 3.6); and
7. headache - RR 1.13 (99% CI 0.88 to 1.45) (5 studies, 1386 participants, Analysis 3.7).

Cognitive effects and quality of life

Two studies incorporated measures of cognitive functions (Banks 1991; Smith 1993 (54 participants)). No significant differences were found on any of the tests used. However, participants receiving lamotrigine showed a marginal (not significant) reduction in general cerebral efficiency as assessed by the third segment of the Stroop colour word test-a test of concentration and distractibility (Table 1).

We provided a narrative discussion for this outcome and more information in Table 1. Meta-analysis of the two studies was not possible due to the differences in cognitive function measured in the two studies.

The results of the health-related quality of life (HRQOL) assessments are given in Table 2. Smith 1993 (54 participants), incorporated an HRQOL measure containing previously validated measures of physical, social and psychological functioning and a novel measure of seizure severity. There were no significant differences for the physical and social components of the HRQOL measure. Participants also reported significant improvements on the seizure severity scale when comparing lamotrigine versus placebo.

We provided a narrative discussion for this outcome and more information in Table 2. Meta-analysis was not possible as only a single study reported on this outcome.

DISCUSSION

Summary of main results

Since publication of the previous version of this review, we did not find any new studies that met the selection criteria for this review.

The baseline phase in all but one trial ranged from four to 12 weeks, the treatment phase from eight to 36 weeks (Schmidt 1993). Eleven of the 14 included trials described adequate methods of concealment of randomisation, only four described adequate blinding. All but one trial was sponsored by the manufacturer of lamotrigine.

This meta-analysis suggested that lamotrigine was more effective than placebo in reducing seizure frequency, when added to conventionally used antiepileptic drugs (AEDs) in people suffering from drug-resistant focal epilepsy. We were unable to examine dose effects in planned subgroup analyses, but the results from Matsuo 1993 suggested increased efficacy with an increased dose. Only one study recruited children (Duchowny 1999), and one study recruited infants (Piña-Garza 2008). We have no evidence from this review to indicate whether lamotrigine is more or less effective in infants and children than in adults. The use of 50% or greater reduction in seizure frequency as a measure of efficacy could be criticised, given that seizure freedom would be a more relevant clinical measure. However, seizure freedom is rarely achieved in the studies involving people with drug-resistant epilepsy.

For a drug to be an attractive option, it would need to have a favourable adverse-effect profile, have little effect on cognition, and have positive effects on quality of life, in addition to reducing seizures. In our review, certain adverse effects (ataxia, dizziness, diplopia, and nausea) were significantly more likely to occur with lamotrigine. It was emphasised that researchers should routinely and regularly enquire about adverse effects, using a standardised check-list thesaurus, and should not record only those volunteered by the patient. More participants had lamotrigine withdrawn than placebo, but this was not statistically significant.

The results of this review apply only to add-on use of lamotrigine. Our results do not inform us how add-on lamotrigine compares with other drugs when used as add-ons. This is an extremely important issue for clinicians who are faced with an ever-increasing number of AEDs from which to choose, and who need to make an evidence-based choice between the AEDs. Indirect comparisons can be made using results of other reviews, but such indirect comparisons require cautious interpretation.

Overall completeness and applicability of evidence

Only two studies evaluated the effects of add-on lamotrigine therapy on cognition and quality of life. The results of these studies suggested that lamotrigine was probably not associated with any significant cognitive decline. Regardless, the limited data available and heterogenous measurement scales for quality of life outcome precluded us from drawing any conclusions about the effects of add-on lamotrigine on cognition and quality of life.

Caution is required when translating the results of clinical trials into everyday practice. The individuals in trials are a highly selected population who may be better motivated, and are closely followed and monitored. Participants who are uncooperative and non-compliant, who are likely to have adverse effects and fewer benefits, are excluded. The results of this review cannot be extrapolated to people with generalised epilepsies, about whom there is a great paucity of data. The safety of lamotrigine during pregnancy and lactation cannot be ascertained from this review. The duration of the studies included in this review was insufficient to detect changes in cognition, social problems, or long-term adverse effects. Trials that include a larger number of individuals, preferably who are using lamotrigine as monotherapy, and which are using reliable, validated measures and longer follow-up are warranted. This review did not have the sensitivity to detect rare but serious adverse effects, such as psychosis, Steven Johnson's syndrome, or aplastic anaemia which may be seen with AEDs. Rare phenomena such as habituation and tolerance may not be evident in short-term trials. The economic aspects of lamotrigine therapy also need to be examined.

Certainty of the evidence

Overall, 11 studies were rated as having low risk of bias and three were judged to have an unclear risk of bias, mainly due to the lack of information regarding study design. Only four trials reported effective methods for blinding. We rated all the included studies, except one, as low risk of bias for incomplete outcome data due to the intention-to-treat (ITT) analyses undertaken by the study authors.

The GRADE approach was used to rate the certainty of evidence for each outcome. The assessments are presented in a 'Summary of findings' table (see Summary of findings for the main comparison). Importantly, we judged that it was not necessary to downgrade for risk of bias because, as stated above, the majority of the included studies were at low risk of bias. For the main outcome of 50% or greater reduction in seizure frequency, the certainty of evidence was rated as moderate (all studies contributed to the analysis). Notably, the evidence for the main outcome was downgraded once from high certainty due to the limited number of events reported.

Tolerability outcomes (withdrawal and adverse effects) were judged as high to moderate certainty. Again, this was largely due to the number of events reported being insufficient to draw conclusions. Only one outcome, the number of participants experiencing dizziness, was downgraded due to inconsistency after significant statistical heterogeneity was detected in the data set. The evidence for two of the outcomes, ataxia and diplopia, was upgraded back to high certainty because the risk ratio estimated exceeded 2.00, indicating a large effect size.

Potential biases in the review process

Although all protocols were requested, the time frame in which the majority of the studies were conducted made retrieval of all of these difficult. This could lead to potential bias through omitted information to which we did not have access. All studies but one were sponsored by GlaxoSmithKline, the manufacturers of lamotrigine and this could be a potential source of bias.

AUTHORS' CONCLUSIONS

Implications for practice

In people with drug-resistant focal epilepsy, lamotrigine when used as an add-on treatment was effective in reducing the seizure frequency. The lowest daily dose tested in the trials included in this review was 75 mg for people on sodium valproate monotherapy, 100 mg in the balanced group receiving enzyme inducing AEDs and valproate, and 200 mg in people receiving enzyme inducing AEDs. However, the trials reviewed were of relatively short duration.

Implications for research

Further evaluation of lamotrigine is required to assess the following effects in the long term:

1. effects on seizures;
2. adverse effects;
3. effects on cognition;
4. effects on quality of life;
5. health economic effects.

In the following scenarios:

1. lamotrigine compared to other add-on treatments in drug-resistant focal epilepsy;
2. lamotrigine for childhood and generalised epilepsies;
3. lamotrigine compared with standard AEDs such as:
   a. lamotrigine as monotherapy in focal epilepsy;
   b. lamotrigine as monotherapy in generalised epilepsy.

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CHARACTERISTICS OF STUDIES

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

Baulac 2010

Methods	Double-blind, placebo-controlled, randomised, parallel-group study. Three arms: 1 placebo, 1 lamotrigine, and 1 pregabalin. Baseline period = 6 weeks; double-blind treatment period = 17 weeks, which included initial 5 weeks dosage titration for lamotrigine and 6 weeks maintenance at 300 mg/day and additional treatment period of 6 weeks with dose escalation to 400 mg/day for those with continuing seizures. Double-blind treatment period was followed by an open-label study or a 2-week taper phase.
Participants	97 centres in Europe, Canada, and Australia. Adults over the age of 18 years and body weight ≥40 kg, with a diagnosis of focal seizures (as defined by the International League Against Epilepsy Classification of Seizures). 546 persons screened, 434 randomised. M:F ratio 39.3:60.7 for placebo and 54.6:45.4 for lamotrigine. Mean age (years) 39.1 in placebo group and 39.4 in lamotrigine group. Minimum seizure frequency of 4 focal seizures during the 6-week baseline period and no 28-day period free of focal seizure, despite treatment with at least three AEDs from at least two different AED classes, each at or above the lowest recommended dose or the lowest adequate plasma concentration given for a minimum of 3 months; were allowed to take one to three AEDs concurrently, one of which had to be an enzyme inducer. Exclusion Criteria: 1. previous treatment with pregabalin; 2. previous treatment with lamotrigine within 6 months before entering baseline; 3. history of rash with lamotrigine; 4. previous treatment with valproic acid products within 2 months of baseline; and 5. previous treatment with gabapentin, felbamate, or vigabatrin < 6 weeks prior to screening. 6. history of status epilepticus in the last 1 year, significant psychiatric disorder, or use of concomitant medication that could interfere with response to study medications or affect seizure frequency. 7. pregnant or planning to conceive, lactation.
Interventions	Group I (n = 141): received placebo. Group II (n = 141): received lamotrigine 300 mg/day after dose titration over 5 weeks, and if seizures occurred during 6-week maintenance, further dose escalation to 400 mg/day from week 12 to 17. Group III (n = 152): received pregabalin. The participants randomised to pregabalin were not included in this review.
Outcomes	1. Seizure frequency. 2. Adverse events, including changes in physical and neurologic examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (haematology, blood chemistry, pregnancy, and urinalysis).
Notes	This study was sponsored by Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement

Baulac 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified.
Allocation concealment (selection bias)	Unclear risk	The details were not mentioned in the publication.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants, study personnel, and outcome assessors. Regarding the medications, blinding was maintained by administering the same numbers of capsules per day per group.
Incomplete outcome data (attrition bias)	Low risk	35 withdrew from placebo group and 40 from lamotrigine group. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	Protocol unavailable to check a priori outcomes, but appears all expected and pre-specified outcomes are reported.
Other bias	Unclear risk	Responder rates were mentioned as percentages and actual numbers were not given. Author has been contacted regarding actual number of responders in each group, but has not been resolved.

Binnie 1989

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, and 1 lamotrigine. Baseline period = 8 weeks.Treatment I and II = 12 weeks each. Washout = 6 weeks, including taper period.
Participants	Single-centre study from the Netherlands. 34 adults aged between 16 to 51 years (mean 37.1 +/- 10.26). 16 were randomised to lamotrigine and 18 to placebo during the first treatment phase. All had drug-resistant focal seizures. The age of onset of epilepsy ranged from 1 to 40 years (mean 14.3 +/- 10.7), the duration of epilepsy was 6 to 49.5 (mean 22.8 +/- 11) years. Maximum number of other AEDs = 4.
Interventions	Add-on lamotrigine, or placebo. Median daily dose of lamotrigine was 200 mg. Participants on valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement

Binnie 1989 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated sequentially-numbered sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and parents were blinded. An unblinded investigator with knowledge of the medication and plasma concentrations instructed the blinded investigators about dispensing the trial medications. Identical tablets and packaging used.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. No participant withdrew from the study during the first treatment phase.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check to priori outcomes.
Other bias	Low risk	None detected.

