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Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review (Review)

Nolan SJ, Tudur Smith C, Weston J, Marson AG

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[Intervention Review]

Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 1, 2006 of the Cochrane Database of Systematic Reviews.

Epilepsy is a common neurological condition in which abnormal electrical discharges from the brain cause recurrent unprovoked seizures. It is believed that with effective drug treatment up to 70% of individuals with active epilepsy have the potential to become seizure-free and to go into long-term remission shortly after starting drug therapy with a single antiepileptic drug (AED) in monotherapy.

The correct choice of first-line antiepileptic therapy for individuals with newly diagnosed seizures is of great importance. It is important that the choice of AEDs for an individual is made using the highest quality evidence regarding the potential benefits and harms of the various treatments. It is also important that the effectiveness and tolerability of AEDs appropriate to given seizure types are compared to one another.

Carbamazepine or lamotrigine are first-line recommended treatments for new onset partial seizures and as a first- or second-line treatment for generalised tonic-clonic seizures. Performing a synthesis of the evidence from existing trials will increase the precision of the results for outcomes relating to efficacy and tolerability and may assist in informing a choice between the two drugs.

Objectives

To review the time to withdrawal, remission and first seizure with lamotrigine compared to carbamazepine when used as monotherapy in people with partial onset seizures (simple or complex partial and secondarily generalised) or generalised onset tonic-clonic seizures (with or without other generalised seizure types).

Search methods

The first searches for this review were run in 1997. For the most recent update we searched the Cochrane Epilepsy Group Specialized Register (17 October 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 17 October 2016) and MEDLINE (Ovid, 1946 to 17 October 2016). We imposed no language restrictions. We also contacted pharmaceutical companies and trial investigators.

Selection criteria

Randomised controlled trials in children or adults with partial onset seizures or generalised onset tonic-clonic seizures comparing monotherapy with either carbamazepine or lamotrigine.

Data collection and analysis

This was an individual participant data (IPD) review. Our primary outcome was time to withdrawal of allocated treatment and our secondary outcomes were time to first seizure post-randomisation, time to six-month, 12-month and 24-month remission, and incidence of adverse events. We used Cox proportional hazards regression models to obtain trial-specific estimates of hazard ratios (HRs) with 95% confidence intervals (CIs), using the generic inverse variance method to obtain the overall pooled HR and 95% CI.

Main results

We included 13 studies in this review. Individual participant data were available for 2572 participants out of 3394 eligible individuals from nine out of 13 trials: 78% of the potential data. For remission outcomes, a HR < 1 indicated an advantage for carbamazepine and for first seizure and withdrawal outcomes a HR < 1 indicated an advantage for lamotrigine.

The main overall results (pooled HR adjusted for seizure type) were: time to withdrawal of allocated treatment (HR 0.72, 95% CI 0.63 to 0.82), time to first seizure (HR 1.22, 95% CI 1.09 to 1.37) and time to six-month remission (HR 0.84, 95% CI 0.74 to 0.94), showing a significant advantage for lamotrigine compared to carbamazepine for withdrawal but a significant advantage for carbamazepine compared to lamotrigine for first seizure and six-month remission. We found no difference between the drugs for time to 12-month remission (HR 0.91, 95% CI 0.77 to 1.07) or time to 24-month remission (HR 1.00, 95% CI 0.80 to 1.25), however only two trials followed up participants for more than one year so the evidence is limited.

The results of this review are applicable mainly to individuals with partial onset seizures; 88% of included individuals experienced seizures of this type at baseline. Up to 50% of the limited number of individuals classified as experiencing generalised onset seizures at baseline may have had their seizure type misclassified, therefore we recommend caution when interpreting the results of this review for individuals with generalised onset seizures.

The most commonly reported adverse events for both of the drugs across all of the included trials were dizziness, fatigue, gastrointestinal disturbances, headache and skin problems. The rate of adverse events was similar across the two drugs.

The methodological quality of the included trials was generally good, however there is some evidence that the design choice of masked or open-label treatment may have influenced the withdrawal rates of the trials. Hence, we judged the quality of the evidence for the primary outcome of treatment withdrawal to be moderate for individuals with partial onset seizures and low for individuals with generalised onset seizures. For efficacy outcomes (first seizure, remission), we judged the quality of evidence to be high for individuals with partial onset seizures and moderate for individuals with generalised onset seizures.

Authors' conclusions

Lamotrigine was significantly less likely to be withdrawn than carbamazepine but the results for time to first seizure suggested that carbamazepine may be superior in terms of seizure control. A choice between these first-line treatments must be made with careful consideration. We recommend that future trials should be designed to the highest quality possible with consideration of masking, choice of population, classification of seizure type, duration of follow-up, choice of outcomes and analysis, and presentation of results.

PLAIN LANGUAGE SUMMARY

Lamotrigine versus carbamazepine monotherapy (single drug treatment) for epilepsy

This is an updated version of the original Cochrane review published in Issue 1, 2006 of the Cochrane Database of Systematic Reviews.

Background

Epilepsy is a common neurological disorder in which abnormal electrical discharges from the brain cause recurrent seizures. We studied two types of epileptic seizures in this review: generalised onset seizures in which electrical discharges begin in one part of the brain and move throughout the brain, and partial onset seizures (also known as focal onset seizures) in which the seizure is generated in and affects one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain). Partial seizures may become generalised

(secondary generalisation) and move from one part of the brain throughout the brain. For around 70% of people with epilepsy, a single antiepileptic drug can control generalised onset or partial onset seizures.

This review applies to people with partial seizures (with or without secondary generalisation) and people with generalised tonic-clonic seizures, a specific generalised seizure type. This review does not apply to people with other generalised seizure types such as absence seizures or myoclonic seizures as the recommended treatments for these seizure types are different.

Objective

Carbamazepine and lamotrigine are first-choice treatments for individuals with recently diagnosed epilepsy. The aim of this review was to compare how effective these drugs are at controlling seizures, to find out if they are associated with side effects that may result in individuals stopping the drug and to inform a choice between these drugs.

Methods

The last search for trials was in October 2016. We assessed the evidence from 13 randomised controlled trials comparing lamotrigine with carbamazepine. We were able to combine data for 2572 people from nine of the 13 trials; for the remaining 822 people from four trials, data were not available to use in this review.

Results

The results of the review suggest that people are more likely to withdraw earlier from carbamazepine than lamotrigine treatment. The most common drug-related reason for withdrawal was adverse events: 51% of total withdrawals in participants on carbamazepine and 36% of total withdrawals in participants on lamotrigine. The second most common drug-related cause for withdrawal was seizure recurrence: 56 of 683 total withdrawals (8%) on carbamazepine and 93 of 610 total withdrawals (15%) on lamotrigine.

The results also suggest that recurrence of seizures after starting treatment with lamotrigine may happen earlier than treatment with carbamazepine and seizure freedom for a period of six months may occur earlier on carbamazepine than lamotrigine. The majority of the people included in the 13 trials (88%) experienced partial seizures, so the results of this review apply mainly to people with this seizure type.

The most common side effects reported by participants during the trials were dizziness, fatigue, gastrointestinal problems, headaches and skin problems. These side effects were reported a similar number of times by people taking lamotrigine or carbamazepine.

Quality of the evidence

For people with partial onset seizures, we judged the quality of the evidence to be high for the outcomes of seizure recurrence and remission of seizures and we judged the quality of the evidence to be moderate for the outcome of treatment withdrawal. The design of the trials (whether the people and treating clinicians knew which drug they were taking) may have influenced the rates of withdrawal from treatments. Up to 50% of people in the trials used in our results may have been wrongly classified as having generalised seizures; for people with generalised onset seizures, we judged the quality of the evidence to be moderate for the outcomes of seizure recurrence and remission of seizures and low quality for the outcome of treatment withdrawal.

Conclusions

For people with partial onset seizures, lamotrigine and carbamazepine are effective treatments and a choice between these two treatments must be made carefully. More information is needed for people with generalised onset seizures. We recommend that all future trials comparing these drugs, or any other antiepileptic drugs, should be designed using high-quality methods. Seizure types of people included in trials should also be classified very carefully to ensure that the results are also of high quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Lamotrigine compared with carbamazepine for epilepsy

Patient or population: adults and children with partial onset or generalised onset seizures (generalised tonic-clonic with or without other generalised seizure types)
Settings: outpatients
Intervention: lamotrigine
Comparison: carbamazepine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)[1]	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Carbamazepine	Lamotrigine				
Time to withdrawal of allocated treatment (adjusted for epilepsy type) Range of follow-up: 0 to 2420 days	396 per 1000	301 per 1000 (269 to 335)	HR 0.71 (0.62 to 0.81)	2481 (9 trials)	⊕⊕⊕◯ **moderate**[2]	HR < 1 indicates an advantage for lamotrigine
Time to withdrawal of allocated treatment Subgroup: partial onset seizures Range of follow-up: 0 to 2420 days	388 per 1000	308 per 1000 (270 to 345)	HR 0.75 (0.64 to 0.86)	2182 (9 trials)	⊕⊕⊕◯ **moderate**[2]	HR < 1 indicates an advantage for lamotrigine
Time to withdrawal of allocated treatment Subgroup: generalised onset seizures Range of follow-up: 0 to 1446 days	458 per 1000	245 per 1000 (168 to 352)	HR 0.46 (0.3 to 0.71)	299 (6 trials)	⊕⊕◯◯ **low**[3,4]	HR < 1 indicates an advantage for lamotrigine

The assumed risk is calculated as the event rate in the carbamazepine treatment group
The corresponding risk in the lamotrigine treatment group (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)
The corresponding risk is calculated as the assumed risk x the relative risk (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk)))/assumed risk
95% CI: 95% confidence interval; HR: hazard ratio

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

[1]Pooled hazard ratio for all participants adjusted for seizure type.
[2]Downgraded due to high risk of bias due to the open-label design of five trials included in the analysis (Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007); the design of the trial may have influenced the withdrawal rates.
[3]Downgraded due to high risk of bias due to the open-label design of three trials included in the analysis (Lee 2011; Reunanen 1996; SANAD A 2007).
[4]Downgraded due to potential misclassification of generalised onset seizures in up to 50% of participants in the trials.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2006) on 'Lamotrigine versus carbamazepine monotherapy for epilepsy' (Gamble 2006).

Description of the condition

Epilepsy is a common neurological condition in which abnormal electrical discharges from the brain cause recurrent unprovoked seizures. Epilepsy is a disorder of many heterogenous seizure types, with an estimated incidence of 33 to 57 per 100,000 person-years worldwide (Annegers 1999; Hirtz 2007; MacDonald 2000; Olafsson 2005; Sander 1996), accounting for approximately 1% of the global burden of disease (Murray 1994). The lifetime risk of epilepsy onset is estimated to be 1300 to 4000 per 100,000 person-years (Hauser 1993; Juul-Jenson 1983), and the lifetime prevalence could be as large as 70 million people worldwide (Ngugi 2010). It is believed that with effective drug treatment, up to 70% of individuals with active epilepsy have the potential to go into long-term remission shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), and around 70% of individuals can achieve seizure freedom using a single antiepileptic drug (AED) in monotherapy (Cockerell 1995). Current National Institute for Health and Care Excellence (NICE) guidelines recommend that both adults and children with epilepsy should be treated with monotherapy wherever possible (NICE 2012). The remaining 30% of individuals experience refractory or drug-resistant seizures, which often require treatment with combinations of antiepileptic drugs (AEDs) or alternative treatments, such as epilepsy surgery (Kwan 2000).

We studied two seizure types in this review: generalised onset seizures in which electrical discharges begin in one part of the brain and move throughout the brain, and partial onset seizures in which the seizure is generated in and affects one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain).

Description of the intervention

Carbamazepine was amongst the earliest 'traditional' drugs licensed for the treatment of epileptic seizures and has been commonly used as monotherapy for partial onset and generalised onset seizures for over 30 years (Shakir 1980). Lamotrigine is among a 'second generation' of AEDs, licensed as monotherapy for epileptic seizures following demonstrations of efficacy compared to 'traditional' AEDs such as carbamazepine (Brodie 1995; Brodie 1999; Reunanen 1996).

Comparative trials have also shown newer AEDs such as lamotrigine to be to be generally well tolerated as monotherapy in both adults and children and related to fewer adverse events, fewer serious adverse events and fewer drug interactions with concomitant AEDs and other concomitant medications than 'traditional' first-line AEDs such as carbamazepine (Brodie 1995; Brodie 1999; French 2007; Reunanen 1996).

Evidence regarding teratogenic effects (disturbances to foetal development) of carbamazepine and lamotrigine is conflicting and uncertain. It is thought that the risk of congenital malformation may be higher for women taking carbamazepine compared to the general population (Meador 2008; Morrow 2006), and carbamazepine has been shown to be associated with neural tube defects (Matlow 2012). The risk of malformations is thought to be lower for women taking lamotrigine than carbamazepine (Meador 2008), but the risk of malformation may increase with an increasing dose of lamotrigine (Morrow 2006). It is unclear whether taking carbamazepine or lamotrigine during pregnancy has any negative neurodevelopmental effects on the child (Bromley 2014).

Current NICE guidelines for adults and children recommend carbamazepine or lamotrigine as a first-line treatments for new onset partial seizures and as a second-line treatment for generalised tonic-clonic seizures (NICE 2012). Lamotrigine is considered a suitable first-line treatment for new onset generalised seizures if sodium valproate is considered unsuitable. Carbamazepine may be a suitable second-line treatment for generalised onset seizures but may exacerbate myoclonic or absence seizures (Liporace 1994; Shields 1983; Snead 1985).

How the intervention might work

Antiepileptic drugs suppress seizures by reducing neuronal excitability (disruption of the usual mechanisms of a neuron within the brain, which may lead to an epileptic seizure) (MacDonald 1995). Lamotrigine and carbamazepine are broad-spectrum treatments suitable for many seizure types, and both have an anticonvulsant mechanism through blocking ion channels and binding with neurotransmitter receptors, or through inhibiting the metabolism or reuptake of neurotransmitters (Brodie 1996; Lees 1993; Ragsdale 1991).

Why it is important to do this review

With evidence that up to 70% of individuals with active epilepsy have the potential to go into long-term remission of seizures shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), the correct choice of first-line antiepileptic therapy for individuals with newly diagnosed seizures is of great importance. It is important that the choice of AEDs for an individual is made using the highest quality evidence regarding the potential benefits and harms of various treatments. It is also important that the effectiveness and tolerability of AEDs appropriate to given seizure types are compared to one another.

Therefore the aim of this review is to summarise efficacy and tolerability from existing randomised controlled trials comparing lam-

otrigine and carbamazepine, two current first-line recommended treatments for use in monotherapy for epileptic seizures. Performing a synthesis of the evidence from existing trials will increase the precision of the results for outcomes relating to efficacy and tolerability and may assist in informing a choice between the two drugs.

There are difficulties in undertaking a systematic review of epilepsy monotherapy trials as the important efficacy outcomes require analysis of time-to-event data (for example, time to first seizure after randomisation). Although methods have been developed to synthesise time-to-event data using summary information (Parmar 1998; Williamson 2002), the appropriate statistics are not commonly reported in published epilepsy trials (Nolan 2013a; Williamson 2000). Furthermore, although most epilepsy monotherapy trials collect seizure data, there has been no uniformity in the definition and reporting of outcomes. For example, trials may report time to 12-month remission but not time to first seizure or vice versa, or some trials may define time to first seizure from the date of randomisation while others use the date of achieving maintenance dose. Trial investigators have also adopted differing approaches to the analysis, particularly with respect to the censoring of time-to-event data. For these reasons, we performed this review using individual participant data (IPD), which helps to overcome these problems. This review is one in a series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons (Nolan 2013b; Nolan 2013c; Nolan 2013d; Nolan 2015a; Nolan 2015b; Marson 2000). These data have also been included in a network meta-analysis (Tudur Smith 2007), undertaken following a previous version of this review, and will be included in an update of this network meta-analysis (Nolan 2014).

OBJECTIVES

To review the time to withdrawal, remission and first seizure with lamotrigine compared to carbamazepine when used as monotherapy in people with partial onset seizures (simple or complex partial and secondarily generalised) or generalised onset tonic-clonic seizures (with or without other generalised seizure types).

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) using either an adequate method of allocation concealment (e.g. sealed, opaque envelopes) or a 'quasi' method of randomisation (e.g. allocation by date of birth).
- Trials may have been double-blind, single-blind or unblinded.
- Trials must have included a comparison of lamotrigine monotherapy with carbamazepine monotherapy in individuals with epilepsy.

Types of participants

- We included children or adults with partial onset seizures (simple partial, complex partial or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures, with or without other generalised seizure types (in other words those who had only generalised tonic-clonic seizures and those who had both generalised onset tonic-clonic seizures and generalised seizures of other types (e.g. absence, myoclonic etc).
- We excluded individuals with other generalised seizure types alone without generalised tonic-clonic seizures (e.g. those who had only absence seizures without any generalised clonic tonic-seizures) due to differences in first-line treatment guidelines for other generalised seizure types (NICE 2012).
- We included individuals with a new diagnosis of epilepsy, or who have had a relapse following antiepileptic monotherapy withdrawal.

Types of interventions

Carbamazepine or lamotrigine as monotherapy.

Types of outcome measures

Below is a list of outcomes investigated in this review. Reporting of these outcomes in the original trial report was not an eligibility requirement for this review.

Primary outcomes

- Time to withdrawal of allocated treatment (retention time). This was a combined outcome reflecting both efficacy and tolerability, as the following may have caused withdrawal of treatment: continued seizures, side effects, noncompliance or the initiation of additional add-on treatment (i.e. allocated treatment had failed). This is an outcome to which the participant makes a contribution and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE 1998; ILAE 2006).

Secondary outcomes

- Time to first seizure post-randomisation.
- Time to achieve six-month remission (seizure-free period).
- Time to achieve 12-month remission (seizure-free period).
- Time to achieve 24-month remission (seizure-free period).

- Incidence of adverse events (all reported whether related or unrelated to treatment) and adverse events leading to treatment withdrawal.

Search methods for identification of studies

Electronic searches

The first searches for this review were run in 1997. Subsequent searches were run in July 2014 and December 2015. For the most recent update we searched the following databases.

- Cochrane Epilepsy Group Specialized Register (17 October 2016) using the search strategy set out in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 17 October 2016) using the search strategy set out in Appendix 2.
- MEDLINE (Ovid, 1946 to 17 October 2016) using the search strategy set out in Appendix 3.

There were no language restrictions.

Searching other resources

We reviewed the reference lists of retrieved studies to search for additional reports of relevant trials. We contacted Ciba Geigy (manufacturers of carbamazepine), GlaxoSmithKline (manufacturers of lamotrigine) and the original investigators of relevant trials identified by our search.

Data collection and analysis

Selection of studies

Two review authors (SJN and AGM) independently assessed trials for inclusion, resolving any disagreements by mutual discussion.

Data extraction and management

We requested the following individual participant data for all trials meeting our inclusion criteria.