Boas 1996

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Five phases: baseline period = 12 weeks; treatment I = 12 weeks; washout I = 4 weeks; treatment II = 12 weeks; washout II = 4 weeks.
Participants	4-centre study from Denmark. 56 adults with drug-resistant focal seizures, aged from 16 to 65 years. 30 were allocated to lamotrigine and 26 to placebo during the first treatment phase. There were 27 men and 29 women. Maximum number of other AEDs = 3.
Interventions	Lamotrigine or placebo was added to the patients' existing AEDs. The dose of lamotrigine varied from 75 mg to 400 mg. Participants on valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Partcipants were allocated sequentially-numbered, sealed packages containing either lamotrigine or placebo.

Boas 1996 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants, study personnel, and outcome assessors. All treatments (tablets) and packaging were identical. Prepacked coded medication was dispensed by pharmacy.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 10 participants withdrew from the study; 8 randomised to lamotrigine and 2 to placebo. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Duchowny 1999

Methods	Randomised, double-blind, parallel group, multi-centre study. Two treatment arms: 1 placebo, 1 lamotrigine. Pre-randomisation baseline period = 8 weeks. Treatment phase = 18 weeks (including 6-week titration). Taper and follow-up = 1 to 6 weeks, including 1-week taper.
Participants	40 centres from USA and France: 199 children with drug-resistant focal seizures, aged from 2 to 16 years (27% were less than 6 years old, 60% aged between 6 to 12 years and 11% were over 12 years age). 98 were allocated to lamotrigine and 101 to placebo. There were 103 boys and 96 girls. Maximum number of other AEDs = 2.
Interventions	Add-on lamotrigine or placebo. Median dose ranged from 2.7 mg/kg/day to 12.9 mg/kg/day depending upon concurrent use of other AEDs. Participants on valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Patients were randomised with a blocked randomisation scheme to treatment with add-on lamotrigine or matched placebo in bottles labelled with pre-generated participant numbers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment assignments were unknown to all study-site personnel, patients and sponsors. Lamotrigine and matching placebo were provided as berry-

Duchowny 1999 *(Continued)*

		flavoured, chewable, dispersible caplets or tablets in strengths of 5 mg, 25 mg, and 100 mg.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 2 enrolled participants withdrew before randomisation. 14 participants allocated to lamotrigine and 18 participants allocated to placebo withdrew during treatment phase. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Jawad 1989

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Five phases: baseline period = 8 weeks; Treatment I = 12 weeks; Washout I = 6 weeks; treatment II = 12 weeks; Washout II = 6 weeks.
Participants	Single-centre study from UK. 24 adults with drug-resistant focal seizures, aged between 16 to 60 years. 12 were allocated to lamotrigine and 12 to placebo in the first treatment phase. Maximum number of other AEDs = 2.
Interventions	Add-on lamotrigine or placebo. The median daily dose of lamotrigine was 250 mg. Participants on valproate received lower doses. Unblinded investigator wrote prescriptions based on plasma concentration.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Partcipants were allocated by sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants, study personnel, and outcome assessors. Identical tablets and packaging used.

Jawad 1989 *(Continued)*

Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. One participant who was allocated to lamotrigine withdrew from the study (the reason for exclusion was reported) and none withdrew from the placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Loiseau 1990

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Five phases: Pre-randomisation baseline = 4 weeks. Treatment I = 8 weeks. Washout I = 4 weeks. Treatment II = 8 weeks. Washout II = 4 weeks.
Participants	Single-centre study from France. 25 adults, aged between 20 to 54 (years mean 34.2 +/- 12.41) years. All had drug-resistant focal epilepsy. 11 were randomised to lamotrigine and 14 to placebo in the first treatment phase. The duration of epilepsy ranged from 3 to 45 years (mean 17.4 +/- 10.81). Maximum number of other AEDs = 2.
Interventions	Add-on lamotrigine or placebo. The median daily lamotrigine dose was 300 mg. Participants on valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated by sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Low risk	Neurologists, participants and parents were blinded. Investigators were blinded. All treatments (tablets) and packaging were identical. Pre-packed coded medication dispensed by pharmacy.

Loiseau 1990 *(Continued)*

Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 2 participants withdrew from the study; 1 receiving lamotrigine and 1 receiving placebo. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Matsuo 1993

Methods	Randomised, double-blind, parallel group, multi-centre study. Three treatment arms: 1 placebo, 1 lamotrigine 300 mg and 1 lamotrigine 500 mg. Pre-randomisation baseline = 12 weeks. Treatment phase = 24 weeks. Taper and follow-up = 3 weeks.
Participants	Multi-centre US study with 216 participants (67 males and 149 females) with a mean age of 33 (range 18 to 63) years. All had drug-resistant focal epilepsy. 73 were randomised to receive placebo, while 71 received lamotrigine 300 mg per day and 72 received lamotrigine 500 mg per day. The mean duration of epilepsy was 21.9 years and the mean age at onset 11 years. Maximum number of other AEDs = 3. People receiving valproate were excluded.
Interventions	Add-on lamotrigine 300 mg or lamotrigine 500 mg or placebo.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Randomisation concealment: allocated sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants, study personnel, and outcome assessors. Identical tablets and packaging used.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 25 participants withdrew from the study; 7 receiving lamotrigine 300 mg, 12 receiving lamotrigine 500 mg and 6 receiving placebo. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	Protocol unavailable to check a priori outcomes, but appears all expected and pre-specified outcomes were reported.

Matsuo 1993 *(Continued)*

Other bias	Low risk	None detected.

Messenheimer 1994

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Total study duration was 43 weeks. Pre-randomisation baseline = 8 weeks. Treatment A = 14 weeks (including 2 weeks blinded tapering). Follow-up period = 3 weeks. Treatment B = 14 weeks (including 2 weeks blinded tapering). Washout = 4 weeks.
Participants	Multi-centre US study with 98 participants (46 men and 52 women) with drug-resistant focal epilepsy. 46 were randomised to receive lamotrigine and 52 to placebo in the first treatment phase. Age range 18 to 64 years with a mean of 35. Age at onset of epilepsy was 12 years; mean duration 23.1 years. Up to 3 other AEDs were permitted. Concomitant use of valproate was not allowed.
Interventions	Add-on lamotrigine or placebo. Median lamotrigine dose 400 mg/day.
Outcomes	1. 50% responder rates 2. Withdrawal from study for any reason. 3. Adverse effects
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated by sequentially-numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigators were blinded. No more information provided regarding blinding of neurologists, participants, and parents. All treatments (tablets) and packaging were identical. Pre-packed coded medication dispensed by pharmacy.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 6 participants withdrew from the study; 2 receiving lamotrigine and 4 receiving placebo. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Naritoku 2007

Methods	Double-blind, randomised, parallel-group, placebo-controlled multi-centre global study. Screening phase of up to 2 weeks during which eligibility was determined; an 8-week baseline phase serving to exclude from randomisation patients who did not meet the minimum seizure frequency criterion; a 7-week, double-blind escalation phase during which lamotrigine XR (Extended Release) was introduced and titrated to its target dose; and a 12-week, double-blind maintenance phase during which dosage of study medication and concomitant AED were maintained.
Participants	International multi-centre study from North and South America, Europe, and Asia. Uncontrolled focal seizures (at least 8 focal seizures in 8 weeks with at least one focal seizure during each 4-week period of the baseline phase). Male and female patients 12 years of age or older with focal seizures with or without generalisation who were treated with a stable regimen of one or two AEDs for at least 4 weeks before starting the baseline phase. Total number enrolled = 244; (121 to treatment arm; 123 to placebo arm); 93% were aged between 16 and 65 years; mean age in lamotrigine group = 35.8 (12.7) and in placebo group = 37.5 (14.4) years. Males constituted 47% of participants in lamotrigine group and 53% of participants in placebo group. Exclusion criteria included: 1. presence of primary generalised seizures, 2. status epilepticus during or within 24 weeks before the start of the baseline phase, 3. chronic treatment with three or more AEDs, 4. current or previous use of lamotrigine, 5. current use of felbamate or adherence to a ketogenic diet, 6. pregnancy or planned pregnancy during the study or within 3 weeks after the last dose of study medication.
Interventions	Treatment group received lamotrigine XR (Extended Release); other group received identical placebo. Dosage of lamotrigine XR was escalated gradually up to 200 mg/day in those receiving valproate, 300 mg/day in those receiving valproate and an enzyme inducing AED, and up to 500 mg/day in those receiving enzyme inducing AEDs without valproate.
Outcomes	1. Seizure frequency. 2. Adverse events 3. Withdrawals from study. 4. US participants had following additional assessments: Profile of Mood States (POMS), Center for Epidemiologic Studies-Depression Scale (CES-D), research version of the Neurological Disorders Depression Inventory-Epilepsy (NDDI-E), Quality of Life in Epilepsy-31-P (QOLIE-31-P), Liverpool Adverse Experience Profile (AEP), Seizure Severity Questionnaire (SSQ), and Epworth Sleepiness Scale (ESS).
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified.

Naritoku 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details not reported in the publication.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias)	Low risk	24 participants withdrew from treatment group and 16 from placebo group. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	There was no protocol available to check a priori outcomes,but appears all expected and pre-specified outcomes were reported.
Other bias	Low risk	None detected.