Trial methods

- Method of generation of random list
- Method of concealment of randomisation
- Stratification factors
- Blinding methods

Participant covariates

- Gender
- Age
- Seizure types
- Time between first seizure and randomisation
- Number of seizures prior to randomisation (with dates)
- Presence of neurological signs
- Electroencephalographic (EEG) results
- Computerised tomography/magnetic resonance imaging (CT/MRI) results

Follow-up data

- Treatment allocation
- Date of randomisation
- Dates of follow-up
- Dates of seizures post-randomisation or seizure frequency data between follow-up visits
- Dates of treatment withdrawal and reasons for treatment withdrawal
- Dose
- Dates of dose changes

For each trial for which we did not obtain individual participant data (IPD), we carried out an assessment to see whether any relevant aggregate level data had been reported or could be indirectly estimated using the methods of Parmar 1998 and Williamson 2002. Where graphical time-to-event data (e.g. Kaplan Meier curves) were published with or without corresponding effective numbers at risk, we used a Microsoft Excel spreadsheet (Excel 2010), to indirectly estimate hazard ratios (Tierney 2007). Four trials including 1391 participants provided seizure data in terms of the number of seizures recorded between each follow-up visit rather than specific dates of seizures (Eun 2012; Lee 2011; SANAD A 2007; Werhahn 2015). To enable the calculation of time-to-event outcomes, we applied linear interpolation to approximate dates of seizures between follow-up visits. For example, if the trial recorded four seizures between two visits that occurred on 1 March 2010 and 1 May 2010 (interval of 61 days), then the date of first seizure would be approximately 13 March 2010. This allowed the computation of an estimate of the time to six-month remission, 12-month remission, 24-month remission and first seizure.

We calculated time to six-month, 12-month and 24-month remission from the date of randomisation to the date (or estimated date) that the individual had first been free of seizures for six, 12 or 24 months, respectively. If the person had one or more seizures during the trial, a six-month, 12-month or 24 month seizure-free period could also occur between the estimated date of the last seizure during the trial and a period of six, 12 or 24 months of seizure freedom.

We calculated time to first seizure from the date of randomisation to the date that we estimated their first seizure to have occurred. If

seizure data were missing for a particular visit, we censored these outcomes at the previous visit. We also censored these outcomes if the individual died or if follow-up ceased prior to the occurrence of the event of interest. We used these methods in five trials including 1383 participants (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996), for which we directly received outcome data (dates of seizures after randomisation).

For all trials we received data for date and reason of withdrawal from the trial. Time to treatment withdrawal was calculated as date of randomisation to date of withdrawal from the trial. For the analysis of time-to-event, we defined an 'event' as the withdrawal of the allocated treatment because of reasons related to the treatment(i.e. lack of efficacy, adverse events, or both lack of efficacy and adverse events), non-compliance with the treatment regimen, withdrawal of consent from the trial etc. We censored the outcome if treatment was withdrawn for reasons not related to the trial treatment: i.e. loss to follow-up, death (not treatment or epilepsy-related), withdrawal due to remission etc. We also censored individuals who were still on allocated treatment at the date of the end of follow-up. We considered documented reasons for withdrawal on a case by case basis for relation to treatment; two authors (SJN and AGM) independently classified reasons for withdrawals as events or censored and resolved any disagreements by discussion. If reasons for withdrawal were classified differently as events or censored in the included trials to our definitions, we conducted sensitivity analyses to account for differences in the definition of a withdrawal 'event' (see Sensitivity analysis).

Assessment of risk of bias in included studies

Two review authors (SJN and JW) independently assessed all included trials for risk of bias, resolving any disagreements by discussion. In the event of the presence of high risk of bias in included trials (due to inadequate allocation concealment or lack of blinding), we planned sensitivity analyses excluding these trials.

Measures of treatment effect

We measured all outcomes in this review as time-to-event outcomes with the hazard ratio and 95% confidence interval used as the measure of treatment effect. We calculated outcomes from IPD provided, where possible, or extracted from published trials if possible.

Unit of analysis issues

The unit of allocation and analysis was the individual for all included trials and no trials included in meta-analyses were of a repeated measures (longitudinal) nature or of a cross-over design.

One included trial allocated participants to three treatment arms, 100 mg/day lamotrigine, 200 mg/day lamotrigine or 600 mg/day carbamazepine (Reunanen 1996). In the primary analysis for all outcomes, we pooled the two lamotrigine arms and calculated a hazard ratio of lamotrigine compared to carbamazepine using the IPD provided. In sensitivity analysis, we calculated separate hazard ratios for 100 mg/day lamotrigine versus carbamazepine and 200 mg/day lamotrigine versus carbamazepine to examine any difference in the doses of lamotrigine compared to carbamazepine.

Dealing with missing data

For each trial that supplied IPD, we reproduced results from trial results where possible and performed consistency checks:

- We cross-checked trial details against any published report of the trial and contacted original trial authors if we found missing data, errors or inconsistencies. If trial authors could not resolve inconsistencies between the IPD and the published data, depending on the extent of the inconsistencies, we performed sensitivity analysis or excluded the data from the meta-analysis.
- We reviewed the chronological randomisation sequence and checked the balance of prognostic factors, taking account of factors stratified for in the randomisation procedure.

Assessment of heterogeneity

We assessed heterogeneity statistically using the Q test (P value < 0.10 for significance) and the I^2 statistic (Higgins 2003) (greater than 50% indicating considerable heterogeneity), with output produced using the generic inverse variance approach in Data and analyses, and visually by inspecting forest plots.

Assessment of reporting biases

Two review authors (SJN and JW) undertook all full quality and 'Risk of bias' assessments according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In theory, a review using IPD should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated. We requested trial protocols with IPD for all trials. Any selective reporting bias detected could be assessed with the Outcome Reporting Bias In Trials (ORBIT) classification system (Kirkham 2010).

Data synthesis

We carried out our analysis on an intention-to-treat basis (that is, we analysed participants in the group to which they were randomised, irrespective of which treatment they actually received). Therefore, for the time-to-event outcomes, 'time to six-month remission', 'time to 12-month remission', 'time to 24 month remission' and 'time to first seizure post-randomisation', we did not censor participants if treatment was withdrawn.

An intention-to-treat analysis tends toward finding no difference between treatments and we would have undertaken a secondary 'protocol correct' analysis as a sensitivity analysis if the primary analyses had suggested equivalence, in which case participants

would have been censored at the time of drug withdrawal for seizure outcomes.

For all outcomes, we investigated the relationship between the time-to-event and treatment effect of the AEDs. We used Cox proportional hazards regression models to obtain trial-specific estimates of log (hazard ratio) or treatment effect and associated standard errors in statistical SAS® software, version 9.3 (SAS software. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). The model assumes that the ratio of hazards (risks) between the two treatment groups is constant over time (i.e. hazards are proportional). We tested this proportional hazards assumption of the Cox regression model for each outcome of each trial by testing the statistical significance of a time varying covariate in the model. We evaluated overall pooled estimates of hazard ratios (with 95% confidence intervals) using the generic inverse variance method. We expressed results as a hazard ratio (HR) and a 95% confidence interval (CI).

By convention, a HR greater than 1 indicates that an event is more likely to occur earlier on lamotrigine than on carbamazepine. Hence, for time to withdrawal of allocated treatment or time to first seizure, a HR greater than 1 indicates a clinical advantage for carbamazepine (e.g. a HR of 1.2 would suggest a 20% increase in risk of withdrawal from lamotrigine compared with carbamazepine), and for time to six-month, 12-month and 24-month remission a HR greater than 1 indicates a clinical advantage for lamotrigine (i.e. the seizure-free period occurs earlier on lamotrigine than carbamazepine).

Summary of findings and quality of the evidence (GRADE)

For the 2015 update, we have added two 'Summary of findings' tables to the review (outcomes in the tables decided before the update started based on clinical relevance).

Summary of findings for the main comparison reports the primary outcome of 'time to treatment withdrawal' in the subgroups of participants with partial onset seizures, generalised onset seizures and overall adjusted by epilepsy type.

Summary of findings 2 reports the secondary outcomes of 'time to first seizure' and 'time to 12-month remission' in the subgroups of participants with partial onset seizures, generalised onset seizures and overall adjusted by epilepsy type.

(We note that due to small numbers of participants with generalised seizures contributing to the outcome of time to 12-month remission, an overall treatment effect for all participants is presented in Summary of findings 2)

We determined the quality of the evidence using the GRADE approach, where we downgraded evidence in the presence of high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results and high probability of publication bias. We downgraded evidence by one level if the limitation was considered serious and two levels if considered very serious, as judged by the review authors. Under the GRADE approach, evidence may also be upgraded if a large treatment effect is demonstrated with no obvious biases or if a dose-response effect exists.

Subgroup analysis and investigation of heterogeneity

There is a strong clinical belief that some AEDs are more effective in some seizure types than others (see Description of the intervention and How the intervention might work), therefore we stratified all analyses by seizure type (partial onset versus generalised onset), according to the classification of main seizure type at baseline. We classified partial seizures (simple or complex) and partial secondarily generalised seizures as partial epilepsy. We classified primarily generalised seizures as generalised epilepsy.

We conducted a Chi² test of interaction between treatment and epilepsy type. If we found significant statistical heterogeneity to be present, we performed meta-analysis with a random-effects model in addition to a fixed-effect model, presenting the results of both models and performing sensitivity analyses to investigate differences in trial characteristics. If heterogeneity is found to be present in future updates and available data allow, we may investigate variables that may contribute to the variability (e.g. participant covariates, trial design) via in regression models

Sensitivity analysis

We performed several sensitivity analyses to test the robustness of our results to characteristics of the included trials:

- Definition of time to treatment withdrawal: we classified reasons for withdrawal that were related to the trial treatment as 'events' and 'censored' reasons not related to treatment in the analysis of 'time to treatment withdrawal.' If reasons for withdrawal were classified differently as events or censored in included trials to our definitions, we conducted sensitivity analyses to account for differences in the definition of a withdrawal 'event'

One trial considered participants to have completed the trial and hence withdrew treatment if they experienced a seizure after week six (Reunanen 1996). This does not correspond with the treatment withdrawal definition recommended by ILAE 1998 and used in this review. Withdrawal data for the participants in Reunanen 1996 is included in the primary analysis of time to treatment withdrawal and excluded in sensitivity analysis to examine any effect of the difference in definition of treatment withdrawal.

- Seizure dates: one trial did not include seizures that occurred during the first four weeks of the trial in efficacy analyses and dates of seizures before week four were not supplied to us (Nieto-Barrera 2001). Therefore, we calculated seizure outcomes as the time to first seizure and time to six-month remission after week four rather than after randomisation. Seizure data for Nieto-Barrera 2001 are included in the primary

analysis of time to first seizure and time to six-month remission and excluded in sensitivity analysis to examine any effect of the difference in origin time of the seizure count.

- Aggregate data: in the four trials for which IPD were not available (Gilad 2007; Rowan 2005; Saetre 2007; Steinhoff 2005), time to treatment withdrawal was presented as summary statistics or graphically in all four of the trials and time to first seizure was presented graphically in three of the trials (Gilad 2007; Rowan 2005; Saetre 2007). In Saetre 2007, hazard ratios and 95% confidence intervals were published for both time-to-event outcomes. In Gilad 2007 and Steinhoff 2005, due to the small number of events for the outcomes, it was possible to estimate individual withdrawal/seizure times from the graphs and therefore calculate an estimated hazard ratio. In Rowan 2005, we used indirect methods and approximate numbers at risk at a range of time points throughout the trials (described in Data extraction and management) to estimate the hazard ratios for the outcomes. These estimated hazard ratios are combined with the hazard ratios calculated from the trials providing IPD in sensitivity analysis.

- Seizure freedom: all included trials were of at least 24 weeks (around six months) duration. Those providing IPD that were over six months duration contributed to the outcome 'time to six-month remission of seizures' (Brodie 1995 A; Brodie 1995 B; Eun 2012; Lee 2011Reunanen 1996; SANAD A 2007; Werhahn 2015). Two trials were of 24 weeks duration (Brodie 1999; Nieto-Barrera 2001).

We conducted sensitivity analysis calculating a pooled risk ratio of seizure freedom at six months and including the data from Brodie 1999 and Nieto-Barrera 2001 (assuming 24 weeks is approximately equal to six months) and the trials for which IPD were not available. We estimated seizure freedom at six months from the graph of time to first seizure published in Saetre 2007. We also conducted sensitivity analysis, calculating a pooled risk ratio of seizure freedom throughout the whole trial combining IPD and aggregated data from all included trials.

- Misclassification of seizure type is a recognised problem in epilepsy, whereby some people with generalised seizures have been mistakenly classed as having partial onset seizures and vice versa. There is clinical evidence that individuals with generalised onset seizures are unlikely to have an 'age of onset' greater than 25 to 30 years (Malafosse 1994). Such misclassification impacted upon the results of three reviews in our series of pair-wise reviews for monotherapy in epilepsy comparing carbamazepine, phenobarbitone, phenytoin and sodium valproate in which around 30% to 50% of participants analysed may have had their seizure type misclassified as generalised onset (Nolan 2013b; Nolan 2015a; Nolan 2015b). Given the potential biases introduced into those reviews, we examined the distribution of age at onset for individuals with generalised seizures in the trials included in this review, to assess the potential impact of misclassification of seizure type on the outcomes.

Eun 2012 and Werhahn 2015 recruited only individuals with partial onset seizures therefore there were no participants with new onset generalised seizures over the age of 30 in these trials.
Two trials were designed to include participants with partial onset seizures only, however three participants in Nieto-Barrera 2001 and nine participants in SANAD A 2007 were classified as having generalised onset seizures. Further, seizure type was missing for 85 participants in SANAD A 2007. We considered the individuals in these two trials to have a misclassification of seizure type. Overall:

- in Brodie 1995 A, 20 out of the 54 participants (37%) classified as having generalised onset seizures were over the age of 30 at entry into the trial (and all over the age of 29 at seizure onset);
- in Brodie 1995 B, 23 out of the 62 participants (37%) classified as having generalised onset seizures were over the age of 30 at entry into the trial (and all over the age of 29 at seizure onset);
- in Brodie 1999, all 45 of the participants (100%) classified as having generalised onset seizures were over the age of 30 at entry into the trial (no age of onset data provided);
- in Lee 2011, 9 out of the 15 participants (60%) classified as having generalised onset seizures were over the age of 30 at entry into the trial (no age of onset data provided);
- in Reunanen 1996, 43 out of the 114 participants (38%) classified as having generalised onset seizures were over the age of 30 at entry into the trial (and all over the age of 23 at seizure onset).

In total 152 out of 302 participants (50%) classified as having generalised onset seizures may have been wrongly classified as having new onset generalised seizures. To investigate misclassification for each outcome, we undertook two sensitivity analyses to investigate misclassification:

- we reclassified the 152 individuals with generalised seizure types and age at onset greater than 30 as having partial onset seizures and repeated subgroup analysis;
- we reclassified the 152 individuals with generalised seizure types and age at onset greater than 30 and the 85 individuals with missing seizure type in SANAD A 2007 into an 'uncertain seizure type' group and repeated subgroup analysis with three groups.

RESULTS

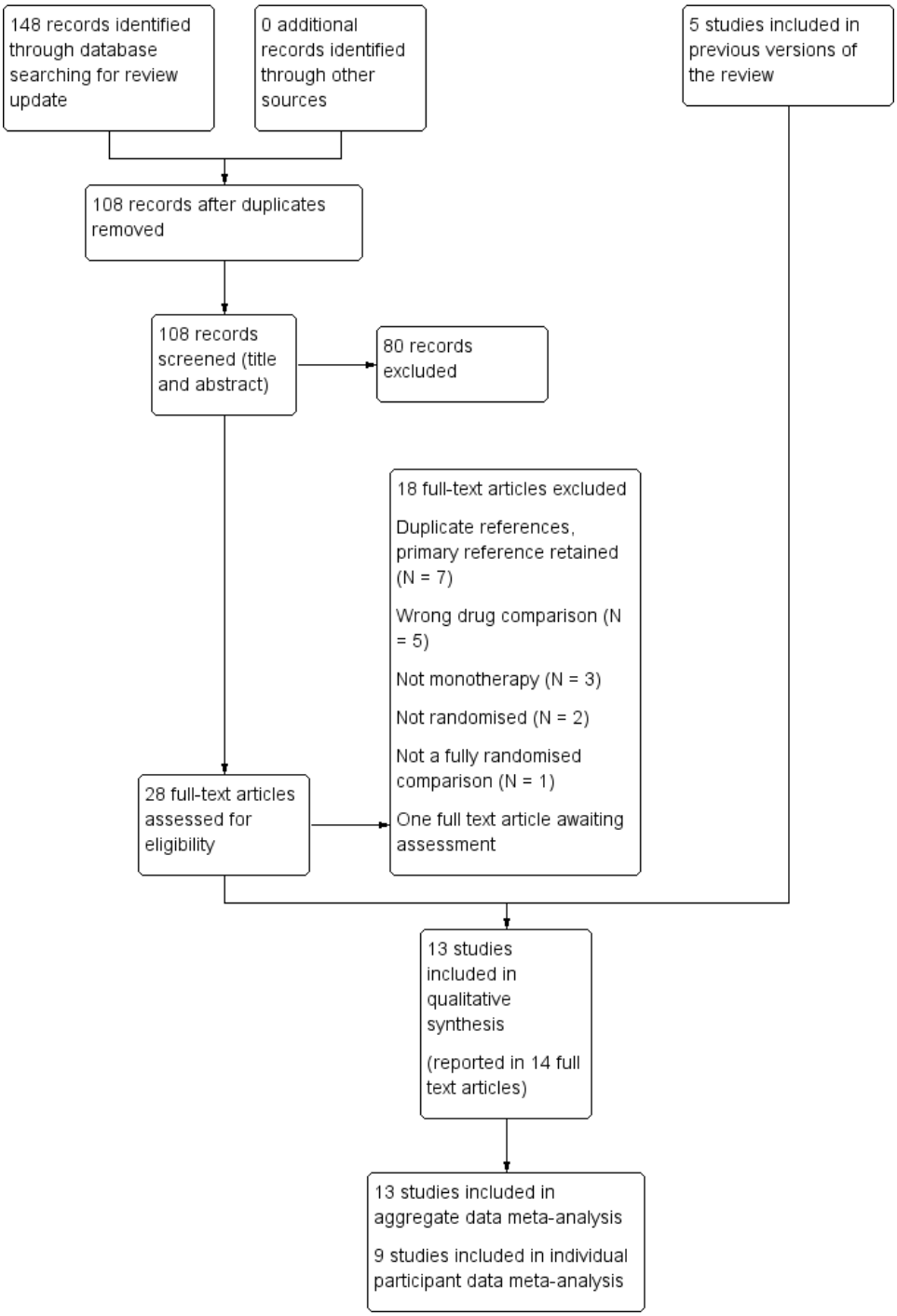
Description of studies

Results of the search

Five trials were included in previous versions of this review (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996).

For the 2016 update of this review, we identified 148 records from the databases and search strategies outlined in Electronic searches. We removed 40 duplicate records and screened 108 records (title and abstract) for inclusion in the review. We excluded 80 records based on the title and abstract and assessed 28 full-text articles for inclusion in the review. We excluded 18 articles from the review (see Excluded studies below), classified one article as awaiting assessment (see Characteristics of studies awaiting classification) and included eight trials (reported in nine full text articles) in the review (see Included studies). Therefore, we included a total of 13 trials in the review. See Figure 1 for a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram.

Figure 1. Study flow diagram.



Included studies

We identified 12 published reports that met the inclusion criteria for this review (Brodie 1995; Brodie 1999; Eun 2012; Gilad 2007; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; Rowan 2005; Saetre 2007; SANAD A 2007; Steinhoff 2005; Werhahn 2015). One of the published reports (Brodie 1995) contained results on two separate randomised controlled trials run on very similar protocols (Brodie 1995 A; Brodie 1995 B). Although the two trials were reported within the same publication we treated them as separate trials within this systematic review; therefore we included a total of 13 trials in the review.

One trial recruited adults of all ages (Gilad 2007), and one trial recruited adults over the age of 16 (Lee 2011). One trial recruited children between the ages of 6 and 12 (Eun 2012). Two trials recruited individuals over the age of 12 (Reunanen 1996; Steinhoff 2005), and two recruited individuals over the age of 13 (Brodie 1995 A; Brodie 1995 B). One trial recruited individuals over the age of two (Nieto-Barrera 2001), and one recruited individuals over the age of four (SANAD A 2007). The remaining four trials recruited the elderly; two trials recruited individuals over the age of 60 (Rowan 2005; Werhahn 2015), and two recruited individuals over the age of 65 (Brodie 1999; Saetre 2007).

Five trials were designed to recruit individuals with partial seizures only (Eun 2012; Lee 2011; Nieto-Barrera 2001; SANAD A 2007; Werhahn 2015); however three of these trials did recruit some individuals with generalised onset seizures (Lee 2011; Nieto-Barrera 2001; SANAD A 2007). We examine this seizure classification in sensitivity analysis. The remaining eight trials recruited individuals with partial or generalised tonic-clonic seizures with or without other generalised seizure types.

Seven trials recruited individuals with new onset seizures (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Saetre 2007; Steinhoff 2005; Werhahn 2015). Three trials recruited individuals with new onset or untreated seizures (Lee 2011; Nieto-Barrera 2001; Reunanen 1996), one trial recruited individuals with new onset, untreated or seizures treated to a "sub-therapeutic" level (Rowan 2005), one trial recruited individuals with new onset, relapsed or recurrent seizures (failure of an AED not randomised in the trial) (SANAD A 2007) and one trial recruited individuals with new onset seizures following ischaemic stroke (Gilad 2007).

Four multicentre trials were conducted in the UK (Brodie 1995 A; Brodie 1995 B; Brodie 1999; SANAD A 2007). Two multicentre trials were conducted across Europe (Saetre 2007; Werhahn 2015), one multicentre trial across Europe and Mexico (Nieto-Barrera 2001), and one multicentre trial across Europe and Australia (Reunanen 1996). One multicentre trial was conducted in Germany (Steinhoff 2005), one multicentre trial in the USA (Rowan 2005), two multicentre trials in the Republic of Korea (Eun 2012; Lee 2011), and one single-centre trial was conducted in Israel (Gilad 2007).

We did not obtain individual participant data (IPD) for four trials including a total of 822 participants. According to trial sponsor, GlaxoSmithKline, data could not be located for one trial (Saetre 2007), and data could not be provided due to restrictions over the anonymisation of datasets of trials conducted in Germany (Steinhoff 2005). For the other two trials, we made contact with the authors/sponsors who expressed interest in collaborating in this IPD meta-analysis but at the time of writing, no data had been received (Gilad 2007; Rowan 2005). If IPD are received from these trials, we will include the data in future updates.

Individual participant data were available for the remaining nine trials, which recruited a total of 2572 participants, representing 76% of 3394 individuals from all 13 identified eligible trials. Data were available for the following participant characteristics (percentage of 2572 participants with data available): drug randomised (100%), sex (99%, data missing for 18 participants in SANAD A 2007), seizure type (97%, data missing for 85 participants in SANAD A 2007), age at randomisation (99%, data missing for 18 participants in SANAD A 2007, one participant in Nieto-Barrera 2001 and two participants in Reunanen 1996), and number of seizures in the six months prior to randomisation (99%, missing for 18 participants in SANAD A 2007, one participant in Reunanen 1996 and six participants in Werhahn 2015). Time since first seizure to randomisation was provided for 691 participants out of 695 participants from four trials (Brodie 1995 A; Brodie 1995 B; Eun 2012 (data missing for one participant); Reunanen 1996 (data missing for three participants)).

Seven trials provided the results of neurological examinations for 1693 out of 1711 participants (99%) (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Reunanen 1996; SANAD A 2007 (data for 18 participants missing)).

Six trials provided electroencephalographic (EEG) results for 710 out of 1044 participants (64%) (134 from Brodie 1995 A, 118 from Brodie 1995 B, 84 from Eun 2012, 110 from Lee 2011, 26 from Reunanen 1996 and 238 from Werhahn 2015).

Seven trials provided computerised tomography/magnetic resonance imaging (CT/MRI) results for 788 out of 1194 participants (66%) (94 from Brodie 1995 A, 92 from Brodie 1995 B, 149 from Brodie 1999, 84 from Eun 2012, 110 from Lee 2011, 21 from Reunanen 1996, and 238 from Werhahn 2015).

See the Characteristics of included studies table, Table 1 and Table 2 for further details.

Excluded studies

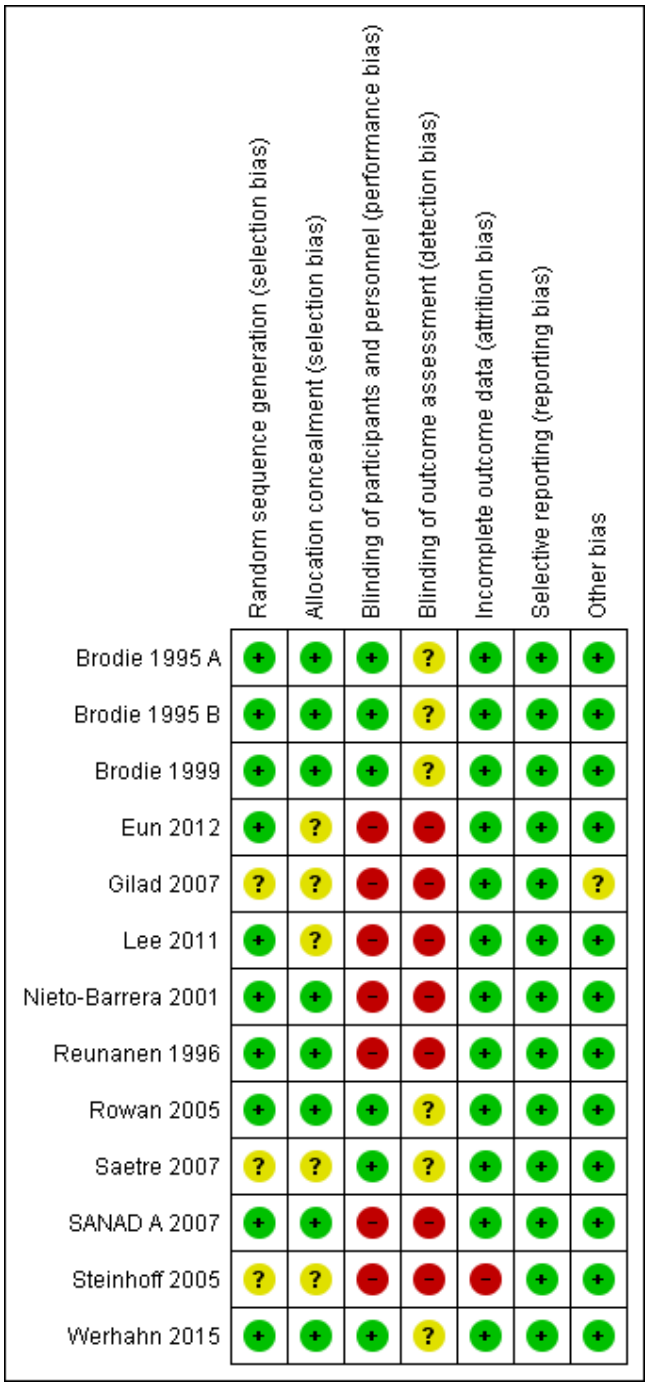
We excluded seven duplicate references (Eun 2008; Lee 2010; Ramsay 2003; Saetre 2006; Saetre 2009; Saetre 2010; Steinhoff

2004), and retained the most relevant primary reference for the trial in the review (Eun 2012; Lee 2011; Rowan 2005; Saetre 2007; Steinhoff 2005, respectively). We excluded five trials that did not compare lamotrigine and carbamazepine (Czapinski 1997; Gilliam 1998; Motte 1997; Steiner 1999; Stolarek 1994). We excluded three trials that were not of a monotherapy design (Carmant 2001; Fakhoury 2000; Jawad 1989). We excluded two trials that were not randomised (Martinez 2000; Zeng 2010). We excluded one trial that did not make a fully randomised comparison of lamotrigine and carbamazepine (Baxter 1998); lamotrigine was compared to the treating physician's choice of carbamazepine or sodium valproate.

Risk of bias in included studies

For further details, see the Characteristics of included studies table and Figure 2.

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



Allocation

(1) Trials for which we received individual participant data (information reported in published papers or provided with IPD)

All nine trials used adequate methods of randomisation via computer-generated random list and we judged them to be at low risk of bias (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015); two trials reported that block randomisation was used (Lee 2011; Werhahn 2015), and one trial reported that minimisation was used (SANAD A 2007).

Seven trials reported adequate methods of allocation concealment and we judged them to be at low risk of bias; five concealed treatment allocation with sealed, opaque envelopes (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996); one trial used telephone randomisation to a central allocation service (SANAD A 2007), and one trial used pharmacy allocation (Werhahn 2015). The remaining two trials did not report how allocation was concealed and we judged them to be at unclear risk of bias (Eun 2012; Lee 2011).

(2) Trials for which no individual participant data were available (information reported in published papers only)

One of the trials reported that blocked randomisation via a computer-generated list and telephone randomisation to a central allocation service were used (Rowan 2005). We judged this trial to be at low risk of selection bias for random sequence generation and allocation concealment. The remaining three trials were described as "randomised" but did not provide information about the method of generation of the random list or allocation concealment so we judged them to be at unclear risk of bias (Gilad 2007; Saetre 2007; Steinhoff 2005).

Blinding

(1) Trials for which we received individual participant data (information reported in published papers or provided with IPD)

Four trials were double-blind (participants and personnel) with the blinding achieved by using tablets of identical appearance; we judged these trials to be at low risk of performance bias (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Werhahn 2015). In all four of these trials, the trial investigator was blinded but no information was provided as to whether other outcome assessors were blinded, therefore we judged all four trials to be at unclear risk of detection bias.

The remaining five trials were open-label and we judged them to be at high risk of performance and detection bias (Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007).

(2) Trials for which no individual participant data were available (information reported in published papers only)

Two trials were double-blind (participants and personnel) with the blinding achieved by using double dummy tablets; we judged these trials to be at low risk of performance bias (Rowan 2005; Saetre 2007). However, for these two trials no information was provided regarding blinding of outcome assessors therefore we judged the two trials to be at unclear risk of detection bias.

The remaining two trials were open-label and we judged them to be at high risk of performance and detection bias (Gilad 2007; Steinhoff 2005).

Incomplete outcome data

(1) Trials for which we received individual participant data (information reported in published papers or provided with IPD)

In theory, a review using individual participant data should overcome issues of attrition bias as unpublished data can be provided, unpublished outcomes calculated and all randomised participants can be analysed by an intention-to-treat approach. All nine trials provided individual participant data for all randomised individuals and reported the extent of follow-up for each individual (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015). We queried any missing data with the original trial authors. From the information provided by the authors, we deemed the small amount of missing data present (see Included studies) to be missing at random and not effecting our analysis.

(2) Trials for which no individual participant data were available (information reported in published papers only)

Three trials reported attrition rates and analysed all randomised participants using an intention-to-treat approach and we judged them to be at low risk of attrition bias (Gilad 2007; Rowan 2005; Saetre 2007). The remaining trial did not analyse data for all randomised participants and did not state to which drug those excluded from analysis were randomised (Steinhoff 2005). This is not an intention-to-treat analysis therefore we judged this trial to be at high risk of attrition bias.

Selective reporting

(1) Trials for which we received individual participant data (information reported in published papers or provided with IPD)

In theory, a review using individual participant data should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated. We sought trial protocols in all individual participant data requests and seven protocols were provided (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015). We received sufficient individual participant data to calculate all outcomes for all nine trials (depending on trial duration; e.g. time to 12-month remission could not be calculated for a trial of 24 weeks etc.)

(2) Trials for which no individual participant data were available (information reported in published papers only)

Protocols were not available for any of the four trials, however a clinical summary report was provided for two trials from the sponsor (Saetre 2007; Steinhoff 2005), and case report forms of data collected were provided for one trial by the sponsor (Rowan 2005). All trials reported seizure and adverse event outcomes well, therefore we judged all four trials to be at low risk of selective reporting bias (Gilad 2007; Rowan 2005; Saetre 2007; Steinhoff 2005).

Other potential sources of bias

No other sources of bias were identified for 12 of the 13 included trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; Rowan 2005; Saetre 2007; SANAD A 2007; Steinhoff 2005; Werhahn 2015). In one trial, it was unclear if all participants were receiving AED monotherapy treatment ('total number of AEDs' described in Table 1 of the publication), so we judged this trial to be at unclear risk of bias (Gilad 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - Lamotrigine compared with carbamazepine for epilepsy (primary outcomes); **Summary of findings 2** Summary of findings - Lamotrigine compared with carbamazepine for epilepsy (secondary outcomes)

Table 3 gives details regarding the number of individuals (with individual participant data (IPD)) contributing to each analysis, Summary of findings for the main comparison summarises the results for the primary outcome 'time to treatment withdrawal' (stratified by epilepsy type) and Summary of findings 2 for the secondary outcomes 'time to first seizure' and 'time to 12-month remission'.

Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9 and Figure 10 show survival curve plots (cumulative incidence). We produced all cumulative incidence plots in Stata software version 11.2 (Stata 2009), using data from all trials providing IPD combined. We would have liked to stratify by trial in survival curve plots, but we do not know of any software that allows for this. We hope that such software may have been developed for future updates of this review. We note that participants with event times of zero (i.e. those who withdrew from treatment or experienced seizure recurrence on the day of randomisation) are not included in the 'Numbers at risk' on the graphs. All figures are intended to provide a visual representation of outcomes, extent of follow-up and visual differences between seizure types. These graphs are not intended to show statistical significance and numerical values may vary compared to the text due to differences in methodology.

Figure 3. Time to withdrawal of allocated treatment

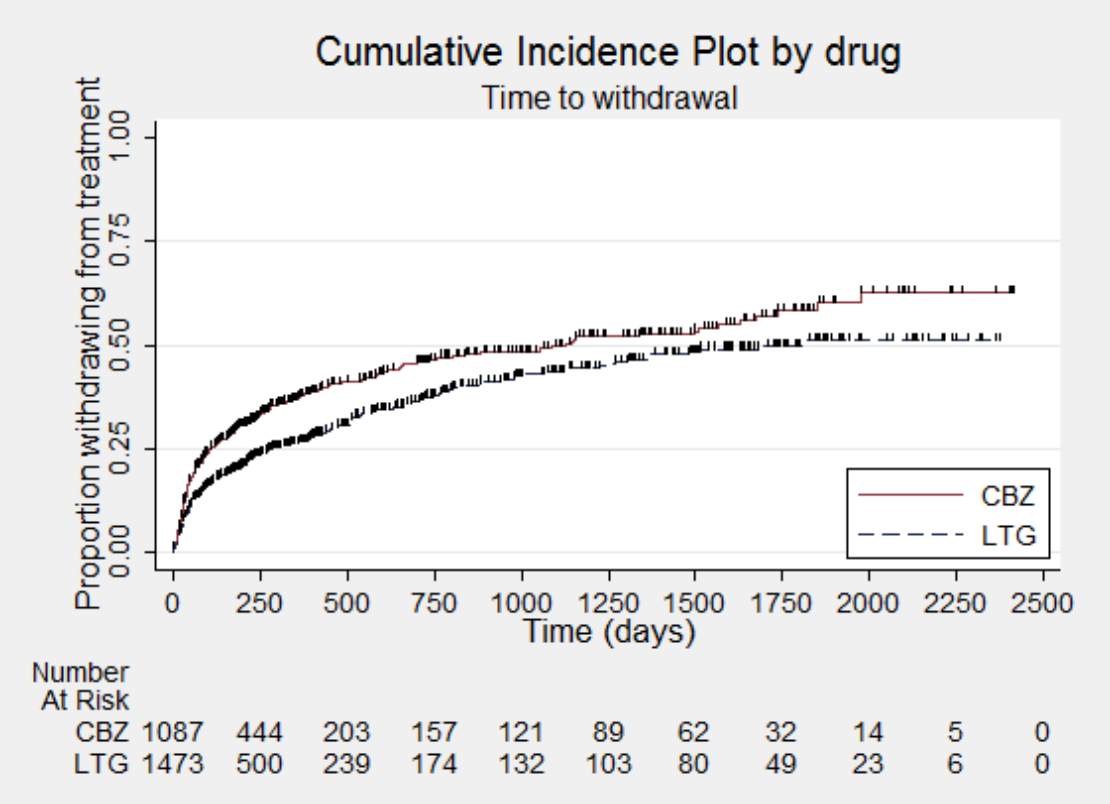


Figure 4. Time to withdrawal of allocated treatment (by epilepsy type)

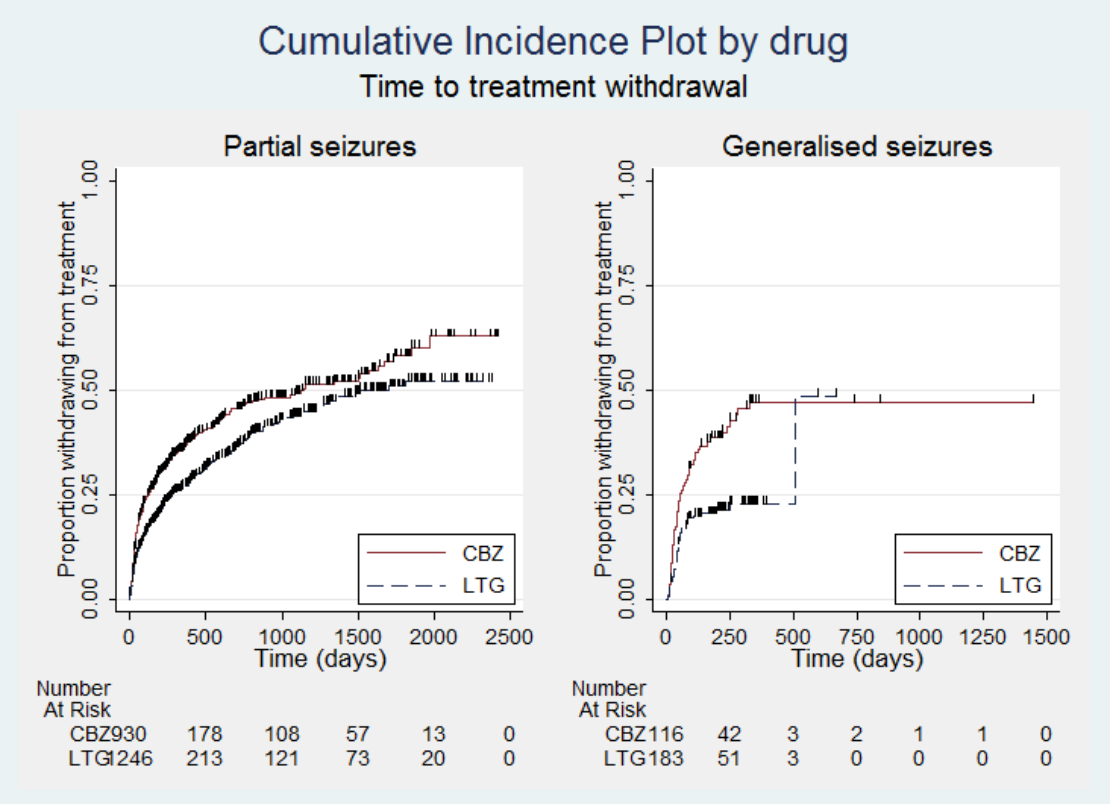


Figure 5. Time to first seizure

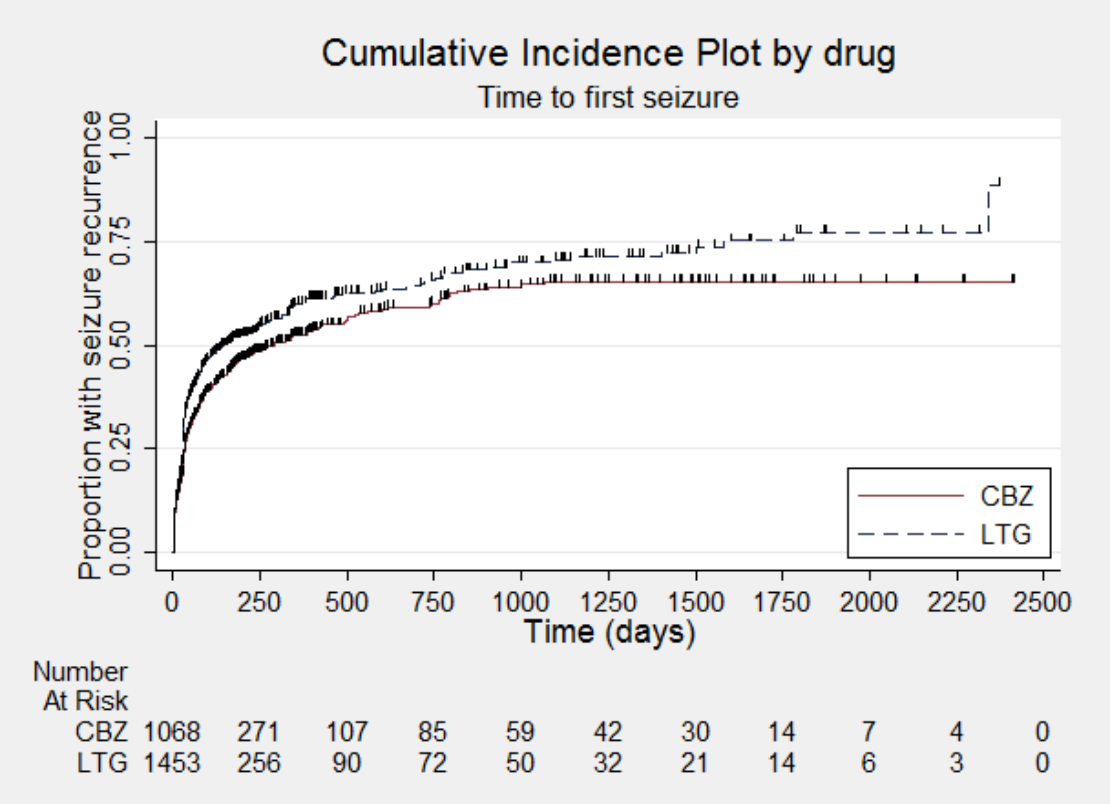


Figure 6. Time to first seizure (by epilepsy type)