Piña-Garza 2008

Methods	Randomised, double-blind, multi-centre placebo-controlled trial. Responder-enriched design in which all patients received adjunctive lamotrigine during an open-label phase (wherein dose was escalated to achieve optimal response); those who had a 40% or greater reduction in the frequency of focal seizures during the last 4 weeks of the optimisation period were randomly assigned to double-blind treatment for up to 8 weeks with continued lamotrigine or placebo.
Participants	Total number enrolled = 38. Male or female infants aged 1 month to 24 months with at least 4 focal seizures (with or without generalisation) per month, uncontrolled by 1 AED and who showed 40% or greater reduction in seizure frequency during an initial open label phase. There were 19 participants in each arm; median age was 13.5 months in lamotrigine arm and 14.2 months in placebo arm; median age of onset of epilepsy was 3 months and median duration of epilepsy was 9.1 months in lamotrigine arm and 8.5 months in placebo arm. Exclusion Criteria: participants with progressive myoclonic epilepsy; progressive neurologic disease, seizures unrelated to epilepsy or resulting from drug withdrawal; use of felbamate, adrenocorticotropic hormone, previous use of lamotrigine, two AEDs as maintenance treatment, presence of hepatic dysfunction, having a functioning vagus nerve stimulator; or being on a ketogenic diet.
Interventions	Intervention group was continued on lamotrigine. Control group participants had their lamotrigine dose tapered and changed to placebo. The maximum maintenance dose was 5.1 mg/kg/day for those on non–enzyme-inducing AEDs or valproate and 15.6 mg/kg/day for those on enzyme-inducing AEDs.
Outcomes	1. Percentage of patients who had treatment failures during the double-blind phase. 2. Cumulative percentage of patients who met escape criteria as a function of days on double-blind study medication. Participants were withdrawn from study if they met one of the following criteria: 1. 50% increase in monthly focal seizure frequency compared with seizure frequency during the last 4 weeks of the open-label optimisation period; 2. a doubling of the highest consecutive 2-day focal seizure count observed during the open-label optimisation period; 3. onset of a new and more severe seizure type; 4. clinically significant worsening of non-focal seizures that were also observed during the historical baseline phase or the open-label optimisation period; 5. the need to use any therapeutic intervention in addition to study medication to control seizures; or

Piña-Garza 2008 *(Continued)*

	6. status epilepticus.
Notes	The protocol was amended midway through the study to randomly assign all patients with at least 40% reduction in seizure frequency, instead of planned inclusion of participants with 40% to 80% reduction in seizure frequency. 43 subjects who had more than 80% reduction in seizure frequency before the protocol amendment were not included in the double-blind study. This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified.
Allocation concealment (selection bias)	Unclear risk	Details not reported in the publication.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias)	Low risk	11 patients (8 in the lamotrigine group and 3 in placebo group) completed the double-blind phase, 25 (9 in the lamotrigine group and 16 in placebo group) met escape criteria, and 2 (both in the lamotrigine group) prematurely withdrew because of protocol violations. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported. Protocol was not available.
Other bias	Low risk	None detected.

Schachter 1995

Methods	Randomised, double-blind, parallel-group study. Two treatment arms: 1 placebo, 1 lamotrigine. Patients were randomised to lamotrigine or placebo in a ratio of 3:1. Pre-randomisation baseline = 4 weeks. Treatment phase = 24 weeks. Taper and follow-up = 3 weeks.
Participants	A 34-centre US study with 446 participants with drug-resistant focal seizures: 334 were randomised to lamotrigine and 112 to placebo. There were 236 men and 210 women. The mean age was 35 years (range 18 to 64). The mean duration of epilepsy was 21 years, median age at onset: 12 years in the lamotrigine group and 11.5 in the placebo group. Maximum number of other AEDs = 3. Concomitant valproate therapy was not permitted.
Interventions	Add-on lamotrigine or placebo. Lamotrigine dose up to 500 mg/day.

Schachter 1995 *(Continued)*

Outcomes	1. Withdrawals from treatment. 2. Adverse effects.
Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated by sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Low risk	Neurologists, participants and parents were blinded. Investigators were blinded. Identical tablets and packaging used.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 73 participants withdrew from the study; 53 receiving lamotrigine and 20 receiving placebo. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Schapel 1993

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Pre-randomisation baseline = 12 weeks. Treatment I and II = 12 weeks each. Washout I and II = 4 weeks each, including 1 week taper.
Participants	Multi-centre Australian study. 41 participants (21 males and 20 females) with drug-resistant focal seizures 20 were randomised to receive placebo and 21 to lamotrigine. The age ranged from 17 to 63 (median 28) years. The mean age at onset was 10.4 +/-9.6 years. Maximum number of other AEDs permitted = 3. People receiving valproate monotherapy were excluded.
Interventions	Add-on lamotrigine or placebo. Median daily dose of lamotrigine was 300 mg. Participants receiving valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.

Schapel 1993 *(Continued)*

Notes	Banks 1991 is linked to this study and investigated cognitive functions: i) concentration and attention; ii) general cerebral efficiency; and iii) mnestic functions (immediate, short term and new learning ability). This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated by sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants, study personnel, and outcome assessors. All treatments and packaging were identical. Pre-packed coded medication dispensed by pharmacy.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. None withdrew from the study.
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appears all expected and pre-specified outcomes were reported.
Other bias	Low risk	None detected.

Schmidt 1993

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Pre-randomisation baseline not known. Treatment I and II = 12 weeks each, including 2-week tapering period. Washout = 2 weeks .
Participants	Single-centre German study. 23 adults (11 men and 12 women) with drug-resistant focal seizures. 11 were randomised to receive lamotrigine and 12 to placebo in the initial treatment phase. Age of participants ranged from 16 to 62 years. Maximum number of other AEDs permitted was 2.
Interventions	Add-on lamotrigine or placebo. Dosage varied from 50 mg to 450 mg (median dose was 300 mg).
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects.

Schmidt 1993 *(Continued)*

Notes	This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated by sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided regarding blinding of participants and parents. Unblinded investigator wrote prescriptions based on plasma concentration. Identical tablets and packaging were used.
Incomplete outcome data (attrition bias)	Low risk	No participants were excluded from analysis. 1 participant receiving lamotrigine and 9 receiving placebo withdrew from the study. The reasons for exclusion were reported.
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appears all expected and pre-specified outcomes were reported.
Other bias	Low risk	None detected.

Smith 1993

Methods	Randomised, double-blind, cross-over study. Two treatment arms: 1 placebo, 1 lamotrigine. Pre-randomisation baseline = 4 weeks. Treatment I and II = 18 weeks each. Washout = 6 weeks.
Participants	Single-centre UK study. 81 participants with drug-resistant focal epilepsy (33 men and 48 women). 41 were randomised to lamotrigine and 40 to placebo in the initial treatment phase. The age range was 15 to 67 years (mean 33.7); duration of epilepsy ranged from 4 to 45 years (mean 21). The mean age at onset was 11.8 years (< 1 to 52 years). Maximum number of other AEDS permitted was 2.
Interventions	Add-on lamotrigine or placebo. Lamotrigine dose up to 400 mg/day. Median daily dose was 300 mg. Participants on valproate received lower doses.
Outcomes	1. 50% responder rates. 2. Withdrawal from study for any reason. 3. Adverse effects. 4. Health-related quality of life (HRQL).
Notes	HRQL model was completed by 40 to 54 of 81 participants.

Smith 1993 *(Continued)*

This study was sponsored by GlaxoSmithKline, the manufacturer of LTG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted blocks.
Allocation concealment (selection bias)	Low risk	Partecipants were allocated sequentially numbered, sealed packages containing either lamotrigine or placebo.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients (46/73) and investigators (52/73) were able to identify lamotrigine treatment. Identical tablets and packaging were used. Prepacked coded medication dispensed by pharmacy.
Incomplete outcome data (attrition bias)	Unclear risk	No participants were excluded from analysis. 9 people withdrew from the study; 6 receiving lamotrigine and 3 receiving placebo. The reasons for exclusion were reported. Patients who discontinued prematurely did not complete the HRQOL measure at the time of discontinuation, the exclusion of treatment failures may introduce a bias in favour of lamotrigine.
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appears all expected and pre-specified outcomes were reported.
Other bias	Low risk	None detected.

AED: antiepileptic drug; LTG: lamotrigine; HRQOL: Health-Related Quality of Life

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

Study	Reason for exclusion
Berg 2015	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Berg 2017	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Biton 2010	Ineligible population: participants included had primary generalised epilepsy and not focal seizures.
Biton 2013	Inelegible population: participants included in the study had uncontrolled focal epilepsy and generalised tonic-clonic seizures.
Brzakovic 2012	Inelegible population: participants included in the study had uncontrolled focal epilepsy and generalised tonic-clonic seizures.
Carignani 2004	Published as conference abstract: details of the methods and results are not available.
Carignani 2006	Published as conference abstract: details of the methods and results are not available.
Chung 2009	Comparative study among lamotrigine and topiramate. Not placebo controlled.

Study	Reason for exclusion
Contin 2016	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Cramer 2013	Not a randomised controlled trial.
French 2012	Not a randomised controlled trial.
Frith 2015	Inelegible population: participants included in the study did not have drug-resistant epilepsy.
Girolineto 2012	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Hammer 2008	Published as conference abstract: details of the methods and results are not available.
Hartung 2012	Inelegible population: participants included in the study had epilepsy, migraine, pain, psychiatric disorders.
Helmstaedter 2013	Participants included in the study had all epileptic types. Lacosamide as add-on for epilepsy and in comparison with lamotrigine and topiramate.
IRCT2013021211560N3 2013	Inelegible population: participants included in the study did not have drug-resistant epilepsy.
Kang 2012	Inelegible population: participants included in the study had all epileptic types.
Lee 2018	Inelegible population: participants included in the study had all epileptic types.
Mintzer 2018	Not randomised controlled trial: it is a post-hoc analyses.
Montouris 2007	Published as conference abstract: details of the methods and results are not available.
NCT00208520	Inelegible population: participants included in the study did not have drug-resistant epilepsy.
NCT00292461	Details of the methods and results are not available.
NCT00807989	Details of the methods and results are not available.
NCT01891890	Details of the methods and results are not available.
NCT02100644	Not a randomised controlled trial.
NCT02429596	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Ohtahara 2008	Comparative study of lamotrigine and zonisamide. Not placebo controlled.
Premoli 2017	No types of outcome measures.
Privitera 2016	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Sander 1990	Study of institutionalised people with severe epilepsy. Participants included in the study had all epileptic types.
Semah 2014	No lamotrigine in add-on.
Sethi 2002	Inelegible population: participants included in the study did not have drug-resistant epilepsy.
Shinnar 2015	Ineligible population: participants included had primary generalised epilepsy and not focal seizures.

Study	Reason for exclusion
Stolarek 1994	Details of the results are not available.
Thangaratinam 2018	Inelegible population: participants included in the study had all epileptic types.
Ting 2015	Comparative study among therapeutic equivalents of lamotrigine. Not placebo controlled.
Tomson 2012	Published as conference abstract: details of the methods and results are not available.
Tomson 2013	Not a randomised controlled trial.
Veendrick-Meekes 2000	Published as conference abstract: details of the methods and results are not available.
Wu 2018	Inelegible population: participants included in the study had all epileptic types.
Yamamoto 2012	Not a randomised controlled trial.

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

NCT03689114

Trial name or title	Efficacy and Tolerability of Low vs. Standard Daily Doses of Antiepileptic Drugs in Newly Diagnosed, Previously Untreated Epilepsy (STANDLOW).
Methods	Multicenter, Randomized, Single-blind, Parallel-group trial.
Participants	Age 18 years or older; focal untreated epilepsy.
Interventions	Low vs Standard dose lamotrigine.
Outcomes	Primary Outcome Measures: Treatment failure [Time Frame: 12 months]The proportion of patients experiencing a treatment failure motivated by the need to change the assigned dose or the assigned drug for seizure relapse during the follow-up. Secondary Outcome Measures: 1. Drug-related adverse events [Time Frame: 12 months]the proportion of patients experiencing a treatment failure motivated by intolerable drug-related adverse events during the follow-up; 2. Quality of life in epilepsy scale 31 items(QOLIE-31), italian version [Time Frame: 12 months]QOLIE-31 total score at baseline and last visit. Maximum total score is 100 (best quality of life possible) and the minimum is 0 (worst quality of life possible). 3. Patients health care's satisfaction (PSQ-18) scale, 18 items [Time Frame: 12 months]The score of the seven PSQ-18 subscales (general satisfaction, technical quality, interpersonal manner, communication, financial aspects, time spent with doctor, accessibility and convenience) at baseline and last visit. Possible scores of each subscale range from 1 (worst satisfaction) to 5 (better satisfaction). There is no total score for this scale. 4. Health care resources utilization. [Time Frame: 12 months]The mean daily patient's cost of health care resources consumed for the management of epilepsy during the first 12 months of the study.
Starting date	September 2018
Contact information	Ettore Beghi, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, ettore.beghi@marionegri.it
Notes	

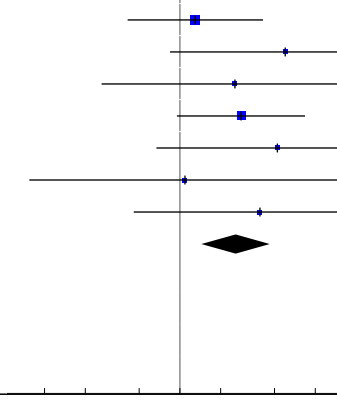
DATA AND ANALYSES

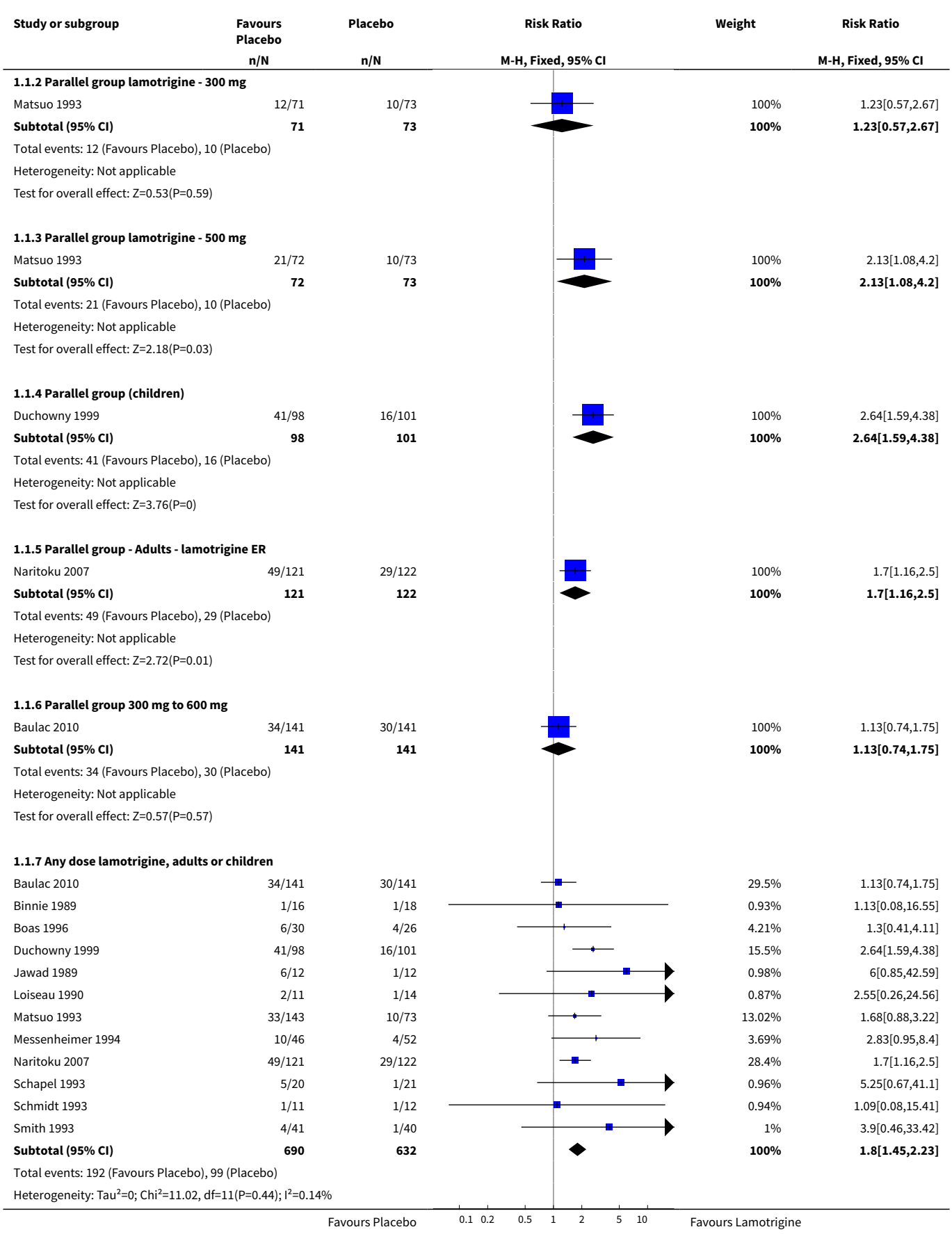
Comparison 1. Efficacy of add-on lamotrigine versus placebo - 50% responders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intention-to-treat analysis	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.44, 4.61]
1.2 Parallel group lamotrigine - 300 mg	1	144	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.57, 2.67]
1.3 Parallel group lamotrigine - 500 mg	1	145	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.08, 4.20]
1.4 Parallel group (children)	1	199	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.59, 4.38]
1.5 Parallel group - Adults - lamotrigine ER	1	243	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.16, 2.50]
1.6 Parallel group 300 mg to 600 mg	1	282	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.74, 1.75]
1.7 Any dose lamotrigine, adults or children	12	1322	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.45, 2.23]
2 Worst-case scenario	12	1322	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
3 Best-case scenario	12	1322	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [2.36, 3.50]

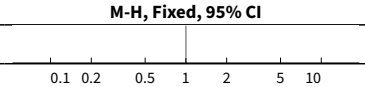
Analysis 1.1. Comparison 1 Efficacy of add-on lamotrigine versus placebo - 50% responders, Outcome 1 Intention-to-treat analysis.

Study or subgroup	Favours Placebo n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Cross-over studies					
Binnie 1989	1/16	1/18		6.82%	1.13[0.08,16.55]
Boas 1996	6/30	4/26		31.04%	1.3[0.41,4.11]
Jawad 1989	6/12	1/12		7.24%	6[0.85,42.59]
Loiseau 1990	2/11	1/14		6.37%	2.55[0.26,24.56]
Messenheimer 1994	10/46	4/52		27.2%	2.83[0.95,8.4]
Schapel 1993	5/20	1/21		7.07%	5.25[0.67,41.1]
Schmidt 1993	1/11	1/12		6.93%	1.09[0.08,15.41]
Smith 1993	4/41	1/40		7.33%	3.9[0.46,33.42]
Subtotal (95% CI)	**187**	**195**		**100%**	**2.58[1.44,4.61]**
Total events: 35 (Favours Placebo), 14 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.47, df=7(P=0.84); I^2=0%					
Test for overall effect: Z=3.19(P=0)					



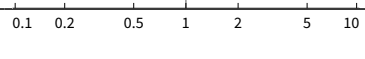


Study or subgroup	Favours Placebo n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=5.34(P<0.0001)					



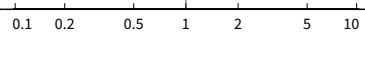
Analysis 1.2. Comparison 1 Efficacy of add-on lamotrigine versus placebo - 50% responders, Outcome 2 Worst-case scenario.

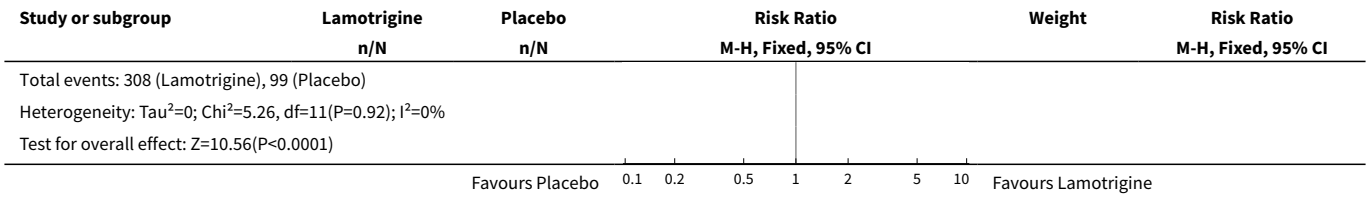
Study or subgroup	Lamotrigine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Baulac 2010	34/141	65/141		34.55%	0.52[0.37,0.74]
Binnie 1989	1/16	1/18		0.5%	1.13[0.08,16.55]
Boas 1996	6/30	6/26		3.42%	0.87[0.32,2.36]
Duchowny 1999	41/98	34/101		17.8%	1.24[0.87,1.78]
Jawad 1989	6/12	1/12		0.53%	6[0.85,42.59]
Loiseau 1990	2/11	2/14		0.94%	1.27[0.21,7.65]
Matsuo 1993	33/143	16/73		11.26%	1.05[0.62,1.78]
Messenheimer 1994	10/46	8/52		3.99%	1.41[0.61,3.28]
Naritoku 2007	49/121	45/122		23.82%	1.1[0.8,1.51]
Schapel 1993	5/20	1/21		0.52%	5.25[0.67,41.1]
Schmidt 1993	1/11	1/12		0.51%	1.09[0.08,15.41]
Smith 1993	4/41	4/40		2.15%	0.98[0.26,3.64]
Total (95% CI)	**690**	**632**		**100%**	**0.97[0.82,1.15]**
Total events: 192 (Lamotrigine), 184 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=21.8, df=11(P=0.03); I^2=49.54%					
Test for overall effect: Z=0.34(P=0.74)					



Analysis 1.3. Comparison 1 Efficacy of add-on lamotrigine versus placebo - 50% responders, Outcome 3 Best-case scenario.