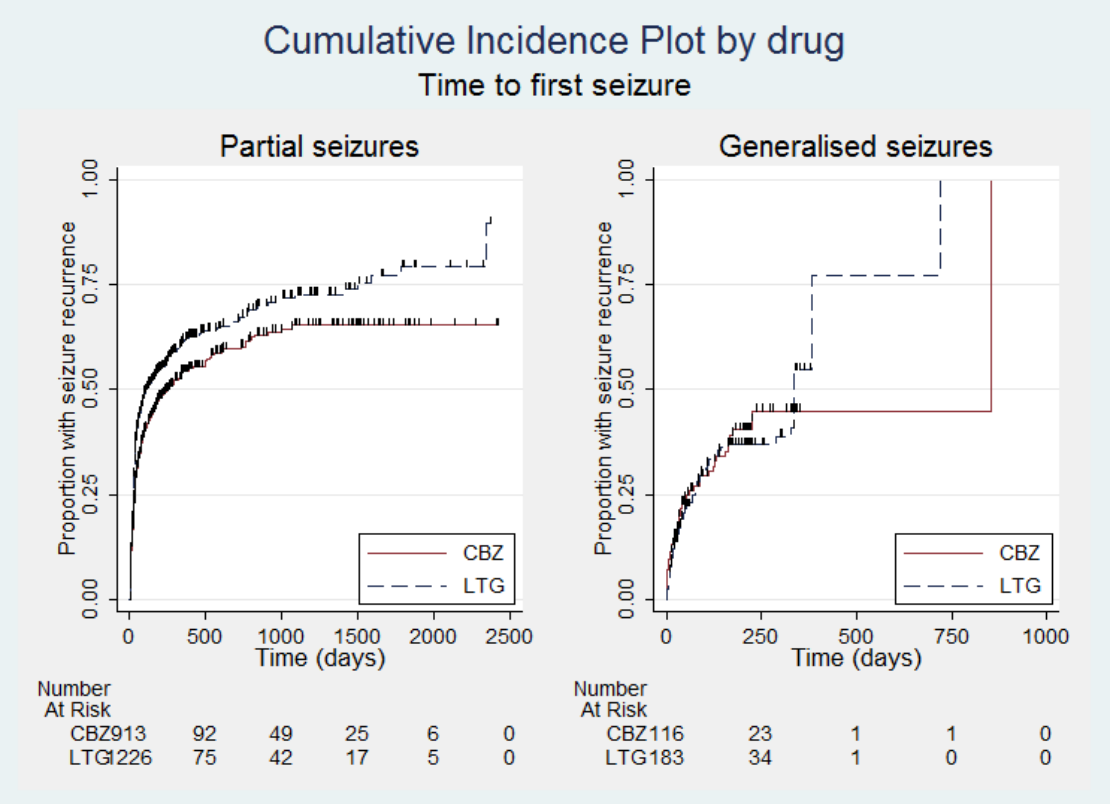


Figure 7. Time to six-month remission

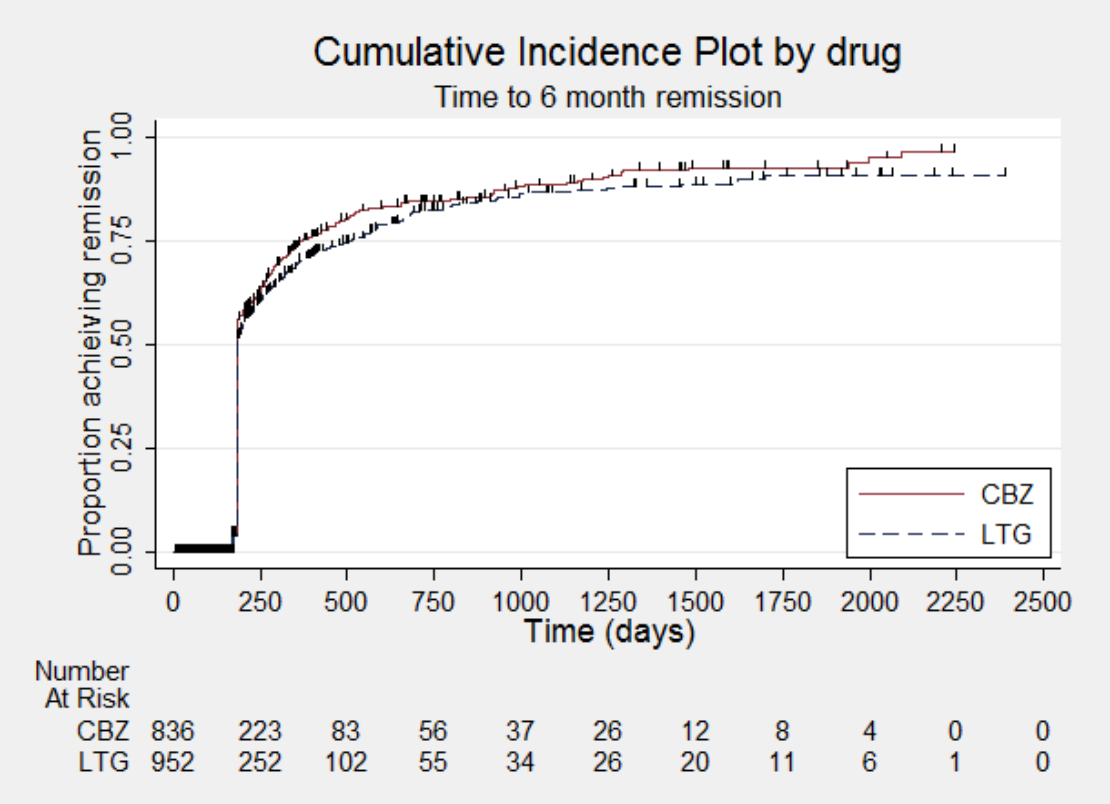


Figure 8. Time to six-month remission (by epilepsy type)

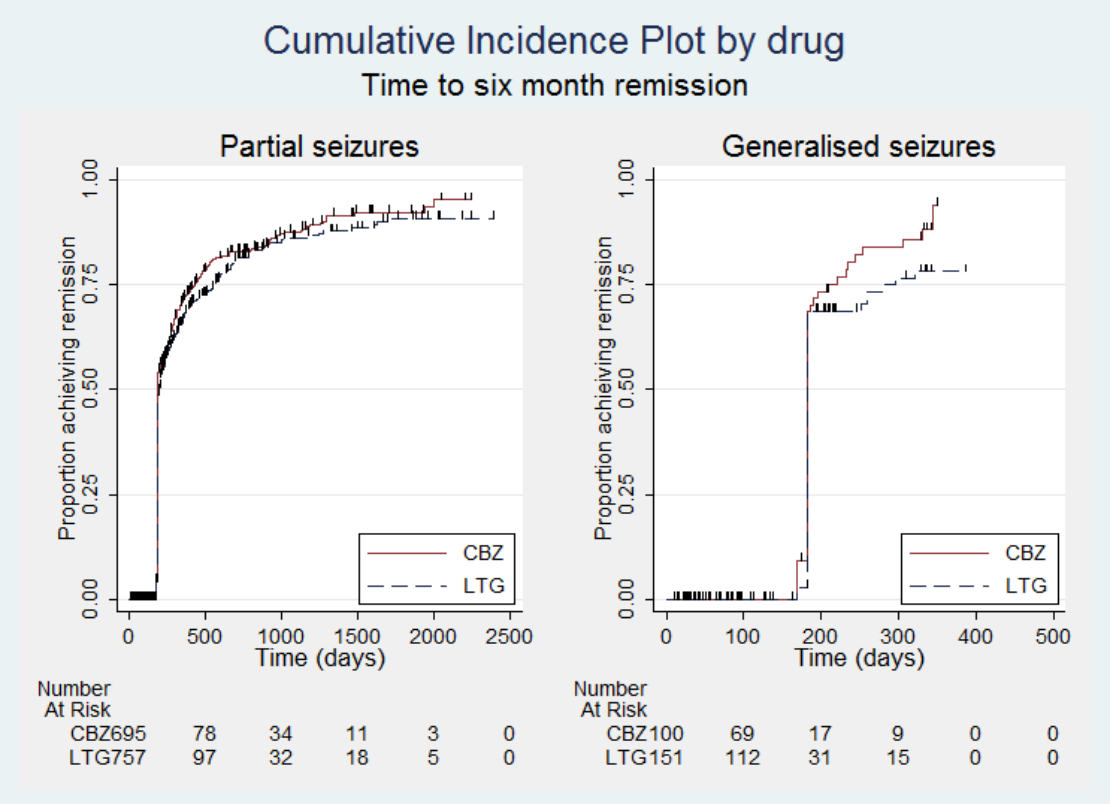


Figure 9. Time to 12-month remission

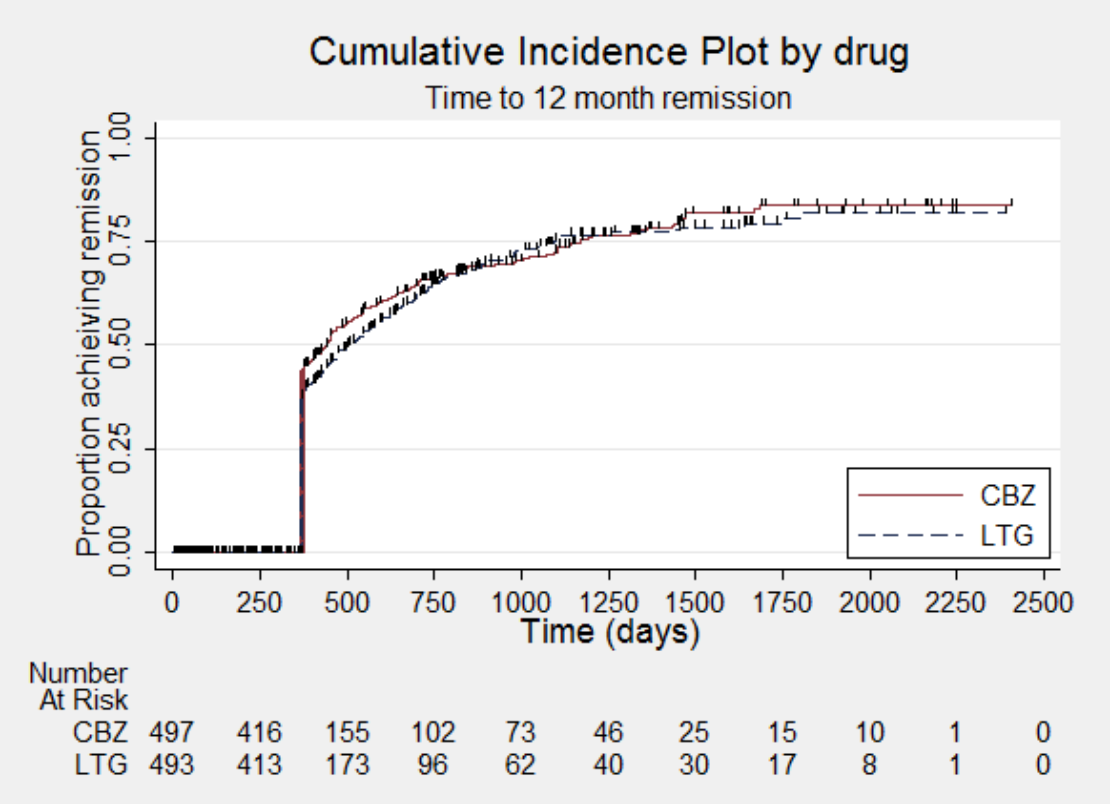
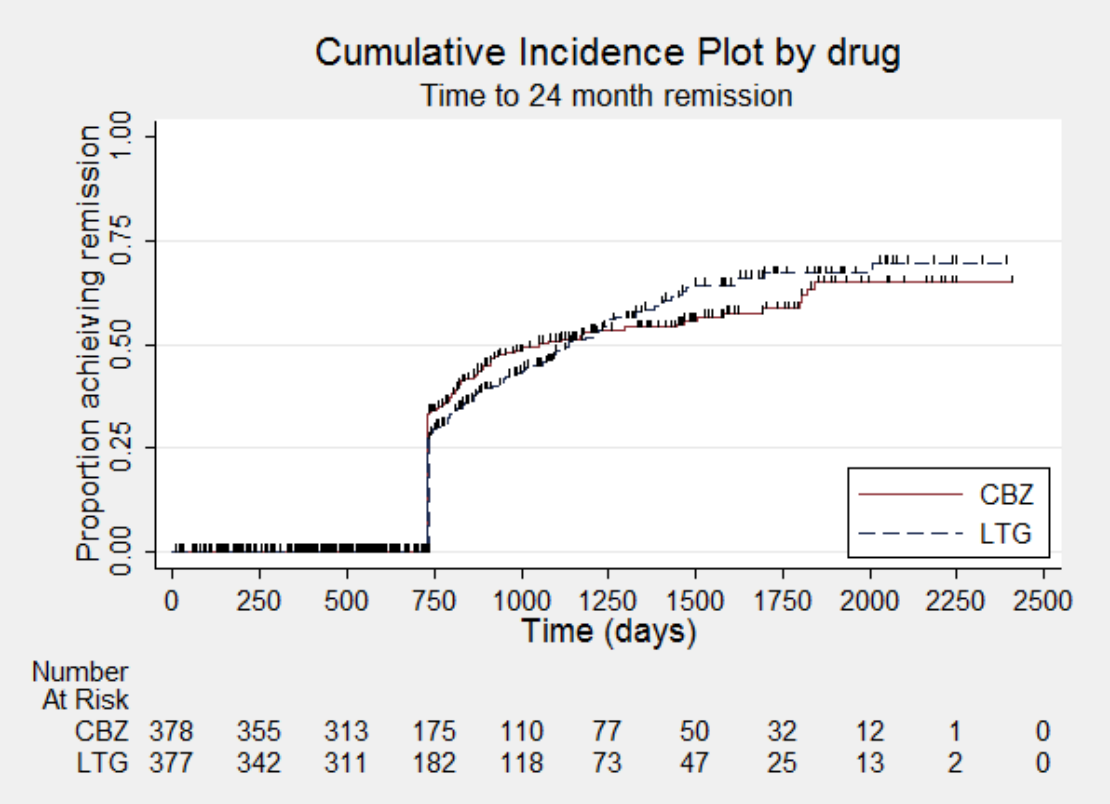


Figure 10. Time to 24-month remission



We calculated all hazard ratios (HRs) presented below by generic inverse variance fixed-effect meta-analysis unless otherwise stated. All analyses met the assumption of proportional hazards (addition of time varying covariate into the model non-significant) unless stated below.

Primary outcome

Time to withdrawal of allocated treatment

For this outcome, a HR less than 1 indicates a clinical advantage for lamotrigine.

Table 4 shows the reasons for premature termination for 3393 participants in all 13 included trials and how we classified these withdrawals in analysis of IPD. One participant randomised to lamotrigine in Nieto-Barrera 2001 had missing date and reason for withdrawal and two participants in SANAD A 2007 has missing dates of withdrawal (one withdrew from lamotrigine due to remission of seizures and one withdrew from carbamazepine due to 'other' reasons not related to the allocated drug).

Times to withdrawal of allocated treatment and reasons for withdrawal were available for 2569 participants from the nine trials providing IPD (99.9% of 2572 participants with IPD available included in this analysis, see Table 3) (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015).

Out of 3393 participants for whom we had reasons for treatment withdrawal, 1293 participants prematurely withdrew from treatment (38%): 610 out of 1891 (32%) participants randomised to lamotrigine and 683 out of 1502 (45%) participants randomised to carbamazepine. We deemed 1106 participants (86% of total withdrawals) to have withdrawn for reasons related to the allocated drug: 516 (85% of withdrawals) on lamotrigine and 590 (86% of withdrawals) on carbamazepine and we classified these withdrawals as 'events' in the analysis. The most common treatment-related reason for withdrawal was adverse events: 569 withdrawals (44% of total withdrawals), 219 (36% of total withdrawals) on lamotrigine and 350 (51% of total withdrawals) on carbamazepine.

We classed the other 187 withdrawals (94 on lamotrigine and 93

on carbamazepine) to be not related to the allocated drug and censored these participants in the analysis, in addition to the 2100 participants (1281 on lamotrigine and 819 on carbamazepine) who completed the trial without withdrawing.

The overall pooled HR (for 2569 participants providing IPD from nine trials) was 0.72 (95% confidence interval (CI) 0.63 to 0.82, P value < 0.00001) indicating a statistically significant advantage to lamotrigine; in other words, participants withdrew significantly earlier from carbamazepine than lamotrigine in the nine included trials (Analysis 1.1). No important heterogeneity was present between trials (I^2= 19%).

Subgroup analyses: seizure type (partial versus generalised onset)

Seizure type was missing for 85 participants from SANAD A 2007 and nine participants were classified as having generalised onset seizures, even though the trial was designed to include only participants with partial onset seizures. Similarly, in Nieto-Barrera 2001, including participants with partial onset seizures, three participants were classified as having generalised onset seizures. The latter three participants were excluded from the subgroup analyses (all completed the trial).

For participants with generalised onset seizures (299 participants providing IPD from six trials), the pooled HR was 0.46(95% CI 0.30 to 0.71, P value = 0.0003) and for participants with partial onset seizures (2182 participants providing IPD from nine trials) the pooled HR was 0.75(95% CI 0.64 to 0.86, P value = 0.0001) (Analysis 1.2), indicating a statistically significant advantage for lamotrigine over carbamazepine for both participants with partial onset and generalised onset seizures. Excluding the nine participants from SANAD A 2007 with generalised onset seizures produced similar results and did not change the conclusions.

The test for subgroup differences between partial and generalised onset seizures was statistically significant (P value = 0.04, I^2 = 77.1% for variability due to subgroup differences). This indicates that the advantage for lamotrigine over carbamazepine may be larger in those with generalised onset seizures than in those with partial onset seizures. However, we recommend caution when interpreting this result due to the imbalance of subgroup sizes (only 13% of individuals had generalised onset seizures) and the potential misclassification of seizure type (see below).

The overall pooled HR (adjusted for epilepsy type for 2481 participants from nine trials) was HR 0.71(95% CI 0.62 to 0.81, P value < 0.00001). No important heterogeneity was present between trials overall or by subgroups (I^2 < 10%).

Sensitivity analyses

Reunanen 1996 considered participants to have completed the trial and hence withdrew treatment if they experienced a seizure after week six. This does not correspond with the treatment withdrawal definition recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy therefore we performed sensitivity analysis excluding this trial from Analysis 1.1 and Analysis 1.2. This sensitivity analysis produced similar results and did not change the conclusions.

One included trial allocated participants to three treatment arms: 100 mg/day lamotrigine (LTG100), 200 mg/day lamotrigine (LTG 200) or 600 mg/day carbamazepine (CBZ) (Reunanen 1996). Table 5 shows a sensitivity analysis comparing the primary analysis (LTG arms pooled versus CBZ), LTG 100 with the other arms in the trial, LTG 200 with the other arms in the trial, LTG 200 versus CBZ and LTG 100 versus CBZ. When including these alternative estimates in meta-analysis, the pooled result is numerically similar and the conclusions unchanged.

We indirectly estimated aggregate hazard ratios of time to withdrawal of allocated treatment due to adverse events (Gilad 2007), time to early termination (Rowan 2005), and retention time (Steinhoff 2005), and we extracted a published hazard ratio for time to all-cause withdrawal (Saetre 2007). We note that these definitions do not directly correspond to our definition of treatment withdrawal (i.e. all withdrawals are classed as events rather than only treatment-related withdrawals, see Table 4). Combining all IPD and aggregate data, the pooled HR for 3391 participants from the 13 included trials was 0.69(95% CI 0.61 to 0.77, P value < 0.00001) (Analysis 1.3). This indicates that the advantage to lamotrigine over carbamazepine remains and is robust to the inclusion of withdrawal data of variable definitions.

Given the subjective nature of the outcome of time to treatment withdrawal, an outcome which can be influenced by the participant and personnel, we conducted a further subgroup analysis separating the trials that were of a double-blind design (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Rowan 2005; Saetre 2007; Werhahn 2015, 1231 participants included in analyses) and those which were an open-label design (Eun 2012; Gilad 2007; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; Steinhoff 2005; SANAD A 2007, 2160 participants included in analyses). Including all withdrawal data from all 13 trials (aggregate data from four trials):

- In the double-blind trials 234 out of 644 (35%) randomised participants withdrew from lamotrigine and 311 out of 587 (53%) withdrew from carbamazepine (in total 45% of participants withdrew from the randomised drug).
- In the open-label trials 313 out of 1246 (25%) randomised participants withdrew from lamotrigine and 318 out of 914 (35%) withdrew from carbamazepine (in total 29% of participants withdrew from the randomised drug).
- The advantage for lamotrigine over carbamazepine was larger in the double-blind trials (HR 0.60, 95% CI 0.51 to 0.71) than in the open-label trials (HR 0.77, 95% CI 0.66 to 0.90) and there was a statistically significant difference between the subgroups (P value = 0.04) (Analysis 1.4).
- When including only the nine trials for which IPD were

provided (double-blind: Brodie 1995 A; Brodie 1995 B; Brodie 1999; Werhahn 2015; open-label: Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007), the advantage for lamotrigine over carbamazepine is still larger in the double-blind trials (HR 0.61, 95% CI 0.48 to 0.77) than the open-label trials (HR 0.78, 95% CI 0.66 to 0.92) but the difference between the subgroups is no longer statistically significant (P value = 0.10).

These results suggest that the design of a trial (i.e. whether or not a participant and their clinician is aware of the treatment a participant is taking) may influence the withdrawal rates of the trial, with participants significantly more likely to withdraw from a double-blind trial than an open-label trial (45% versus 29%: risk ratio (RR) 1.48 (95% CI 1.34 to 1.62, P value < 0.0001)), and in turn this may influence the perceived effectiveness of the two drugs under comparison.

Following reclassification of 152 individuals from seven trials with potentially misclassified generalised onset seizures (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007), and 85 individuals with missing seizure type from one trial (SANAD A 2007), the results of the two sensitivity analyses are shown in Table 6. In summary, the results overall by seizure type and for individuals with partial onset seizures are very similar. Also, following reclassification, the advantage for lamotrigine over carbamazepine in those with generalised onset seizures is reduced and the test of difference between subgroups is no longer significant. There is a statistically significant advantage for lamotrigine over carbamazepine in those with uncertain seizure type.

Secondary outcomes

Time to first seizure post-randomisation

For this outcome, a HR less than 1 indicates a clinical advantage for lamotrigine.

Times to first seizure were available for 2564 participants from the nine trials providing IPD (99% of 2572 participants with IPD available included in this analysis, see Table 3) (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015).

Seizure recurrence was experienced by 1330 out of 2564 participants (52%), 805 out of 1476 (55%) on lamotrigine and 525 out of 1088 (48%) on carbamazepine. The overall pooled HR (for 2564 participants) was 1.22 (95% CI 1.09 to 1.37, P value = 0.0004) indicating a statistically significant advantage to carbamazepine; in other words, participants experienced first seizure recurrence earlier on lamotrigine than carbamazepine in the nine included trials (Analysis 1.5). No important heterogeneity was present between trials (I^2 = 0%).

Subgroup analyses: seizure type (partial versus generalised onset)

Seizure type was missing for 85 participants from SANAD A 2007 and nine participants were classified as having generalised onset seizures, even though the trial was designed to include only participants with partial onset seizures. Similarly, in Nieto-Barrera 2001, including participants with partial onset seizures, three participants were classified as having generalised onset seizures. The latter three participants were excluded from the subgroup analyses (all completed the trial).

For participants with generalised onset seizures (299 participants providing IPD from six trials), the pooled HR was 0.98 (95% CI 0.65 to 1.48, P value = 0.94), indicating no difference between the two drugs and for participants with partial onset seizures (2177 participants providing IPD from nine trials) the pooled HR was 1.29 (95% CI 1.14 to 1.45, P value < 0.0001) (Analysis 1.6), indicating a statistically significant advantage for carbamazepine. There was no evidence of a difference between the subgroups (test for subgroup differences P value = 0.22). Excluding the nine participants from SANAD A 2007 with generalised onset seizures produced similar results and did not change the conclusions.

The overall pooled HR (adjusted for epilepsy type for 2476 participants from nine trials) was HR 1.26 (95% CI 1.12 to 1.41, P value < 0.0001). No important heterogeneity was present between trials overall or by subgroups (I^2 =0%).

Sensitivity analyses

Data from Nieto-Barrera 2001 could not be included for this outcome as the dates of seizures that occurred during the first four weeks of the trial were not supplied. A total of 216 participants (lamotrigine 160, carbamazepine 56) (35% of the number in the trial) experienced at least one seizure during the first four weeks, however dates of these seizures were not supplied. Therefore, for Nieto-Barrera 2001, this outcome is calculated as 'time to first seizure after four weeks of treatment' rather than 'time to first seizure after randomisation'. Excluding this trial in sensitivity analysis produces very similar numerical results and the conclusions are unchanged

One included trial allocated participants to three treatment arms: 100 mg/day lamotrigine (LTG100), 200 mg/day lamotrigine (LTG 200) or 600 mg/day carbamazepine (CBZ) (Reunanen 1996). Table 5 shows sensitivity analysis comparing the primary analysis (LTG arms pooled versus CBZ), LTG 100 with the other arms in the trial, LTG 200 with the other arms in the trial, LTG 200 versus CBZ and LTG 100 versus CBZ. When including these alternative estimates in meta-analysis, the pooled result is numerically similar and the conclusions unchanged.

We indirectly estimated aggregate hazard ratios of time to first seizure from published graphs in two trials (Gilad 2007; Rowan 2005), and extracted a published hazard ratio of time to first seizure (Saetre 2007). We were unable to estimate or extract an estimate

from Steinhoff 2005. Combining all IPD and aggregate data, the pooled HR for 3216 participants from the 12 included trials was HR 1.24 (95% CI 1.12 to 1.37, P value < 0.00001) (Analysis 1.7). This again shows an advantage to carbamazepine over lamotrigine. We were able to calculate or extract seizure freedom throughout the whole trial for all trials included in this review (Rowan 2005 did not state whether any participants who withdrew experienced seizure recurrence, therefore we have conducted an intention-to-treat analysis of seizure freedom rather than seizure recurrence). For consistency with the primary analysis of the outcome, in Analysis 1.8 we have swapped event and non-event so that a RR less than 1 indicates a clinical advantage for lamotrigine.

The pooled RR of seizure freedom (for 3358 participants from 13 trials) is RR 1.13 (95% CI 1.06 to 1.20, P value = 0.0003), indicating a statistically significant advantage to carbamazepine. Therefore, following the inclusion of seizure freedom/recurrence data from all included trials, the advantage to carbamazepine remains. There is now a large amount of heterogeneity present between the trials, which was not present in the IPD meta-analysis (I^2 =55%, Analysis 1.8). This may reflect the variable follow-up lengths of the trials (from 24 weeks to over six years), or may reflect the way the aggregate data are presented in some of the trials; for example Rowan 2005 presents seizure freedom rates for those who have completed the trial.

Following reclassification of 152 individuals from seven trials with potentially misclassified generalised onset seizures (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007), and 85 individuals with missing seizure type from one trial (SANAD A 2007), the results of the two sensitivity analyses are shown in Table 6. In summary, the results overall by seizure type and for individuals with partial onset seizures are very similar. Following reclassification, there is a slight advantage to carbamazepine, which is not statistically significant, for those with generalised onset seizures. For those with uncertain seizure type, there is a slight advantage to lamotrigine that is not statistically significant.

Time to achieve six-month remission

For this outcome, a HR less than 1 indicates a clinical advantage for carbamazepine.

Times to six-month remission were available for 1793 participants from the seven trials providing IPD (70% of 2572 participants with IPD available included in this analysis, see Table 3) (Brodie 1995 A; Brodie 1995 B; Eun 2012; Lee 2011; Reunanen 1996; SANAD A 2007; Werhahn 2015). The remaining two trials were of 24 weeks duration so were not included in the analysis of time to six-month remission but are included in the sensitivity analysis of seizure freedom (Brodie 1999; Nieto-Barrera 2001).

Six-month remission was achieved by 1113 out of 1793 participants (62%), 572 out of 955 (60%) on lamotrigine and 541 out of 838 (65%) on carbamazepine. The overall pooled HR (for 1793 participants) was 0.84 (95% CI 0.74 to 0.94, P value = 0.003) indicating a statistically significant advantage to carbamazepine; in other words, participants experienced six-month remission earlier on lamotrigine than carbamazepine in the seven included trials (Analysis 1.9). No important heterogeneity was present between trials (I^2 = 0%).

Subgroup analyses: seizure type (partial versus generalised onset)

Seizure type was missing for 85 participants from SANAD A 2007 and nine participants were classified as having generalised onset seizures, even though the trial was designed to include only participants with partial onset seizures.

For participants with generalised onset seizures (254 participants providing IPD from five trials), the pooled HR was 0.78 (95% CI 0.55 to 1.11, P value = 0.16), indicating an advantage to carbamazepine that is not statistically significant, and for participants with partial onset seizures (1454 participants providing IPD from seven trials) the pooled HR was 0.87 (95% CI 0.77 to 1.00, P value = 0.04) (Analysis 1.10), indicating a statistically significant advantage for carbamazepine. There was no evidence of a difference between the subgroups (test for subgroup differences P value = 0.54). Excluding the nine participants from SANAD A 2007 with generalised onset seizures produced similar results and did not change the conclusions.

The overall pooled HR (adjusted for epilepsy type for 1708 participants from seven trials) was HR 0.86(95% CI 0.76 to 0.97, P value = 0.02). No important heterogeneity was present between trials overall or by subgroups (I^2 <= 25%).

Sensitivity analyses

One included trial allocated participants to three treatment arms, 100 mg/day lamotrigine (LTG100), 200 mg/day lamotrigine (LTG 200) or 600 mg/day carbamazepine (CBZ) (Reunanen 1996). Table 5 shows a sensitivity analysis comparing the primary analysis (LTG arms pooled versus CBZ), LTG 100 with the other arms in the trial, LTG 200 with the other arms in the trial, LTG 200 versus CBZ and LTG 100 versus CBZ. When including these alternative estimates in meta-analysis, the pooled result is numerically similar and the conclusions unchanged.

We were able to calculate or extract seizure freedom at six months for all trials included in this review (estimated from the graph published in Saetre 2007). A RR less than 1 indicates a clinical advantage for carbamazepine.

The pooled RR of seizure freedom at six months (for 3356 participants from 13 trials) is RR 0.96 (95% CI 0.88 to 1.03, P value = 0.26) (Analysis 1.11), indicating no statistically significant advantage to either drug. As above, we note that the way the aggregate data are presented in some trials may influence the results; for example Rowan 2005 presents seizure freedom rates for those who have completed the trial.

Following reclassification of 152 individuals from seven trials with potentially misclassified generalised onset seizures (Brodie 1995 A; Brodie 1995 B; Lee 2011; Reunanen 1996; SANAD A 2007), and 85 individuals with missing seizure type from one trial (SANAD A 2007), the results of the two sensitivity analyses are shown in Table 6. In summary, the results overall by seizure type are very similar to the subgroup analysis described above and the conclusions are unchanged. For those with uncertain seizure type, there is a slight advantage to carbamazepine that is not statistically significant.

In Lee 2011 (analysis adjusted for epilepsy type), there was some evidence that the proportional hazards assumption of the Cox model may have been violated; the P value of the time-varying covariate was 0.051. However, the time varying covariate is not significant in the analysis without adjustment for seizure type (P value = 0.146).

Following visual inspection of a cumulative incidence plot (not shown but available from the authors), the curves appear to cross around 200 days, when less than 20% of randomised participants remain at risk in the trial. Therefore, we conclude that the crossing of the curves is likely to be due to small numbers of participants with generalised seizure types and small numbers remaining in the trial leading to changes and events being magnified at this time. The proportional hazards assumption of the Cox model was satisfied for all other trials included in analysis.

Time to achieve 12-month (one-year) remission

For this outcome, a HR less than 1 indicates a clinical advantage for carbamazepine.

Times to 12-month remission were available for 988 participants from the two trials providing IPD of sufficient duration (70% of 2572 participants with IPD available included in this analysis, see Table 3) (SANAD A 2007; Werhahn 2015).

Twelve-month remission was achieved by 564 out of 998 participants (57%), 276 out of 474 (58%) on lamotrigine and 288 out of 474 (61%) on carbamazepine. The overall pooled HR (for 998 participants) was HR 0.91 (95% CI 0.77 to 1.07, P value = 0.26), indicating an advantage to carbamazepine that was not statistically significant (Analysis 1.12). No important heterogeneity was present between trials (I^2 = 0%).

Subgroup analysis and sensitivity analysis

All participants included in Werhahn 2015 had partial onset seizures and SANAD A 2007 was designed to include only those with partial onset seizures. However, seizure type was missing for 85 participants and nine participants were classified as having generalised onset seizures. Given the small numbers in the generalised onset group (which are likely to have been misclassified), we did not perform a sensitivity analysis by seizure type.

Instead we performed a subgroup analysis of those with partial seizures specified at baseline (all participants in Werhahn 2015 and 661 participants in SANAD A 2007) and those with uncertain seizure type (85 with missing seizure type and nine with generalised onset seizures in SANAD A 2007).

For those with uncertain seizure type (94 participants providing IPD from one trial), the pooled HR was 0.81 (95% CI 0.47 to 1.37, P value = 0.43), indicating an advantage to carbamazepine that is not statistically significant, and for those with partial onset seizures (894 participants providing IPD from two trials), the pooled HR was 0.91 (95% CI 0.77 to 1.09, P value = 0.31), also indicating an advantage to carbamazepine that is not statistically significant (Analysis 1.13). There was no evidence of a difference between the subgroups (test for subgroup differences P value = 0.66).

Time to achieve 24 month (two-year) remission

For this outcome, a HR less than 1 indicates a clinical advantage for carbamazepine.

Times to 24-month remission were available for 755 participants from one trial providing IPD of sufficient duration (29% of 2572 participants with IPD available included in this analysis, see Table 3) (SANAD A 2007).

Twenty-four month remission was achieved by 296 out of 755 participants (39%), 149 out of 377 (40%) on lamotrigine and 147 out of 378 (39%) on carbamazepine. The overall HR (for 755 participants from one trial) was HR 1.00 (95% CI 0.80 to 1.25, P value = 0.99), indicating no statistically significant difference between the drugs (Analysis 1.14).

Subgroup analysis and sensitivity analysis

Seizure type was missing for 85 participants from SANAD A 2007 and nine participants were classified as having generalised onset seizures, even though the trial was designed to include only participants with partial onset seizures.

Given the small numbers in the generalised onset group (which are likely to have been misclassified), we did not perform a sensitivity analysis by seizure type.

Instead we performed a subgroup analysis of those with partial seizures specified at baseline (661 participants) and those with uncertain seizure type (85 with missing seizure type and nine with generalised onset seizures). For those with uncertain seizure type (94 participants providing IPD from one trial), the HR was 0.86(95% CI 0.44 to 1.67, P value = 0.65), indicating an advantage to carbamazepine that is not statistically significant, and for those with partial onset seizures (661 participants providing IPD from two trials), the pooled HR was 1.06 (95% CI 0.83 to 1.35, P value = 0.66), indicating an slight advantage to lamotrigine that is not statistically significant (Analysis 1.15). There was no evidence of a difference between the subgroups (test for subgroup differences P value = 0.57).

In SANAD A 2007 (analyses with and without adjustment for epilepsy type), there was evidence that the proportional hazards

assumption of the Cox model may have been violated; the P value of the time-varying covariate was 0.025.

Following visual inspection of a cumulative incidence plot (Figure 10), the curves appear to cross around 1200 days. Considering the distribution of events, all 24-month remission events occurred before 1200 days; none of the 164 participants (82 in each treatment group) experienced remission after 1200 days. This observation would explain the apparent change in treatment effect over time (i.e. a difference in censoring times). The proportional hazards assumption of the Cox model was satisfied for all other trials included in analysis.

Incidence of adverse events

We were provided with individual participant data for adverse events experienced during the trial for nine trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015), and we extracted information relating to adverse events from the remaining four publications (Gilad 2007; Rowan 2005; Saetre 2007; Steinhoff 2005). Due to the wide range of events reported in the trials and the different methods of recording adverse events, we have not analysed adverse event data in meta-analysis and provide a narrative report.

Seven trials provided very detailed information regarding all adverse events experienced by all participants during the trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015). This information is summarised in Table 7, Table 8 and Table 9.