Study or subgroup	Lamotrigine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Baulac 2010	74/141	30/141		29.5%	2.47[1.73,3.52]
Binnie 1989	1/16	1/18		0.93%	1.13[0.08,16.55]
Boas 1996	14/30	4/26		4.21%	3.03[1.14,8.08]
Duchowny 1999	55/98	16/101		15.5%	3.54[2.19,5.74]
Jawad 1989	7/12	1/12		0.98%	7[1.01,48.54]
Loiseau 1990	3/11	1/14		0.87%	3.82[0.46,31.84]
Matsuo 1993	52/143	10/73		13.02%	2.65[1.43,4.91]
Messenheimer 1994	12/46	4/52		3.69%	3.39[1.18,9.79]
Naritoku 2007	73/121	29/122		28.4%	2.54[1.79,3.6]
Schapel 1993	5/20	1/21		0.96%	5.25[0.67,41.1]
Schmidt 1993	2/11	1/12		0.94%	2.18[0.23,20.84]
Smith 1993	10/41	1/40		1%	9.76[1.31,72.74]
Total (95% CI)	**690**	**632**		**100%**	**2.88[2.36,3.5]**

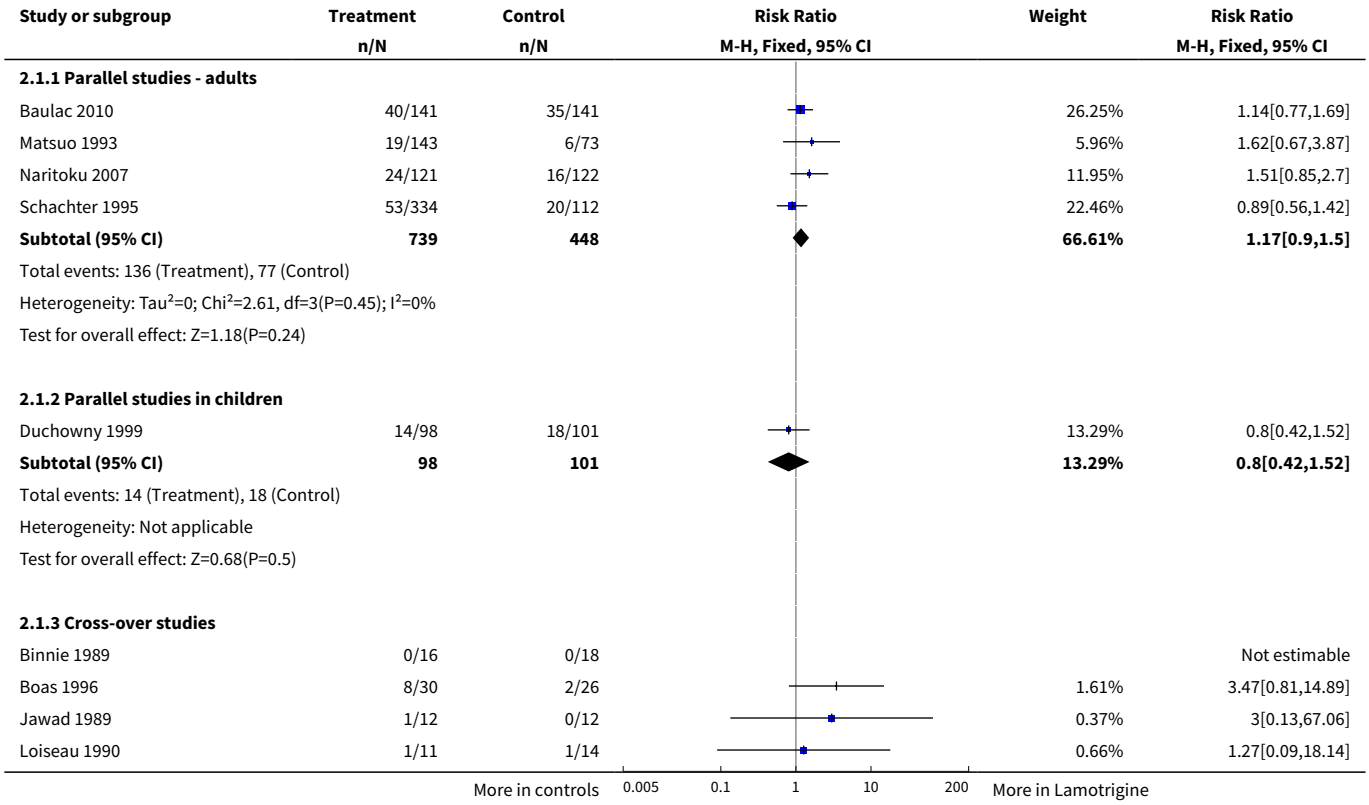


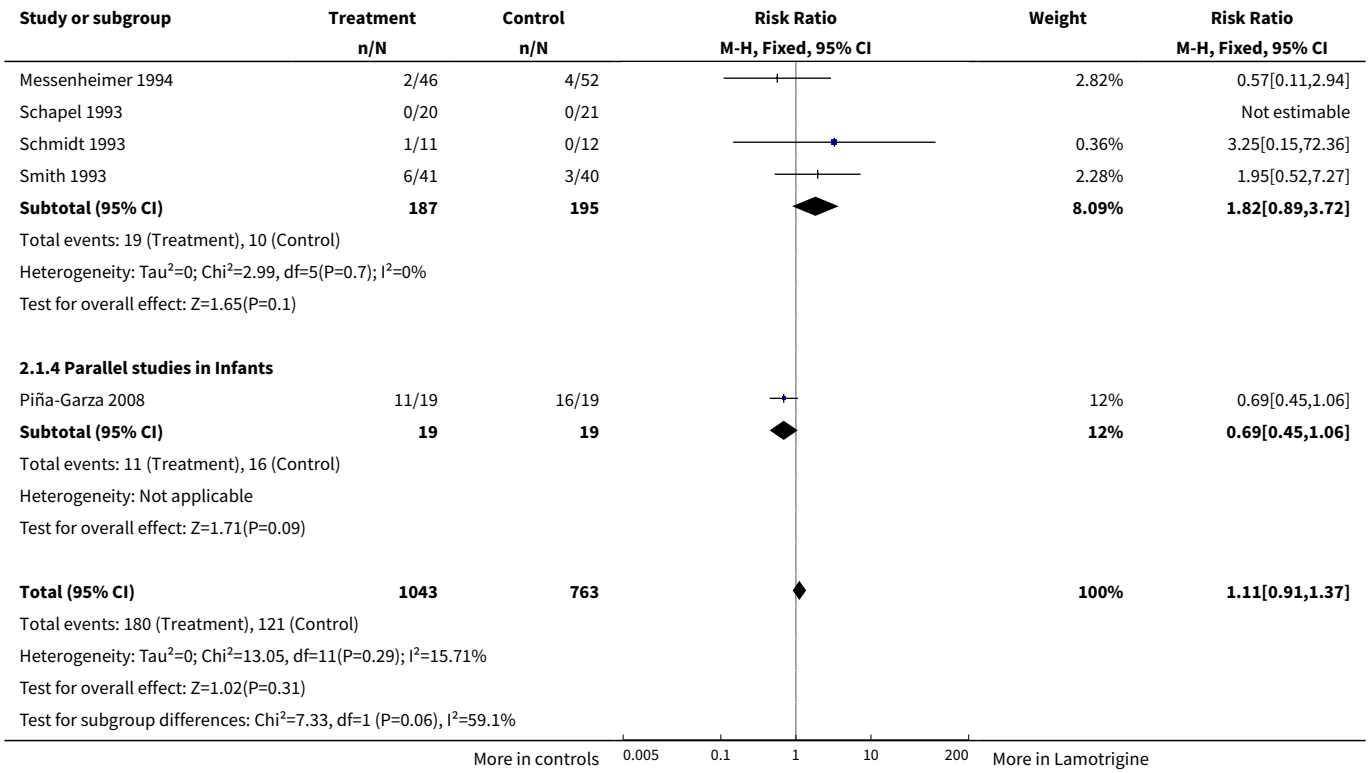


Comparison 2. Treatment withdrawal (global outcome)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawal from treatment	14	1806	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.91, 1.37]
1.1 Parallel studies - adults	4	1187	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.90, 1.50]
1.2 Parallel studies in children	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.42, 1.52]
1.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.89, 3.72]
1.4 Parallel studies in Infants	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.06]

Analysis 2.1. Comparison 2 Treatment withdrawal (global outcome), Outcome 1 Withdrawal from treatment.





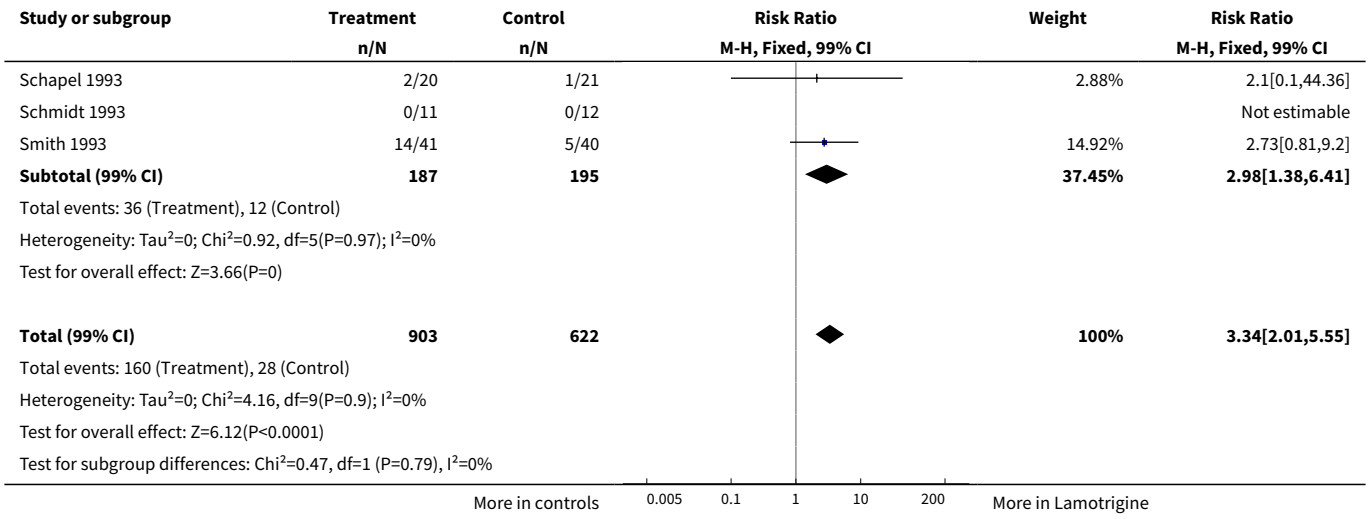
Comparison 3. Adverse effects

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Ataxia	12	1525	Risk Ratio (M-H, Fixed, 99% CI)	3.34 [2.01, 5.55]
1.1 Parallel studies - adults	3	944	Risk Ratio (M-H, Fixed, 99% CI)	3.40 [1.67, 6.90]
1.2 Parallel studies - children	1	199	Risk Ratio (M-H, Fixed, 99% CI)	5.15 [0.72, 36.64]
1.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 99% CI)	2.98 [1.38, 6.41]
2 Dizziness	13	1768	Risk Ratio (M-H, Fixed, 99% CI)	2.00 [1.52, 2.64]
2.1 Parallel studies - adults	4	1187	Risk Ratio (M-H, Fixed, 99% CI)	2.09 [1.49, 2.94]
2.2 Parallel studies - children	1	199	Risk Ratio (M-H, Fixed, 99% CI)	4.33 [1.27, 14.79]
2.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 99% CI)	1.41 [0.83, 2.38]
3 Fatigue	12	1552	Risk Ratio (M-H, Fixed, 99% CI)	0.82 [0.55, 1.22]
3.1 Parallel studies - adults	3	971	Risk Ratio (M-H, Fixed, 99% CI)	0.81 [0.46, 1.42]
3.2 Parallel studies - children	1	199	Risk Ratio (M-H, Fixed, 99% CI)	1.89 [0.54, 6.63]

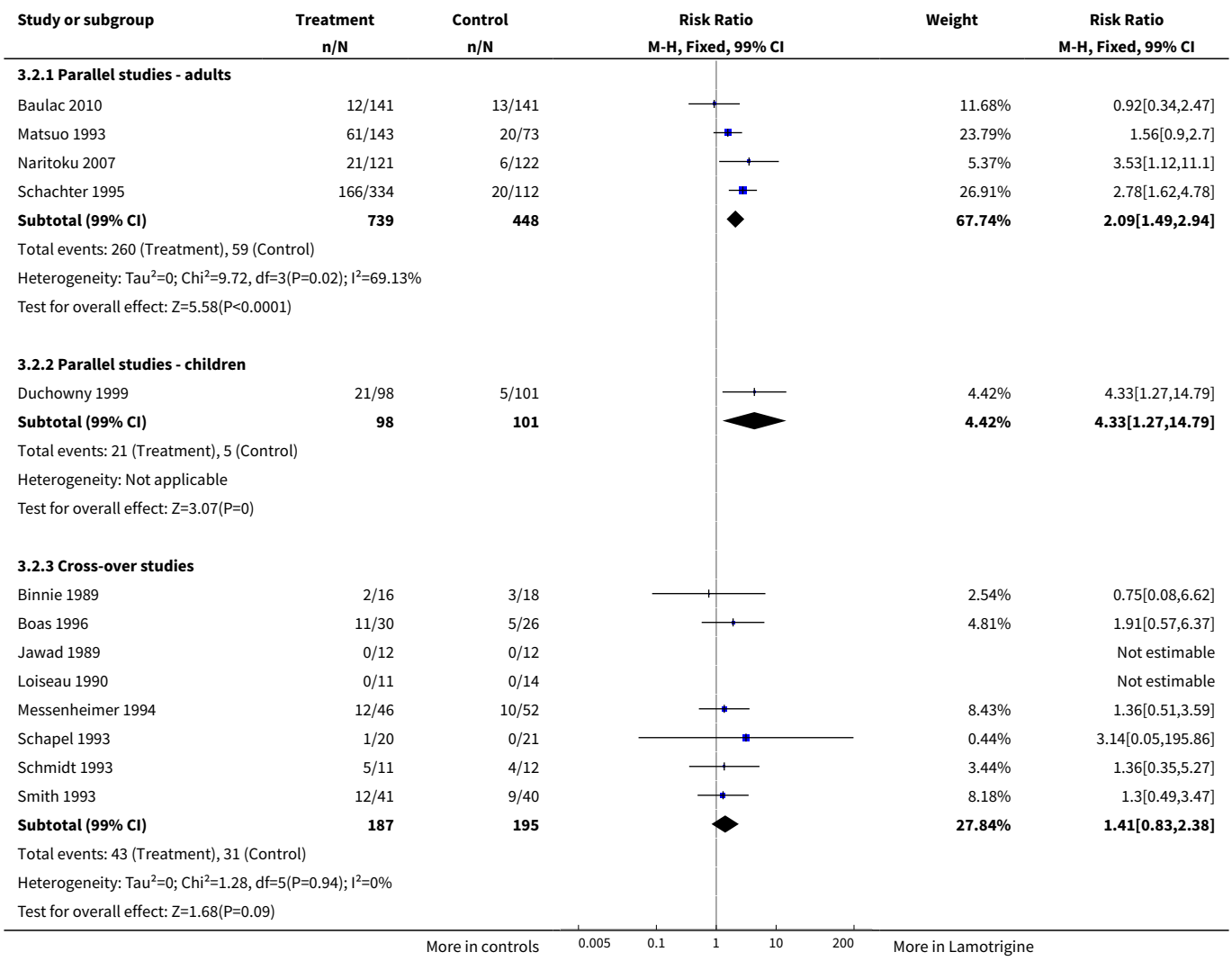
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 99% CI)	0.65 [0.34, 1.23]
4 Nausea	12	1486	Risk Ratio (M-H, Fixed, 99% CI)	1.81 [1.22, 2.68]
4.1 Parallel studies - adults	3	905	Risk Ratio (M-H, Fixed, 99% CI)	1.68 [1.02, 2.78]
4.2 Parallel studies - children	1	199	Risk Ratio (M-H, Fixed, 99% CI)	5.67 [0.81, 39.69]
4.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 99% CI)	1.67 [0.85, 3.29]
5 Somnolence	13	1768	Risk Ratio (M-H, Fixed, 99% CI)	1.39 [0.96, 2.00]
5.1 Parallel studies - adults	4	1187	Risk Ratio (M-H, Fixed, 99% CI)	1.58 [0.93, 2.68]
5.2 Parallel studies - children	1	199	Risk Ratio (M-H, Fixed, 99% CI)	1.37 [0.67, 2.81]
5.3 Cross-over studies	8	382	Risk Ratio (M-H, Fixed, 99% CI)	1.06 [0.51, 2.17]
6 Diplopia	3	944	Risk Ratio (M-H, Fixed, 99% CI)	3.79 [2.15, 6.68]
7 Headache	5	1386	Risk Ratio (M-H, Fixed, 99% CI)	1.13 [0.88, 1.45]

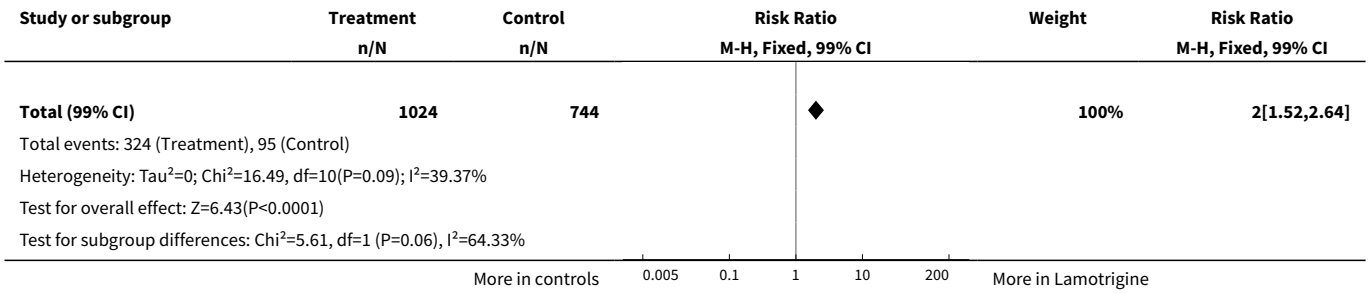
Analysis 3.1. Comparison 3 Adverse effects, Outcome 1 Ataxia.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
3.1.1 Parallel studies - adults					
Baulac 2010	7/141	1/141		2.95%	7[0.45,108.03]
Matsuo 1993	27/143	7/73		27.32%	1.97[0.7,5.5]
Schachter 1995	80/334	6/112		26.48%	4.47[1.56,12.82]
Subtotal (99% CI)	**618**	**326**		**56.75%**	**3.4[1.67,6.9]**
Total events: 114 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=2(P=0.25); I^2=28.14%					
Test for overall effect: Z=4.45(P<0.0001)					
3.1.2 Parallel studies - children					
Duchowny 1999	10/98	2/101		5.81%	5.15[0.72,36.64]
Subtotal (99% CI)	**98**	**101**		**5.81%**	**5.15[0.72,36.64]**
Total events: 10 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					
3.1.3 Cross-over studies					
Binnie 1989	1/16	1/18		2.77%	1.13[0.03,38.53]
Boas 1996	1/30	0/26		1.58%	2.61[0.04,165.96]
Jawad 1989	2/12	0/12		1.47%	5[0.11,237.43]
Loiseau 1990	0/11	0/14			Not estimable
Messenheimer 1994	16/46	5/52		13.83%	3.62[1.08,12.16]
		More in controls	0.005 0.1 1 10 200	More in Lamotrigine	