The most common adverse events, reported 10 or more times in at least one of the seven trials are: accidental injury/fracture, aggression, anorexia/weight loss, anxiety/depression, aphasia, ataxia, chest infection/bronchitis, cold/influenza, concentration, confusion, cough/wheeze, dental, dizzy/faint, drowsy/fatigued, gastrointestinal disturbances, hair loss, headache/migraine, impotence, increased/worsened seizures, kidney/urinary problems, memory problems, menstrual problems, mood/behavioural change, nausea/vomiting, pain, pins and needles/tingling, rash/skin problems, sleep problems/dreams, throat/tonsil infection, tremor/twitch, visual disturbance/nystagmus, weight gain.

The five most commonly reported adverse events on both drugs were: dizzy/faint, drowsy/fatigued, gastrointestinal disturbances, headache/migraine and rash/skin problems. Across all the trials, the rates of these common adverse events were similar for the two drugs. We did not statistically analyse adverse event data.

In summary for the other six trials:

In Eun 2012, five events related to treatment were reported in three participants taking lamotrigine (all skin rashes). Eight events related to treatment were reported in six participants taking carbamazepine (six with tiredness/lethargy, two with skin rashes). All adverse events were described as non-serious.

In Gilad 2007, two participants taking lamotrigine had adverse events: somnolence and dizziness, respectively. Twelve participants in the carbamazepine group had adverse events: three with nausea and vomiting, three with skin eruptions, two with confusion and one with overdose symptoms who was hospitalised

In Lee 2011, four participants taking lamotrigine reported skin rash (related to treatment), five participants taking carbamazepine reported skin rash (related to treatment) and one participant on carbamazepine reported mitral stenosis (unrelated to treatment).

In Rowan 2005, systemic and neurologic toxicities experienced were weight gain or weight loss (87.4% of participants on lamotrigine and 80.1% of carbamazepine), gastrointestinal problems (33.9% on lamotrigine and 32.2% on carbamazepine), hypersensitivity/severe hypersensitivity (3.3% on lamotrigine and 13.4% on carbamazepine), water retention (10.4% on lamotrigine and 8.8% on carbamazepine), hyponatraemia (6.6% on lamotrigine and 11.1% on carbamazepine), impotence (4.4% on lamotrigine and 7.6% on carbamazepine), and renal or liver disease (1.6% on lamotrigine and 4.1% on carbamazepine).

In Saetre 2007, for lamotrigine, 82 participants reported 378 events: 36 participants reported 53 gastrointestinal events, 20 participants reported 26 infections, 19 participants reported 36 musculoskeletal events, 44 participants reported 111 events of the nervous system, 13 participants reported 23 psychiatric events, 12 participants reported 20 skin problems, 11 participants reported 11 vascular disorders and two participants reported two events of the immune system and 24 participants reported 37 other events. For carbamazepine, 79 participants reported 310 events: 29 participants reported 46 gastrointestinal events, 13 participants reported 23 infections, 18 participants reported 29 musculoskeletal events, 45 participants reported 76 events of the nervous system, 12 participants reported 16 psychiatric events, 21 participants reported 25 skin problems, five participants reported six vascular disorders and 11 participants reported 14 events of the immune system and 27 participants reported 41 other events. For both treatments around half of the events were thought to be related to treatment, particularly dizziness, rash, headache, somnolence and gastrointestinal symptoms.

In Steinhoff 2005, the most frequent adverse events for lamotrigine were fatigue (14.8% of participants), rash, headache and nausea (5.7%), nervousness, sleep disorders, pruritus, alopecia and dizziness (4.5%). Three severe adverse events were reported, all possibly related to treatment (nausea and diarrhoea, leucopenia and fatigue). Most frequent adverse events for carbamazepine were fatigue (43.2%), amnesia and pruritus (10.2%), rash (9.1%), abnormal thoughts and abnormal gait (8%). Seven severe adverse events were reported - four were almost certainly related to treatment (rash, dermatitis, abnormal gait and fatigue), two were probably related to treatment (rash and hyponatraemia) and one was unrelated (astrocytoma).

Serious adverse events or adverse events requiring hospitalisation were reported in the seven trials providing detailed IPD (we note that some events were reported multiple times by participants):

In Brodie 1995 A, 16 serious adverse events were reported in seven participants. On lamotrigine, there were 13 events in five participants: suicidal ideation (unknown if related to treatment), knee arthroscopy (not related to treatment), recurrent seizures (related to treatment), aggression (unknown if related to treatment) and headache, diplopia, vertigo, photophobia and vomiting (in a single participant, all related to treatment) and on carbamazepine there were three events in two participants (meningioma not related to treatment and pain possibly related to treatment).

In Brodie 1995 B, seven serious adverse events were reported in six participants. On lamotrigine, there were five events in four participants: haematemesis and stomach ulcer (both related to treatment), appendicitis and tumour in two participants (none related to treatment). On carbamazepine, there were, two events in two participants: meningioma and tumour (neither related to treatment).

In Brodie 1999, 69 serious adverse events were reported in 36 participants. On lamotrigine, there were 36 events in 21 participants: six events in four participants were thought to be related to treatment (sickness, abdominal pain and vomiting in one participant, fracture, seizure recurrence and paranoia) and 30 events in 17 participants were not thought to be related to treatment (asthma, stroke in four participants, glaucoma and vomiting in one participant, urinary retention in one participant, chest infection and vomiting blood in one participant, fracture in two participants, seizure recurrence, vomiting, myalgia and chest pain in one participant, bronchospasm, atrial fibrillation and cardiac failure in one participant, tachycardia in one participant, myocardial infarction and pancreatitis in one participant). On carbamazepine, there were 33 events in 15 participants: eight events in four participants were thought to be related to treatment (rashes in three participants and diarrhoea and vomiting in one participant) and 25 events in 11 participants were not thought to be related to treatment (cerebrovascular accident and upper respiratory tract infection in two participants, leg cramps, myocardial infarction and collapse in one participant, stroke and bronchopneumonia in one participant, dizziness and syncope in one participant, high temperature, chest infection and vomiting in one participant, hyperglycaemic coma, pneumonia and septicaemia in one participant, angina and atrial fibrillation in one participant, falls and vagueness in one participant, ventricular failure and intestinal obstruction in one participant, and seizure recurrence in two participants).

In Nieto-Barrera 2001, 40 serious adverse events were reported in 32 participants. On lamotrigine, there were 27 events in 23 participants: six events in five participants were thought to be related to treatment (rash, raised intracranial pressure, increased seizures, allergic reaction and vertigo) and 23 events in 18 participants were not thought to be related to treatment (change in seizure type, gastric infection, two participants with back pain, broken clavicle, febrile convulsions, tonic-clonic seizures and related injury, intracranial bleeding, haematoma, low pressure of shunt system, complex seizure, traffic accident, pneumonia, gingivostomatitis, fractured elbow, infection, two sudden deaths and cerebral tumour). On carbamazepine, there were 13 events in nine participants: five events in three participants were thought to be related to treatment (diarrhoea and difficulty walking, allergic reaction and atrial fibrillation and hydrothorax) and eight events in six participants were not thought to be related to treatment (tumour, pneumonia, infection, febrile convulsions, embolisation, hepatitis B and cardiac arrest).

In Reunanen 1996, 12 serious adverse events were reported in seven participants (none related to treatment). On lamotrigine, there were 10 events in five participants: haematemesis and cerebral infarct, uterine bleeding and hysterectomy, cerebral and retinal emboli, pain and postoperative infection, and stroke. Three life-threatening events were reported in three participants on lamotrigine (none related to treatment): carbon monoxide poisoning (fatal), myocardial infarction (fatal) and brain tumour. On carbamazepine, there were two events in two participants: pulmonary oedema and angioma.

In SANAD A 2007, 177 events resulting in hospitalisation were reported for 99 participants (it is not stated if the events were related to treatment). On lamotrigine, there were 86 events in 53 participants: worsening of seizures in 13 participants, seizure-related injury in seven participants, cardiovascular events in five participants, stomach ulcer in two participants, infection in two participants, attempted suicide in one participant, rectal bleeding in one participant, pneumonia in one participant; swollen ear in one participant, enlarged prostate in one participant, bowel infection in one participant, malignancy in one participant, legionnaires disease in one participant, haemorrhage in one participant, stroke in one participant, meningioma in one participant, vomiting in one participant, hepatitis in one participant, constipation in one participant, allergic rash in one participant, aneurysm in one participant, vertigo in one participant, carcinoma in one participant, occipital arteriovenous malformations in one participant, Bell's palsy in one participant, allergic rash in one participant, lymphadenopathy in one participant, fractured clavicle in one participant, childbirth in one participant, miscarriage in one participant and toxicity in one participant. On carbamazepine, there were 91 events in 46 participants: worsening of seizures in 12 participants, cardiovascular events in five participants, attempted suicide in three participants, seizure-related injury in three participants, allergic rash in two participants, antiphospholipid syndrome in one participant, arthritis in one participant, stomach cancer in one participant, urinary tract infection in one participant, disorientation in one participant, psychotic illness in one participant, exacerbation of chronic obstructive pulmonary disease in one participant, hysterectomy in one participant, torsion of testis in one participant, myringotomy in one participant, infection in one participant, worsening of seizures and visual disturbance in one participant, constipation in one participant, low serum in one participant, breast cancer in one participant, abdominal pain in one participant, ataxia in one participant, child birth in one participant,

pneumonia in two participant and headache in one participant.

In Werhahn 2015, 120 serious adverse events were reported in 70 participants. On lamotrigine, there were 58 events in 34 participants: two events in two participants were thought to be related or possibly related to treatment (psychiatric disorder and hallucination) and 56 events in 33 participants were not thought to be related to treatment (worsening seizures in eight participants, gastroenteritis in one participant, transient ischaemic attack in two participants, myocardial infarction in two participants, alcohol poisoning in one participant, prostatic hyperplasia in one participant, sudden hearing loss in one participant, sudden death in one participant, cerebral infarction in one participant, astrocytoma in one participant, brain neoplasm in one participant, radius fracture in one participant, bursitis in one participant, head injury in one participant, osteoarthritis in one participant, pneumonia in one participant, urinary tract infection in one participant, herpes in one participant, angina in one participant, asthma in one participant, memory impairment in one participant, intestinal obstruction in one participant, vertebral fracture in one participant, suicidal ideation in one participant, meningioma in one participant and hernia in one participant). On carbamazepine, there were 62 events in 36 participants: four events in three participants were thought to be related to treatment (hepatic enzyme increased, liver disorder and allergic rash), 13 events in four participants were thought to be probably related to treatment (diarrhoea in one participant, headache and hyponatraemia in one participant, dizziness and nausea in two participants), eight events in five were thought to be possibly related to treatment (purpura in one participant, gastroenteritis in two participants, confusion in one participant, lupus erythematosus in one participant), and 28 events in 25 participants were not thought to be related to treatment (worsening seizures in six participants, pneumonia in two participants, sleep apnoea in one participant, cholecystitis in one participant, abdominal pain and nausea in one participant, pain in one participant, spine fusion surgery in one participant, acute coronary syndrome in one participant, gastrointestinal haemorrhage in one participant, death in one participant, hypertension in one participant, device occlusion in one participant, carcinoma in one participant, intestinal obstruction in one participant, melanoma in one participant, dementia in one participant, infectious peritonitis in one participant, pulmonary embolism in one participant, renal cancer in one participant and constipation in one participant).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Lamotrigine compared with carbamazepine for epilepsy

Patient or population: adults and children with partial onset or generalised onset seizures (generalised tonic-clonic with or without other generalised seizure types)
Settings: outpatients
Intervention: lamotrigine
Comparison: carbamazepine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)[1]	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Carbamazepine	Lamotrigine				
Time to first seizure (adjusted for epilepsy type) Range of follow-up: 0 to 2420 days	480 per 1000	561 per 1000 (519 to 602)	HR 1.26 (1.12 to 1.41)	2476 (9 trials)	⊕⊕⊕⊕ **high**[2]	HR < 1 indicates an advantage for lamotrigine
Time to first seizure Subgroup: partial onset seizures Range of follow-up: 0 to 2420 days	495 per 1000	585 per 1000 (541 to 628)	HR 1.29 (1.14 to 1.45)	2177 (9 trials)	⊕⊕⊕⊕ **high**[2]	HR < 1 indicates an advantage for lamotrigine
Time to first seizure Subgroup: generalised onset seizures Range of follow-up: 0 to 853 days	364 per 1000	359 per 1000 (255 to 489)	HR 0.98 (0.65 to 1.48)	277 (6 trials)	⊕⊕◯◯ **low**[2,3]	HR < 1 indicates an advantage for lamotrigine

Time to 12-month remission Range of follow-up: 0 to 2420 days	583 per 1000	549 per 1000 (490 to 608)	HR 0.91 (0.77 to 1.07)	988 (2 trials)	⊕⊕⊕⊕ **high**[2]	HR < 1 indicates an advantage for carbamazepine

The assumed risk is calculated as the event rate in the carbamazepine treatment group
The corresponding risk in the lamotrigine treatment group (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)
The corresponding risk is calculated as the assumed risk x the relative risk (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk)))/assumed risk
95% CI: 95% confidence interval; HR: hazard ratio

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

[1]Pooled hazard ratio for all participants adjusted for seizure type.
[2]High risk of bias due to the open-label design in some of the included trials, however outcomes are objective and unlikely to be influenced by knowledge of drug allocation. No downgrade made.
[3]Downgraded due to potential misclassification of generalised onset seizures in up to 50% of participants in the trials.

DISCUSSION

Summary of main results

The results of this review provide statistically significant evidence of an advantage for lamotrigine over carbamazepine for our primary global effectiveness outcome, time to withdrawal of allocated treatment. For 2569 participants providing individual participant data (IPD) from nine trials, the pooled hazard ratio (HR) was 0.72(95% confidence interval (CI) 0.63 to 0.82, P value < 0.0001). This advantage was also present in the 2182 participants with partial onset seizures (pooled HR 0.75, 95% CI 0.64 to 0.86, P value = 0.0001) and the 299 participants with generalised onset seizures (pooled HR 0.46, 95% CI 0.30 to 0.71, P value = 0.0003) from the nine trials providing IPD.

The advantage also remained when incorporating aggregate data from four trials for which IPD were not available, allowing for alternative definitions of treatment withdrawal from the definition used in this review (ILAE 1998), and allowing for blinded trial design.

The results of this review provide statistically significant evidence of an advantage for carbamazepine over lamotrigine for our secondary efficacy outcomes, time to first seizure (pooled HR for 2564 participants, 1.22, 95% CI 1.09 to 1.37, P value = 0.0004) and time to six-month remission (pooled HR for 1793 participants, 0.84, 95% CI 0.74 to 0.94, P value =0.003). As above, this advantage was present in the subgroup of participants with partial onset seizures, but in the smaller subgroup of participants with generalised onset seizures we found no significant difference between the drugs.

We found no statistically significant difference between the drugs for the longer-term outcomes of time to 12-month remission and time to 24-month remission; however fewer data were available for inclusion in analyses at these time points due to the short duration of most included trials.

The most commonly reported adverse events for both of the drugs across all of the included trials were dizziness, fatigue, gastrointestinal disturbances, headache and skin problems. The rate of adverse events and serious adverse events was similar across the two drugs.

Overall completeness and applicability of evidence

We believe that our systematic electronic searches identified all relevant evidence for this review. We have gratefully received individual participant data (IPD) for 2572 individuals (76% of 3394 individuals from all eligible trials) from the authors or sponsors of nine trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Eun 2012; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015), which included a comparison of lamotrigine with carbamazepine for the treatment of epilepsy.

At the time of review, we have not been able to obtain IPD for the remaining four included trials with a total of 822 participants. For two trials including 360 individuals (Saetre 2007; Steinhoff 2005), the trial sponsor confirmed that data could not be made available. For the other two trials, we made contact with the authors/sponsors who expressed interest in collaborating in this IPD meta-analysis but at the time of writing, no data had been received (Gilad 2007; Rowan 2005).

If IPD are received from these trials, we will include the data in future updates. We were able to extract aggregate data from all four trial publications to include in meta-analysis for our primary outcome of 'time to treatment withdrawal,' resulting in a similar pooled estimate to that from IPD only. Therefore, we do not believe that our failure to obtain IPD from 24% of eligible participants from four trials has had a large impact on the applicability of the results of the review. We do, however, encourage caution when interpreting the numerical results of the review, particularly longer-term remission outcomes for which only two trials were of sufficient duration. Given the results of this meta-analysis it could be that, compared to carbamazepine, the initial doses of lamotrigine chosen were too low. Hence lamotrigine fared better for treatment withdrawal as the dose chosen caused comparatively fewer side effects but was less effective at preventing seizures. This highlights the importance of measuring longer-term seizure outcomes such as time to one- or two-year remission from seizures, which would be much less affected by initial drug titration and initial target doses.

We have good evidence from previous reviews conducted by the Cochrane Epilepsy Group that misclassification of seizure type, particularly generalised seizure types, is an important issue in epilepsy trials (Nolan 2013b; Nolan 2015a; Nolan 2015b). It is also likely in this review that a large proportion of individuals who were classified as experiencing generalised onset seizures at baseline had their seizure type wrongly classified, meaning that the results of the original trials and therefore the results of this review may have been confounded by classification bias. Following sensitivity analyses to account for this potential misclassification, the overall conclusions for our primary and secondary outcomes were not changed (see Summary of main results). However, due to the small proportion of total participants included experiencing generalised onset seizures (302 out of 2572, 12% of total participants) and up to 50% of those participants with potentially misclassified seizure type, the results of this review are primarily applicable to participants with partial onset seizures.

Quality of the evidence

The nine trials for which IPD were made available (as well as additional trial design information from trial authors/sponsors) were of generally good quality. Less information was available for trials without IPD available where risk of bias assessments were made only based on published information. Six trials were of

a double-blind design (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Rowan 2005; Saetre 2007; Werhahn 2015), and seven trials were of an open-label design (Eun 2012; Gilad 2007; Lee 2011; Nieto-Barrera 2001; Reunanen 1996; Steinhoff 2005; SANAD A 2007). The results of this review suggest that the design of a trial (double-blind versus open-label) may influence the withdrawal rates of the trial, an outcome that is subjective and can be influenced by the participant or clinician. It is argued that an open-label design is more pragmatic and reflective of 'real world' treatment for a trial of a chronic condition such as epilepsy where treatments are likely to be taken long-term by participants (SANAD A 2007), and it is shown in this review that a significantly higher proportion of participants withdrew from treatment in the trials with a double-blind design compared to the open-label trials (45% versus 29%, P value < 0.0001, see Effects of interventions). However, in a trial of a 'new' compared to a 'standard' intervention, knowledge of the treatment allocation may influence the choice of the participant or clinician to continue taking the treatment, which may then influence the perceived effectiveness of the two drugs under comparison. Therefore, we have considered an open-label design to potentially introduce bias into the results for the subjective outcomes of time to treatment withdrawal, but not for the objective secondary outcomes of time to first seizure and remission.

Due to this potential risk of bias from an open-label design, we have rated the evidence provided in this review according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for our primary outcome of time to treatment withdrawal as 'moderate' for all participants and the subgroup of participants with partial onset seizures. Due to the limited number of participants with generalised onset seizures (and potential misclassification of seizure type), we have rated this evidence as low quality for the primary outcome(see Summary of findings for the main comparison).

For our secondary (objective) outcomes of time to first seizure and remission, we have rated the evidence as high quality (moderate quality in the subgroup of generalised onset seizures for the reasons stated above)(see Summary of findings 2).

Potential biases in the review process

We were able to include individual participant data (IPD) for 2572 out of 3394 eligible participants (76%) from nine out of 13 trials in this review and we were able to analyse all outcomes using IPD. Such an approach has many advantages, such as allowing the standardisation of definitions of outcomes across trials, and attrition and reporting biases are reduced as we can perform additional analyses and calculate additional outcomes from unpublished data. For the outcomes we used in this review that are of a time-to-event nature, an IPD approach is considered to be the 'gold standard' approach to analysis (Parmar 1998).