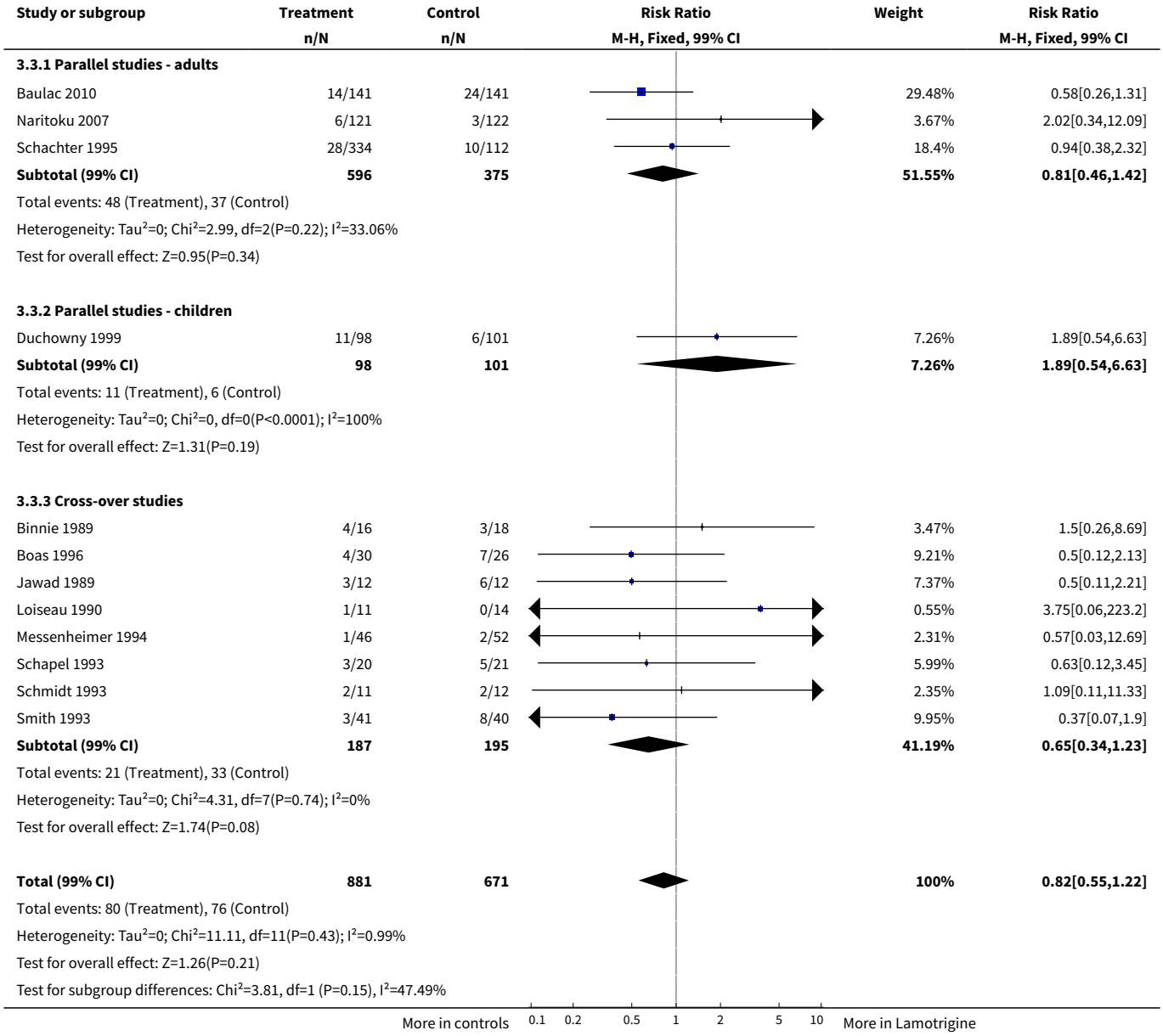


Analysis 3.2. Comparison 3 Adverse effects, Outcome 2 Dizziness.



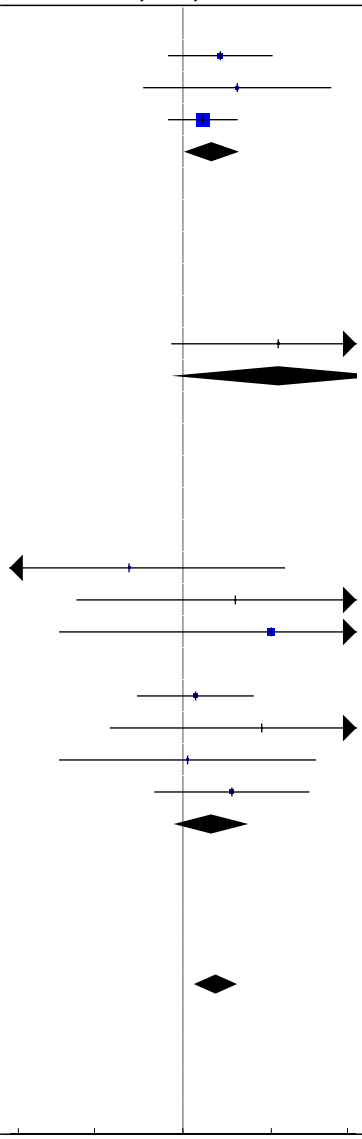


Analysis 3.3. Comparison 3 Adverse effects, Outcome 3 Fatigue.



Analysis 3.4. Comparison 3 Adverse effects, Outcome 4 Nausea.

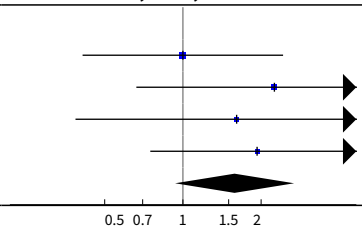
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
3.4.1 Parallel studies - adults					
Matsuo 1993	31/143	8/73		17.42%	1.98[0.76,5.12]
Naritoku 2007	8/121	3/122		4.91%	2.69[0.49,14.9]
Schachter 1995	73/334	17/112		41.88%	1.44[0.76,2.71]
Subtotal (99% CI)	**598**	**307**		**64.22%**	**1.68[1.02,2.78]**
Total events: 112 (Treatment), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.09, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=2.66(P=0.01)					
3.4.2 Parallel studies - children					
Duchowny 1999	11/98	2/101		3.24%	5.67[0.81,39.69]
Subtotal (99% CI)	**98**	**101**		**3.24%**	**5.67[0.81,39.69]**
Total events: 11 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.3(P=0.02)					
3.4.3 Cross-over studies					
Binnie 1989	1/16	3/18		4.64%	0.38[0.02,6.42]
Boas 1996	3/30	1/26		1.76%	2.6[0.14,46.93]
Jawad 1989	2/12	0/12		0.82%	5[0.11,237.43]
Loiseau 1990	0/11	0/14			Not estimable
Messenheimer 1994	10/46	9/52		13.9%	1.26[0.43,3.63]
Schapel 1993	4/20	1/21		1.6%	4.2[0.26,66.7]
Schmidt 1993	2/11	2/12		3.15%	1.09[0.11,11.33]
Smith 1993	10/41	4/40		6.66%	2.44[0.59,10.01]
Subtotal (99% CI)	**187**	**195**		**32.54%**	**1.67[0.85,3.29]**
Total events: 32 (Treatment), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.44, df=6(P=0.62); I^2=0%					
Test for overall effect: Z=1.94(P=0.05)					
Total (99% CI)	**883**	**603**		**100%**	**1.81[1.22,2.68]**
Total events: 155 (Treatment), 50 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.16, df=10(P=0.61); I^2=0%					
Test for overall effect: Z=3.88(P=0)					
Test for subgroup differences: Chi^2=2.49, df=1 (P=0.29), I^2=19.73%					



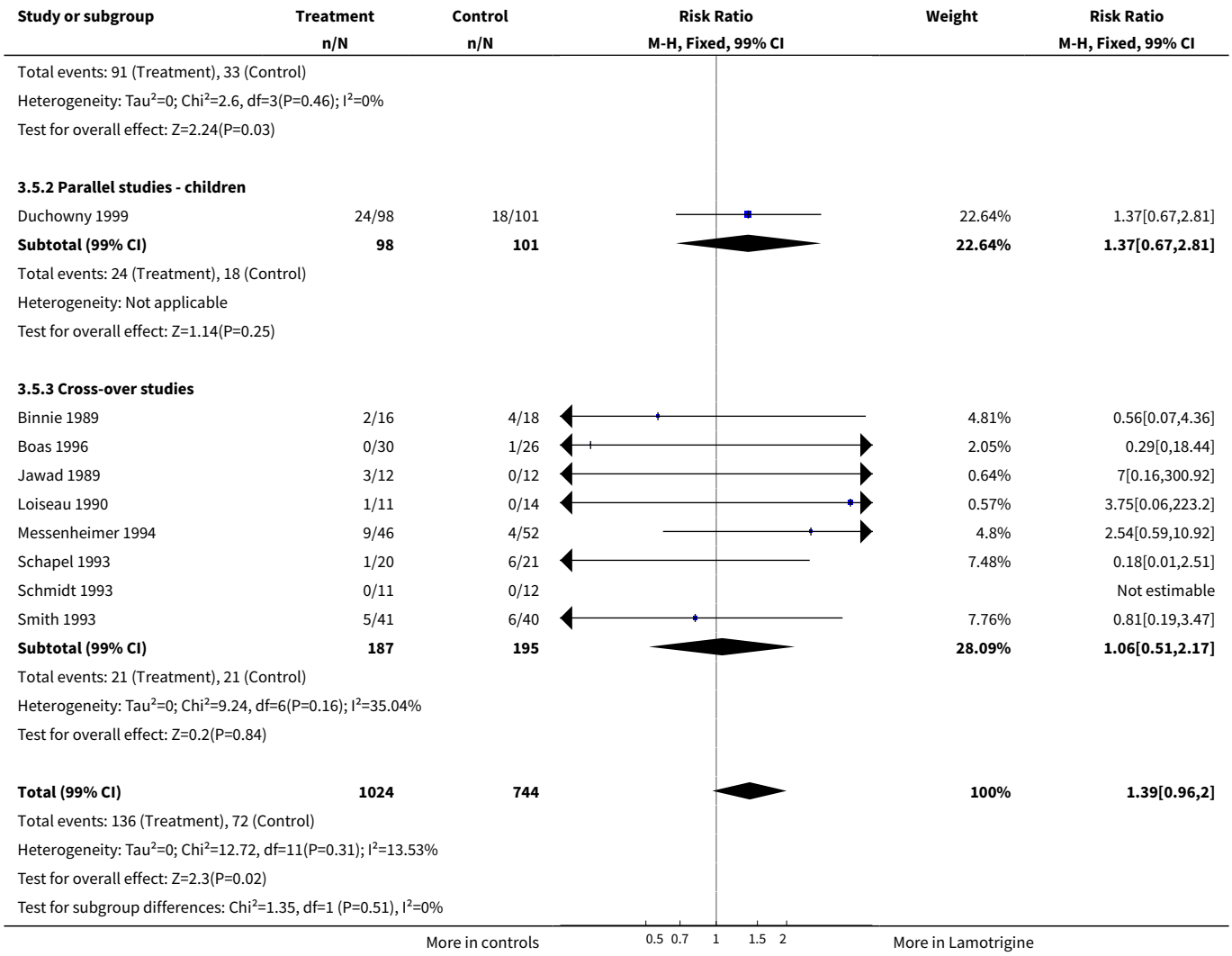
More in controls — More in Lamotrigine

Analysis 3.5. Comparison 3 Adverse effects, Outcome 5 Somnolence.