For reasons outside of our control, we were unable to obtain IPD for 822 participants from four trials for inclusion in this review. However, following sensitivity analyses using aggregate data, we do not believe that the exclusion of 24% of eligible participants is likely to have impacted on the conclusions of this review (see Overall completeness and applicability of evidence).

Finally, we made some assumptions in the statistical methodology used in this review. Firstly, when we received only follow-up dates and seizure frequencies, we used linear interpolation to estimate. We are aware that an individual's seizure patterns may be non-linear; therefore, we recommend caution when interpreting the numerical results of the seizure-related outcomes.

We also made an assumption that treatment effect for each outcome did not change over time (proportional hazards assumption, see Data synthesis). We are aware that in trials of long duration (e.g. SANAD A 2007 and Werhahn 2015 of over one year duration), the assumption of treatment effect remaining constant over time is unlikely to be appropriate, for example, there is likely to be a difference between participants who achieve immediate remission compared with participants who achieve later remission. Therefore, if future updates of this review include more trials of long duration, we would like to perform statistical analyses that allow for treatment effects to vary over time.

Agreements and disagreements with other studies or reviews

To our knowledge, together with previous versions of this review, this is the only systematic review and meta-analysis that compares lamotrigine and carbamazepine monotherapy for partial onset seizures and generalised onset tonic-clonic seizures. A network meta-analysis has been published (Tudur Smith 2007), comparing all direct and indirect evidence from lamotrigine, carbamazepine and other standard and new antiepileptic drugs licensed for monotherapy. The results of this review generally agree with the results of the network meta-analysis. The network meta-analysis is currently being updated to include more recently published trials, such as SANAD A 2007 and Werhahn 2015; therefore, we will compare the results of this review with the updated network meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Current UK guidelines recommend carbamazepine or lamotrigine as first-line treatment for adults and children with new onset partial seizures and sodium valproate for adults and children with new onset generalised seizures (NICE 2012).

For individuals with new onset partial seizures, the results of this review suggest that lamotrigine is likely to be a more effective drug than carbamazepine in terms of treatment retention (withdrawals due to lack of efficacy or adverse events or both). However, the results also suggest that individuals are likely to achieve earlier remission and later seizure recurrence when taking carbamazepine compared to lamotrigine. Therefore a choice between these two first-line treatments for individuals with new onset partial seizures must be carefully considered, taking the personal circumstances of an individual into account.

For individuals with new onset generalised seizures, the evidence in the review is limited due to small numbers of participants with certain generalised seizure types recruited into the included trials. There is evidence that carbamazepine may exacerbate some generalised seizure types so should be used with caution in individuals with this seizure type (Liporace 1994; Shields 1983; Snead 1985). Lamotrigine may be an effective treatment option for new onset generalised seizures, but more evidence is required to confirm this.

Implications for research

This review highlights the need for the design of future antiepileptic drug monotherapy trials that recruit individuals with specific epilepsy syndromes to be powered to detect a difference between particular antiepileptic drugs. An approach likely to reflect and inform clinical practice, as well as being statistically powerful, would be to recruit heterogeneous populations for whom epilepsy syndromes have been adequately defined, with testing for interaction between treatment and epilepsy syndrome. In view of potential problems of misclassification, syndromes will have to be well defined, with adequate checking mechanisms to ensure that classifications are accurate and a system to recognise uncertainty surrounding epilepsy syndromes in individuals within trials. It is also important that future trials are of a sufficient duration to measure long-term effectiveness of antiepileptic drugs(treatments that will be life-long for many individuals with epilepsy), as well as psychosocial, quality of life and health economic outcomes.

Consideration is also required in the design of a trial regarding whether to blind participants and outcome assessors to treatment allocation. While an open-label design is a more pragmatic and practical approach for large, long-term trials, when trials involve a new intervention compared to an established 'standard' intervention, masking of treatment may be important to avoid preconceptions over the relative effectiveness of the drugs.

The choice of outcomes at the design stage of a trial and the presentation of the results of outcomes, particularly of a time-to-event nature, require very careful consideration. While the majority of trials of a monotherapy design record an outcome measuring efficacy (seizure control) and an outcome measuring tolerability (adverse events), there is little uniformity between the definition of the outcomes and the reporting of the summary statistics related to the outcomes (Nolan 2013a), making an aggregate data approach to meta-analysis in reviews of monotherapy trials impossible. Where trial authors cannot or will not make individual participant data available for analysis, we are left with no choice but to exclude a proportion of relevant evidence from the review, which may impact upon the interpretation of the results of the review and the applicability of the evidence and conclusions. The International League Against Epilepsy recommends that trials of a monotherapy design should adopt a primary effectiveness outcome of 'time to withdrawal of allocated treatment (retention time)' and should be of a duration of at least 48 weeks to allow for assessment of longer-term outcomes, such as remission (ILAE 1998; ILAE 2006). If trials followed these recommendations, an aggregate data approach to meta-analysis may be feasible, reducing the resources and time required from an individual participant data approach.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brodie 1995 A

Methods	Randomised, double-blind, parallel-group trial conducted in 8 centres in the UK 2 treatment arms: LTG and CBZ
Participants	Adults and children over the age of 13 with newly diagnosed epilepsy Number randomised: LTG = 70, CBZ = 66; 56 males (41%) 82 with partial seizures (60%) None had received previous AED treatment Mean age (range): 34 (13 to 71) years
Interventions	Monotherapy with LTG or CBZ for 48 weeks 4-week escalation phase leading to LTG = 150 mg/day, CBZ = 600 mg/day Range of follow-up: 0 to 398 days
Outcomes	Time to first seizure after 6 weeks of treatment Time to withdrawal Proportion of randomised patients remaining seizure-free during the last 40 and 24 weeks of trial Percentages of patients who reported adverse events
Notes	IPD provided by trial sponsor GlaxoSmithKline for time to treatment withdrawal, time to first seizure and time to 6-month remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence (information provided by drug manufacturer) . Stratification by seizure type
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded

Brodie 1995 A (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 1995 B

Methods	Randomised, double-blind, parallel-group trial conducted in 8 centres in the UK 2 treatment arms: LTG and CBZ
Participants	Adults and children over the age of 13 with newly diagnosed epilepsy Number randomised: LTG = 61, CBZ = 63 56 males (45%) 62 with partial seizures (50%) None had received previous AED treatment Mean age (range): 30 (14 to 86) years
Interventions	Monotherapy with LTG or CBZ for 48 weeks 4-week escalation phase leading to LTG = 150 mg/day, CBZ = 600 mg/day Range of follow-up: 0 to 398 days
Outcomes	Time to first seizure after 6 weeks of treatment Time to withdrawal Proportion of randomised patients remaining seizure-free during the last 40 and 24 weeks of trial Percentages of patients who reported adverse events
Notes	IPD provided by trial sponsor GlaxoSmithKline for time to treatment withdrawal, time to first seizure and time to 6-month remission

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random sequence (information provided by drug manufacturer) . Stratification by seizure type
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed opaque envelopes (information provided by drug manufacturer)

Brodie 1995 B (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 1999

Methods	Randomised, multicentre, double-blind, parallel-group trial conducted in the UK 2 treatment arms: LTG and CBZ randomised in a 2:1 ratio
Participants	Adults over the age of 65 with newly diagnosed epilepsy with 2 or more seizures in the previous year with at least 1 seizure in the last 6 months Number randomised: LTG = 102, CBZ = 48 83 males (55%) 105 with partial seizures (70%) Not stated if any participants had received previous AED treatment Mean age (range): 77 (65 to 94) years
Interventions	Monotherapy with LTG or CBZ for 24 weeks 4-week escalation phase leading to LTG = 100 mg/day, CBZ = 400 mg/day Range of follow-up = 0 to 280 days
Outcomes	Time to first seizure after 6 weeks of treatment Time to withdrawal Percentage of patients reporting an adverse event Proportion of patients who were both seizure-free in the last 16 weeks of the trial and did not discontinue treatment
Notes	IPD provided by trial sponsor GlaxoSmithKline for time to treatment withdrawal and time to first seizure (plus seizure freedom rates at 24 weeks)

Risk of bias

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

Brodie 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer). Participants randomised in a 2:1 ratio (LTG:CBZ)
Allocation concealment (selection bias)	Low risk	Allocation concealed with pharmacy-dispensed treatment packs labelled with participant's trial number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Eun 2012

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in 7 hospitals in the Republic of Korea 2 treatment arms: LTG and CBZ
Participants	Children between the ages of 6 and 12 with a new diagnosis of partial epilepsy and at least 2 seizures in the last 6 months Number randomised: LTG = 43, CBZ = 41 48 males (57%) 100% partial epilepsy Not stated if any participants had received previous AED treatment Mean age (range): 9 (5 to 13) years
Interventions	Monotherapy with LTG or CBZ for 32 weeks 8-week escalation phase leading to LTG = 3 to 6 mg/kg/day, CBZ = 10 to 20 mg/kg/day Range of follow-up: 12 to 788 days
Outcomes	Seizure-free rate over 6 months (maintenance period) by treatment group Change in cognition (neuropsychological), behaviour and quality of life from screening to the end of the maintenance phase by treatment group Incidence of adverse events

Eun 2012 (*Continued*)

Notes	IPD provided by trial author for time to treatment withdrawal, time to first seizure and time to 6-month remission No source of funding stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre received a separate and independent computer-generated random code list
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Gilad 2007

Methods	Randomised single-centre, open-label, parallel-group trial conducted at Tel Aviv University and Medical Centre, Israel 2 treatment arms: LTG and CBZ
Participants	Adults admitted to the neurological department with a first seizure event after an ischaemic stroke Number randomised: LTG = 32, CBZ = 32 46 males (72%) 100% partial seizures Unclear if any participants had received previous AED treatment Mean age (range): 67.5 (38 to 90) years
Interventions	Monotherapy with LTG or CBZ for 12 months Dose escalation phase (length not stated) leading to LTG 100 mg/day, CBZ 300 mg/day

Gilad 2007 (*Continued*)

	Range of follow-up: not stated
Outcomes	The appearance of a second seizure under treatment or by finishing the 12-month follow-up without seizures Tolerability: incidence of adverse events Withdrawals due to adverse events
Notes	Contact made with trial author who was willing to provide IPD but data never received. Aggregate data extracted from graphs in the publication. Stated in the title of the paper that LTG and CBZ were monotherapy treatments but Table 1 of the paper refers to total no. AED; unclear if all participants were receiving monotherapy treatment. No source of funding stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised in a 1:1 ratio, no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate reported; all randomised participants included in analysis
Selective reporting (reporting bias)	Low risk	No protocol available. Seizure outcomes and adverse events well reported
Other bias	Unclear risk	Unclear if all participants were receiving monotherapy treatment

Lee 2011

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the Republic of Korea 2 treatment arms: LTG and CBZ
Participants	Adults over the age of 16 with newly diagnosed partial epilepsy or untreated partial epilepsy for at least 1 year Number randomised: LTG = 57, CBZ = 53

Lee 2011 (*Continued*)

	57 males (52%) 95 partial seizures (86%) Not stated how many participants had received previous AED treatment Mean age (range): 36 (16 to 60) years
Interventions	Monotherapy with LTG or CBZ for 48 weeks 8-week escalation phase leading to LTG = 200 mg/day, CBZ = 600 mg/day Range of follow-up: 14 to 337 days
Outcomes	Change of neuropsychological and cognitive scores from baseline: general intellectual ability, learning and memory, attention and executive function (group-by-time interaction) Frequency of psychological and health-related quality of life symptoms Proportion with seizure freedom during the maintenance period
Notes	IPD provided by trial author for time to treatment withdrawal, time to first seizure and time to 6-month remission This trial was supported by a grant from GlaxoSmithKline Korea. No other funding sources stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation (block size 4) via a computer randomisation program (information provided by trial author)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Nieto-Barrera 2001

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in Europe and Mexico 2 treatment arms: LTG and CBZ randomised in a 2:1 ratio
Participants	Adults and children over the age of 2 with newly diagnosed or currently untreated partial epilepsy with 2 or more seizures in the previous 6 months and with at least 1 seizure in the last 3 months Number randomised: LTG = 420, CBZ = 202 329 males (53%) 619 with partial seizures (99.5%) Not stated how many participants had received previous AED treatment Mean age (range): 27 (2 to 84) years
Interventions	Monotherapy with LTG or CBZ for 24 weeks 6-week escalation phase leading to minimum of LTG 2 mg/kg/day age range 2 to 12 years, 200 mg/day age range 13 to 64 years and 100 mg/day age > 65 years. CBZ aged 2 to 12 years 5 to 40 mg/kg, age > 12 years 100 to 1500 mg/day Range of follow-up: 0 to 245 days
Outcomes	Proportion of patients seizure-free during the last 16 weeks of treatment Efficacy success: proportion of patients who did not withdraw before the end of week 18 and were seizure-free in the last 16 weeks of the trial Time to withdrawal from the trial (proportion of patients completing the trial) Proportion of patients experiencing adverse events Withdrawals due to adverse events
Notes	IPD provided by trial sponsor GlaxoSmithKline for time to treatment withdrawal and time to first seizure (plus seizure freedom rates at 24 weeks) Dates of seizures during the first 4 weeks not provided with individual participant data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence. Participants randomised in a 2:1 ratio (LTG:CBZ), stratified by age group and country
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial

Nieto-Barrera 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Reunanen 1996

Methods	Randomised, double-blind, parallel-group trial conducted in 56 centres in Europe and Australia 3 treatment arms: LTG (200 mg/day), LTG (100 mg/day) and CBZ
Participants	Adults and children over the age of 12 with newly diagnosed, currently untreated or recurrent epilepsy with 2 or more seizures in the previous 6 months and with at least 1 seizure in the last 3 months. Participants must not have taken antiepileptic medication in the previous 6 months Number randomised: LTG (200 mg) = 115, LTG (100 mg) = 116, CBZ = 121 188 males (54%) 237 with partial seizures (68%) Not stated how many participants had received previous AED treatment Mean age (range): 32 (12 to 71) years
Interventions	Monotherapy with LTG or CBZ for 30 weeks 4-week escalation phase leading to LTG = 100 mg/day, LTG = 200 mg/day, CBZ = 600 mg/day Range of follow-up: 0 to 378 days
Outcomes	Proportion seizure-free after the first 6 weeks of treatment Time to first seizure Time to withdrawal Frequency of adverse events with at least 5% incidence in any treatment group
Notes	IPD provided by trial sponsor GlaxoSmithKline for time to treatment withdrawal, time to first seizure and time to 6-month remission Participants considered to complete the trial if they experienced a seizure after the first 6 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer)

Reunanen 1996 (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Rowan 2005

Methods	Randomised, double-blind, parallel-group trial conducted in 18 Veterans Affairs Medical Centres in the United States 3 treatment arms: LTG, CBZ and gabapentin (GBP)
Participants	Adults over the age of 60 with newly diagnosed seizures, untreated or treated with sub-therapeutic AED levels, with at least 1 seizure in the previous 3 months Number randomised: LTG = 200, CBZ = 198 378 males (95%) 299 with partial seizures (75%) Not stated how many participants had received previous AED treatment Mean age: 72 years, range not stated
Interventions	Monotherapy with LTG or CBZ for 12 months 6-week escalation phase leading to LTG = 150 mg/day, CBZ = 600 mg/day Range of follow-up: not stated
Outcomes	Retention in the trial for 12 months Seizure freedom at 12 months Time to 1st, 2nd, 5th and 10th seizure (time to seizures) Drug toxicity (incidence of systemic and neurologic toxicities) Serum drug levels and compliance Seizure-free retention rates

Notes	IPD requested from trial sponsor, the Department of Veterans Affairs, USA. At the time of review, IPD have not been received. Aggregate data extracted from graphs in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (varying sizes) performed by site via a computer-generated list
Allocation concealment (selection bias)	Low risk	Telephone randomisation used and pharmacy dispensed a prescription of the allocated drug (part of a blinded drug kit) to participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding achieved with double dummy tablets; doses of both increased and decreased simultaneously
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. Most of the randomised participants included in analysis; 3 excluded due to site closure (not related to treatment)
Selective reporting (reporting bias)	Low risk	No protocol available but case report forms of data collected provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

Saetre 2007

Methods	Randomised, double-blind, parallel-group trial conducted in 29 centres across Croatia, Finland, France, Finland and Norway. 2 treatment arms: LTG, CBZ
Participants	Adults over the age of 65 with newly diagnosed seizures, with a history of at least 2 seizures and at least 1 seizure in the previous 6 months. Participants must not have taken antiepileptic medication for more than 2 weeks in the previous 6 months and never taken CBZ or LTG Number randomised: LTG = 94, CBZ = 92 102 males (54%) Proportion with partial seizures not stated

Saetre 2007 (*Continued*)

	Not stated how many participants had received previous AED treatment Mean age: 74 (65 to 91) years
Interventions	Monotherapy with LTG or CBZ for 40 weeks 4-week escalation phase leading to LTG = 100 mg/day, CBZ = 400 mg/day Range of follow-up: not stated
Outcomes	Retention in the trial (time to treatment withdrawal for any cause) Seizure freedom after week 4 Seizure freedom after week 20 Time to first seizure Adverse event reports Tolerability according to the Liverpool Adverse Event profile (AEP)
Notes	IPD requested from trial sponsor Glaxo Smith Kline but data could not be located Aggregate summary data extracted from the publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding achieved with double dummy tablets, packaged together
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all participants who received trial treatment were included in an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No protocol available but clinical trial summary provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

SANAD A 2007

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the UK 5 treatment arms: LTG, CBZ, GBP, topiramate (TPM) and oxcarbazepine (OXC)
Participants	Adults and children over the age of 4 years with newly diagnosed partial epilepsy, relapsed partial epilepsy or failed treatment with a previous drug not used in this trial Number randomised: LTG = 378, CBZ = 378 409 males (54%) 662 partial epilepsy (88%) 139 had received previous AED treatment (18%) Mean age (range): 38 (5 to 83) years
Interventions	Monotherapy for LTG or CBZ (no fixed trial duration) Titration doses and maintenance doses decided by treating clinician Range of follow-up: 17 to 2420 days
Outcomes	Time to treatment failure Time to 1-year (12-month) remission Time to 2-year remission Time to first seizure Health-related quality of life via the NEWQOL (Newly Diagnosed Epilepsy Quality of Life Battery) Health economic assessment and cost-effectiveness of the drugs (cost per QALY gained and cost per seizure avoided) Frequency of clinically important adverse events
Notes	IPD provided for time to treatment withdrawal, time to first seizure, time to 6-month, time to 12-month and time to 24-month remission (trial conducted at our site and sponsored by the Health Technology Assessment programme of the National Institute of Health Research)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer minimisation program stratified by centre, sex and treatment history
Allocation concealment (selection bias)	Low risk	Telephone randomisation to a central randomisation allocation service
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial

SANAD A 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Steinhoff 2005

Methods	Randomised, open-label, parallel-group trial conducted in 24 centres across Germany 4 treatment arms: LTG (2 arms), CBZ and sodium valproate (SV) Participants with partial and generalised epilepsy randomised separately to LTG or CBZ and LTG or SV respectively
Participants	Adults and children over the age of 12 with newly diagnosed epilepsy; at least 1 seizure and electroencephalographic imaging suggesting epilepsy Number randomised not stated; number included in analysis: LTG = 88, CBZ = 88 106 males (64%) 100% partial seizures Not stated how many participants had received previous AED treatment Mean age: 47.5 years, range not stated
Interventions	Monotherapy with LTG or CBZ for 22 to 26 weeks 4-week escalation phase leading to LTG = 100 to 200 mg/day, CBZ = 600 to 1200 mg/day in adults and 600 to 1000 mg/day in children aged 11 to 15 Range of follow-up: not stated
Outcomes	Number of seizure-free patients during trial weeks 17 to 24 "Leaving the study" (retention rates) Adverse event rates
Notes	IPD requested from trial sponsor GlaxoSmithKline but data could not be provided due to restrictions over the de-identification of datasets from trials conducted in Germany Aggregate data extracted from graphs in the publication Data from participants with partial seizures only included as this is the randomised comparison of LTG and CBZ

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

Steinhoff 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants randomised to each group not reported (254 randomised and 239 analysed in the 4 arms of the trial) . Reasons for exclusion stated but not to which drug these participants were randomised
Selective reporting (reporting bias)	Low risk	No protocol available but clinical trial summary provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

Werhahn 2015

Methods	Randomised, double-blind, parallel-group trial conducted in 47 centres across Germany, Austria and Switzerland 3 treatment arms: LTG, CBZ and levetiracetam (LEV)
Participants	Adults over the age of 60 with newly diagnosed partial seizures, with a history of at least 2 seizures and at least 1 seizure in the previous 6 months. Participants must not have taken antiepileptic medication for more than 4 weeks Number randomised: LTG = 118, CBZ = 121 135 males (56%) 100% partial epilepsy Not stated how many participants had received previous AED treatment Mean age (range): 71 (60 to 89) years
Interventions	Monotherapy with LTG or CBZ for 58 weeks 6-week escalation phase leading to LTG = 100 mg/day, CBZ = 400 mg/day Range of follow-up: 0 to 1508 days
Outcomes	Retention rate at week 58 Time to discontinuation from randomisation Seizure freedom rates at week 30 and week 58 Time to first seizure from randomisation Time to first drug-related adverse event Adverse events (by severity)

Notes	IPD provided by trial author for time to treatment withdrawal, time to first seizure, time to 6-month and time to 12-month remission Trial was sponsored by UCB

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomisation list for each centre (random permuted blocks) was prepared by the Interdisciplinary Centre for Clinical Trials (IZKS), Mainz, Germany
Allocation concealment (selection bias)	Low risk	The pharmacy of the University Hospital Mainz encapsulated the trial drugs and labelled the blinded medication including the randomisation number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and trial investigator blinded by the use of matching capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded; not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

[1]Abbreviations
AED: antiepileptic drug
CBZ: carbamazepine
IPD: individual participant data
ITT: intention-to-treat
LTG: lamotrigine
QALY: quality-adjusted life year
[2]For trials for which IPD were provided attrition and reporting bias are reduced as attrition rates and unpublished outcome data are requested (Brodie 1995 A; Brodie 1995 B; Brodie 1999 Nieto-Barrera 2001; Reunanen 1996).