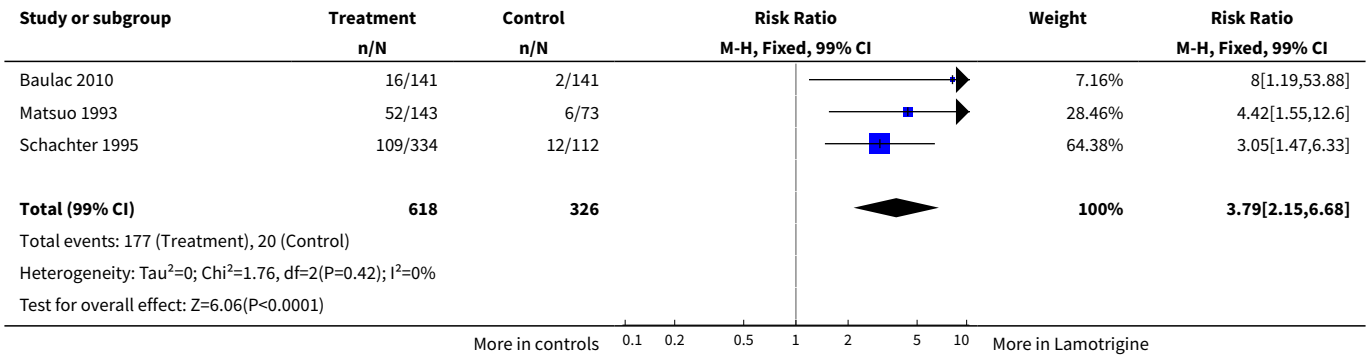
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
3.5.1 Parallel studies - adults					
Baulac 2010	15/141	15/141		19.16%	1[0.41,2.43]
Matsuo 1993	22/143	5/73		8.45%	2.25[0.66,7.62]
Naritoku 2007	8/121	5/122		6.36%	1.61[0.39,6.75]
Schachter 1995	46/334	8/112		15.3%	1.93[0.75,4.96]
Subtotal (99% CI)	**739**	**448**		**49.27%**	**1.58[0.93,2.68]**



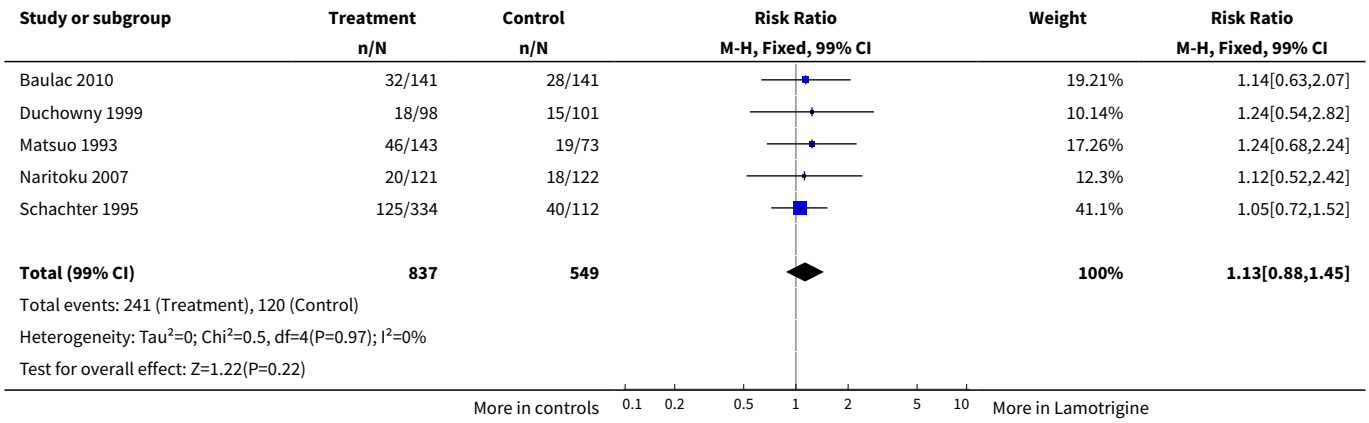
More in controls — More in Lamotrigine



Analysis 3.6. Comparison 3 Adverse effects, Outcome 6 Diplopia.



Analysis 3.7. Comparison 3 Adverse effects, Outcome 7 Headache.



ADDITIONAL TABLES

Table 1. Cognitive outcomes

Outcome	Study	Number tested	Lamotrigine mean	Placebo mean
Stroop time	Smith 1993	41	93.98	98.39
Stroop error	Smith 1993	44	2.18	2.41
Stroop colour word (Total score)	Banks 1991	10	32.4+/-10.9	35.6+/-9.42
Number cancellation: AC	Smith 1993	44	51.36	49.7
Number cancellation: AE	Smith 1993	43	3.6	3.04
Number cancellation: BC	Smith 1993	42	48.21	48.54
Number cancellation: C	Smith 1993	42	38.19	39.29
Critical flicker fusion	Smith 1993	40	30.44	30.37
Choice reaction time	Smith 1993	40	0.675	0.669
Digit symbol (Scaled score)	Banks 1991	10	5 +/-2.45	6.6 +/- 2.71
Rey complex figure recall percentile	Banks 1991	10	22+/-17.51	30.5+/-27.33
Trail making part B percentile	Banks 1991	10	26+/-30.35	30.5+/-32.09

Table 2. Health-related quality of life outcomes (Smith 1993)

Outcome	Number tested	Lamot-rigine - Mean	Placebo - Mean	Clinical relevance

Table 2. Health-related quality of life outcomes (Smith 1993) *(Continued)*

PSYCHOLOGICAL				
Depression	54	4.24	4.26	No significant difference
Happiness	51	3.8	1.96	Higher scores in LTG group; P = 0.003
Mood	50	24.36	26.8	No significant difference
Self-esteem	50	30.06	29.16	No significant difference
Mastery	50	20.02	18.78	Higher scores in LTG group; P = 0.003
Anxiety	54	6.87	6.83	No significant difference
PHYSICAL (Nottingham Health Profile)				
Energy	53	0.68	0.68	No significant difference
Pain	53	0.6	0.69	No significant difference
Emotional reaction	53	1.96	1.96	No significant difference
Sleep	53	0.89	0.76	No significant difference
Social isolation	53	0.92	0.94	No significant difference
Physical mobility	53	0.96	0.91	No significant difference
SEIZURE SEVERITY SCALE				
Percept	53	25.19	25.47	No significant difference
Ictal	53	19.47	20.53	Less severe seizures in LTG group; P = 0.017
Caregivers	53	20.35	21.80	Less severe seizures in LTG group; P = 0.035

LTG: lamotrigine

APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web)

1. MESH DESCRIPTOR Lamotrigine EXPLODE ALL AND CENTRAL:TARGET

2. (elmendos OR epilepax OR lamictal OR lamictin OR lamotrigin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2

4. MESH DESCRIPTOR Epilepsies, Partial EXPLODE ALL AND CENTRAL:TARGET

5. ((partial or focal) and (seizure* or epilep*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

6. #4 OR #5 AND CENTRAL:TARGET

7. #3 AND #6

8. (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND CENTRAL:TARGET

9. #7 NOT #8

10. #9 AND >13/12/2018:CRSCREATED

Appendix 2. MEDLINE (Ovid) 1946-

This strategy includes the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2019).

1. exp Lamotrigine/

2. (elmendos or epilepax or lamictal or lamictin or lamotrigin$).tw.

3. 1 or 2

4. exp Epilepsies, Partial/

5. ((partial or focal) and (seizure$ or epilep$)).tw.

6. 4 or 5

7. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

8. clinical trials as topic.sh.

9. trial.ti.

10. 7 or 8 or 9

11. exp animals/ not humans.sh.

12. 10 not 11

13. 3 and 6 and 12

14. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.

15. 13 not 14

16. limit 15 to ed=20181206-20200309

17. 15 not (1$ or 2$).ed.

18. 17 and (2018$ or 2019$ or 2020$).dt.

19. 16 or 18

20. remove duplicates from 19

WHAT'S NEW

Date	Event	Description
9 March 2020	New search has been performed	Searches updated 09 March 2020; no new studies were identified.
9 March 2020	New citation required but conclusions have not changed	Conclusions remain unchanged. The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 3, 2000

Date	Event	Description
28 May 2015	New citation required but conclusions have not changed	Conclusions remain unchanged.
28 May 2015	New search has been performed	Searches updated 28 May 2015. No new relevant studies were identified.
6 January 2010	New search has been performed	Searches updated 6th January 2010. Two new studies have been included (Naritoku 2007 and Piña-Garza 2008); the conclusions are unchanged.
10 September 2008	Amended	Converted to new review format.
25 April 2007	New search has been performed	Searches updated 25th April 2007. One new conference abstract (Carignani 2006) has been added to the 'Studies Awaiting Classification' section. This will be assessed for inclusion at a later date.
16 November 2005	Amended	We re-ran our search on 31 March 2005. One new study (Carignani 2004) has been added to the 'studies awaiting assessment' section.

CONTRIBUTIONS OF AUTHORS

Mariangela Panebianco was primarily responsible for the writing of this update and completed data extraction and 'Risk of bias' assessments. The same author assessed the studies for eligibility, extracted data, and assessed risk of bias. The assessment and interpretation of psychological data was done by Gus Baker in the original version of this review. Anthony Marson and Rebecca Bresnahan provided guidance and manuscript feedback during the update process. Rebecca Bresnahan was responsible for GRADE-assessing evidence.

DECLARATIONS OF INTEREST

MP: none known.
SR: none known.
RB: none known
AGM: A consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by the Applied Research Collaboration North West Coast (ARC NWC).

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- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes have been made to the format and content of the methods from the original protocol, in line with current MECIR standards (MECIR 2012) and the Cochrane Style Manual.

We have replaced the term 'partial' with 'focal', and 'refractory' with 'drug-resistant' in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*administration & dosage] [adverse effects]; Cognition [drug effects]; Cross-Over Studies; Drug Resistance; Drug Therapy, Combination; Epilepsies, Partial [*drug therapy]; Lamotrigine; Quality of Life; Randomized Controlled Trials as Topic; Triazines [*administration & dosage] [adverse effects]

MeSH check words

Adult; Child; Humans