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

Study	Reason for exclusion
Baxter 1998	Participants randomised to lamotrigine and physician's choice of carbamazepine or valproate. No fully randomised comparison between lamotrigine and carbamazepine
Carmant 2001	Not monotherapy
Czapinski 1997	Wrong drug comparison
Eun 2008	Conference abstract for full publication Eun 2012
Fakhoury 2000	Withdrawn to monotherapy. Design excluded.
Gilliam 1998	Wrong drug comparison
Jawad 1989	Not monotherapy
Lee 2010	Conference abstract for full publication Lee 2011
Martinez 2000	Not randomised
Motte 1997	Wrong drug comparison
Ramsay 2003	Abstract of full publication Rowan 2005
Saetre 2006	Conference abstract for full publication Saetre 2007
Saetre 2009	Subset of Saetre 2007
Saetre 2010	Subset of Saetre 2010
Steiner 1999	Wrong drug comparison
Steinhoff 2004	Abstract of full publication Steinhoff 2005
Stolarek 1994	Wrong drug comparison
Zeng 2010	Not randomised

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

Korean Lamotrigine Study Group 2008

Methods	Phase IV, open label, randomised, multicentre trial conducted in 21 Centres in Korea Two treatment arms: CBZ and LTG
Participants	Participants were untreated epileptics who had at least 2 unprovoked seizures (partial or generalised tonic clonic) during the last 24 weeks before the study start, more than 24 hours apart Number randomised: CBZ=129, LTG=264 (ITT population) 154 male participants (39%); 288 participants (73%) with partial epilepsy Mean age (SD): CBZ=37.6 (15.8), LTG=34.2 (16.3) years
Interventions	Monotherapy with CBZ or LTG Permitted doses LTG: 100mg/day - 500mg/day for LTG , CBZ: 400mg/day - 1200mg/day
Outcomes	Retention Rate at Study End Terminal 24 week seizure free rate and time interval from the end of dose titration phase to the first seizure
Notes	Full text of the trial published in Korean. Abstract and clinical trial summary available in English Awaiting translation of full text before initiating an individual participant data request

DATA AND ANALYSES

Comparison 1. Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to withdrawal of allocated treatment	9	2569	Hazard Ratio (Fixed, 95% CI)	0.72 [0.63, 0.82]
2 Time to withdrawal of allocated treatment by seizure type	9	2481	Hazard Ratio (Fixed, 95% CI)	0.71 [0.62, 0.81]
2.1 Partial	9	2182	Hazard Ratio (Fixed, 95% CI)	0.75 [0.64, 0.86]
2.2 Generalised	6	299	Hazard Ratio (Fixed, 95% CI)	0.46 [0.30, 0.71]
3 Time to withdrawal of allocated treatment (with aggregate data)	13	3391	Hazard Ratio (Fixed, 95% CI)	0.69 [0.61, 0.77]
4 Time to withdrawal of allocated treatment - subgroup analysis (blinding)	13	3391	Hazard Ratio (Fixed, 95% CI)	0.69 [0.61, 0.77]
4.1 Double-blind	6	1231	Hazard Ratio (Fixed, 95% CI)	0.60 [0.51, 0.71]
4.2 Open-label	7	2160	Hazard Ratio (Fixed, 95% CI)	0.77 [0.66, 0.90]
5 Time to first seizure	9	2564	Hazard Ratio (Fixed, 95% CI)	1.22 [1.09, 1.37]
6 Time to first seizure by seizure type	9	2476	Hazard Ratio (Fixed, 95% CI)	1.26 [1.12, 1.41]
6.1 Partial	9	2177	Hazard Ratio (Fixed, 95% CI)	1.29 [1.14, 1.45]
6.2 Generalised	6	299	Hazard Ratio (Fixed, 95% CI)	0.98 [0.65, 1.48]
7 Time to first seizure (with aggregate data)	12	3216	Hazard Ratio (Fixed, 95% CI)	1.24 [1.12, 1.37]
8 Seizure freedom (whole study)	13	3386	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.06, 1.20]
9 Time to 6-month remission	7	1793	Hazard Ratio (Fixed, 95% CI)	0.84 [0.74, 0.94]
10 Time to 6-month remission by seizure type	7	1708	Hazard Ratio (Fixed, 95% CI)	0.86 [0.76, 0.97]
10.1 Partial	7	1454	Hazard Ratio (Fixed, 95% CI)	0.87 [0.77, 1.00]
10.2 Generalised	5	254	Hazard Ratio (Fixed, 95% CI)	0.78 [0.55, 1.11]
11 Seizure freedom at 6 months	13	3386	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.88, 1.03]
12 Time to 12-month remission	2	988	Hazard Ratio (Fixed, 95% CI)	0.91 [0.77, 1.07]
13 Time to 12-month remission by seizure type	2	988	Hazard Ratio (Fixed, 95% CI)	0.90 [0.76, 1.07]
13.1 Partial	2	894	Hazard Ratio (Fixed, 95% CI)	0.91 [0.77, 1.09]
13.2 Uncertain	1	94	Hazard Ratio (Fixed, 95% CI)	0.81 [0.47, 1.37]
14 Time to 24-month remission	1	755	Hazard Ratio (Fixed, 95% CI)	1.00 [0.80, 1.25]
15 Time to 24-month remission by seizure type	1	755	Hazard Ratio (Fixed, 95% CI)	1.03 [0.82, 1.30]
15.1 Partial	1	661	Hazard Ratio (Fixed, 95% CI)	1.06 [0.83, 1.35]
15.2 Uncertain	1	94	Hazard Ratio (Fixed, 95% CI)	0.86 [0.44, 1.67]

Analysis 1.1. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 1 Time to withdrawal of allocated treatment.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 1 Time to withdrawal of allocated treatment

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brodie 1995 A	70	66	-0.51434 (0.26671)		6.8 %	0.60 [0.35, 1.01]
Brodie 1995 B	61	63	-0.61476 (0.3076)		5.1 %	0.54 [0.30, 0.99]
Brodie 1999	102	48	-0.88791 (0.27065)		6.6 %	0.41 [0.24, 0.70]
Eun 2012	43	41	0.53465 (0.62742)		1.2 %	1.71 [0.50, 5.84]
Lee 2011	57	53	-0.09296 (0.32895)		4.5 %	0.91 [0.48, 1.74]
Nieto-Barrera 2001	419	202	-0.30944 (0.19489)		12.7 %	0.73 [0.50, 1.08]
Reunanen 1996	230	121	-0.53433 (0.25288)		7.6 %	0.59 [0.36, 0.96]
SANAD A 2007	377	377	-0.21988 (0.10813)		41.4 %	0.80 [0.65, 0.99]
Werhahn 2015	118	121	-0.26297 (0.18521)		14.1 %	0.77 [0.53, 1.11]
Total (95% CI)	**1477**	**1092**			**100.0 %**	**0.72 [0.63, 0.82]**

Heterogeneity: $Chi^2 = 9.83$, $df = 8$ ($P = 0.28$); $I^2 = 19\%$

Test for overall effect: $Z = 4.75$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

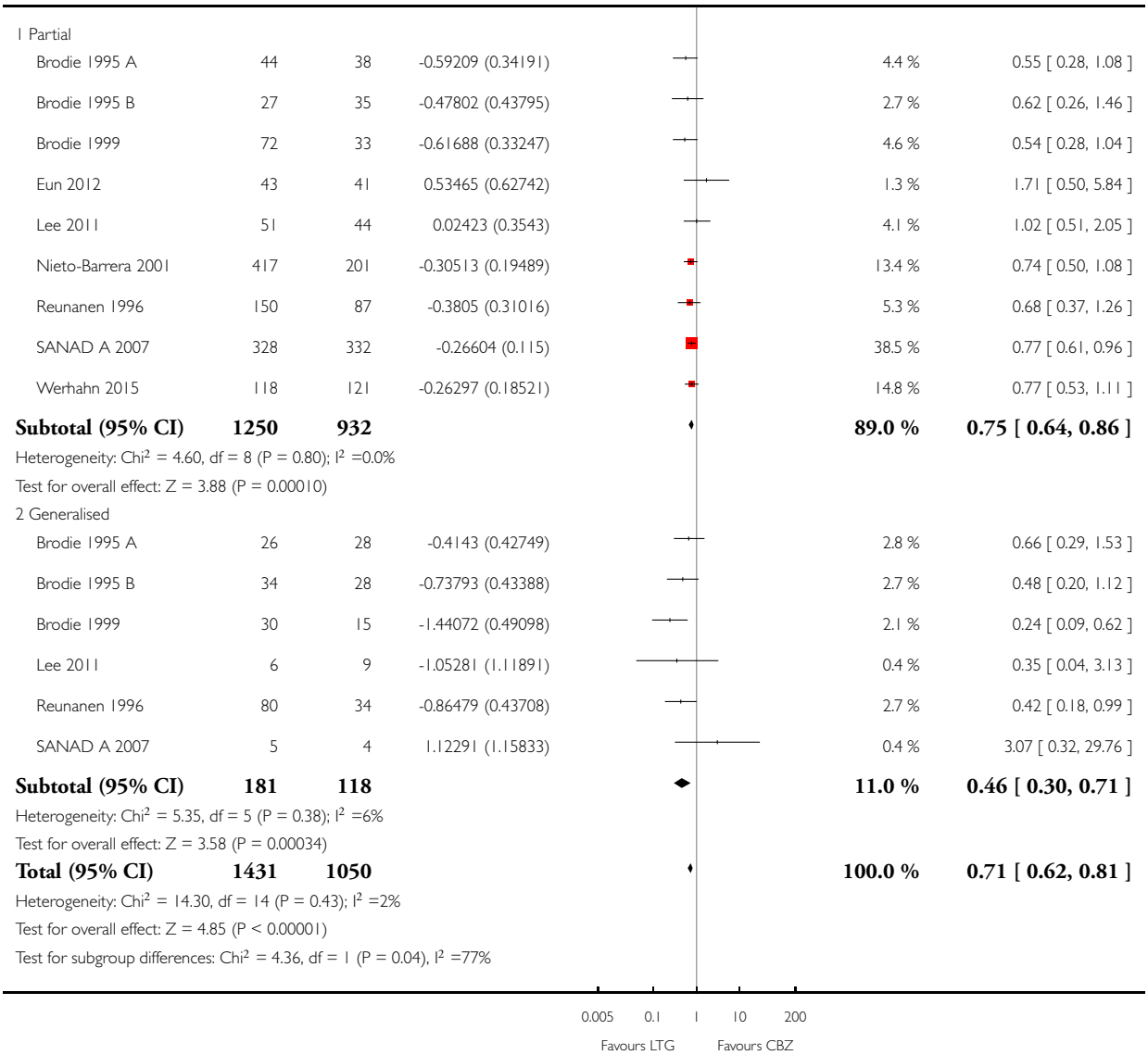
Analysis 1.2. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 2 Time to withdrawal of allocated treatment by seizure type.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 2 Time to withdrawal of allocated treatment by seizure type

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Partial						
Brodie 1995 A	44	38	-0.59209 (0.34191)		4.4 %	0.55 [0.28, 1.08]
Brodie 1995 B	27	35	-0.47802 (0.43795)		2.7 %	0.62 [0.26, 1.46]
Brodie 1999	72	33	-0.61688 (0.33247)		4.6 %	0.54 [0.28, 1.04]
Eun 2012	43	41	0.53465 (0.62742)		1.3 %	1.71 [0.50, 5.84]
Lee 2011	51	44	0.02423 (0.3543)		4.1 %	1.02 [0.51, 2.05]
Nieto-Barrera 2001	417	201	-0.30513 (0.19489)		13.4 %	0.74 [0.50, 1.08]
Reunanen 1996	150	87	-0.3805 (0.31016)		5.3 %	0.68 [0.37, 1.26]
SANAD A 2007	328	332	-0.26604 (0.115)		38.5 %	0.77 [0.61, 0.96]
Werhahn 2015	118	121	-0.26297 (0.18521)		14.8 %	0.77 [0.53, 1.11]
Subtotal (95% CI)	**1250**	**932**			**89.0 %**	**0.75 [0.64, 0.86]**
Heterogeneity: Chi^2 = 4.60, df = 8 (P = 0.80); I^2 =0.0%						
Test for overall effect: Z = 3.88 (P = 0.00010)						
2 Generalised						
Brodie 1995 A	26	28	-0.4143 (0.42749)		2.8 %	0.66 [0.29, 1.53]
Brodie 1995 B	34	28	-0.73793 (0.43388)		2.7 %	0.48 [0.20, 1.12]
Brodie 1999	30	15	-1.44072 (0.49098)		2.1 %	0.24 [0.09, 0.62]
Lee 2011	6	9	-1.05281 (1.11891)		0.4 %	0.35 [0.04, 3.13]
Reunanen 1996	80	34	-0.86479 (0.43708)		2.7 %	0.42 [0.18, 0.99]
SANAD A 2007	5	4	1.12291 (1.15833)		0.4 %	3.07 [0.32, 29.76]
Subtotal (95% CI)	**181**	**118**			**11.0 %**	**0.46 [0.30, 0.71]**
Heterogeneity: Chi^2 = 5.35, df = 5 (P = 0.38); I^2 =6%						
Test for overall effect: Z = 3.58 (P = 0.00034)						
Total (95% CI)	**1431**	**1050**			**100.0 %**	**0.71 [0.62, 0.81]**
Heterogeneity: Chi^2 = 14.30, df = 14 (P = 0.43); I^2 =2%						
Test for overall effect: Z = 4.85 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 4.36, df = 1 (P = 0.04), I^2 =77%						



Analysis 1.3. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 3 Time to withdrawal of allocated treatment (with aggregate data).

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 3 Time to withdrawal of allocated treatment (with aggregate data)

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brodie 1995 A	70	66	-0.51434 (0.26671)		4.9 %	0.60 [0.35, 1.01]
Brodie 1995 B	61	63	-0.61476 (0.3076)		3.7 %	0.54 [0.30, 0.99]
Brodie 1999	102	48	-0.88791 (0.27065)		4.8 %	0.41 [0.24, 0.70]
Eun 2012	43	41	0.53465 (0.62742)		0.9 %	1.71 [0.50, 5.84]
Gilad 2007	32	32	-2.424 (1.0493)		0.3 %	0.09 [0.01, 0.69]
Lee 2011	57	53	-0.09296 (0.32895)		3.2 %	0.91 [0.48, 1.74]
Nieto-Barrera 2001	419	202	-0.30944 (0.19489)		9.2 %	0.73 [0.50, 1.08]
Reunanen 1996	230	121	-0.53433 (0.25288)		5.5 %	0.59 [0.36, 0.96]
Rowan 2005	200	198	-0.59 (0.14)		17.9 %	0.55 [0.42, 0.73]
Saetre 2007	93	91	-0.26 (0.27)		4.8 %	0.77 [0.45, 1.31]
SANAD A 2007	377	377	-0.21988 (0.10813)		30.0 %	0.80 [0.65, 0.99]
Steinhoff 2005	88	88	-0.222 (0.276)		4.6 %	0.80 [0.47, 1.38]
Werhahn 2015	118	121	-0.26297 (0.18521)		10.2 %	0.77 [0.53, 1.11]
Total (95% CI)	**1890**	**1501**			**100.0 %**	**0.69 [0.61, 0.77]**

Heterogeneity: Chi^2 = 16.90, df = 12 (P = 0.15); I^2 =29%

Test for overall effect: Z = 6.34 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 4 Time to withdrawal of allocated treatment - subgroup analysis (blinding).

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 4 Time to withdrawal of allocated treatment - subgroup analysis (blinding)

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Double-blind						
Brodie 1995 A	70	66	-0.51434 (0.26671)		4.9 %	0.60 [0.35, 1.01]
Brodie 1995 B	61	63	-0.61476 (0.3076)		3.7 %	0.54 [0.30, 0.99]
Brodie 1999	102	48	-0.88791 (0.27065)		4.8 %	0.41 [0.24, 0.70]
Rowan 2005	200	198	-0.59 (0.14)		17.9 %	0.55 [0.42, 0.73]
Saetre 2007	93	91	-0.26 (0.27)		4.8 %	0.77 [0.45, 1.31]
Werhahn 2015	118	121	-0.26297 (0.18521)		10.2 %	0.77 [0.53, 1.11]
Subtotal (95% CI)	**644**	**587**			**46.3 %**	**0.60 [0.51, 0.71]**
Heterogeneity: Chi^2 = 5.03, df = 5 (P = 0.41); I^2 =1%						
Test for overall effect: Z = 5.84 (P < 0.00001)						
2 Open-label						
Eun 2012	43	41	0.53465 (0.62742)		0.9 %	1.71 [0.50, 5.84]
Gilad 2007	32	32	-2.424 (1.0493)		0.3 %	0.09 [0.01, 0.69]
Lee 2011	57	53	-0.09296 (0.32895)		3.2 %	0.91 [0.48, 1.74]
Nieto-Barrera 2001	419	202	-0.30944 (0.19489)		9.2 %	0.73 [0.50, 1.08]
Reunanen 1996	230	121	-0.53433 (0.25288)		5.5 %	0.59 [0.36, 0.96]
SANAD A 2007	377	377	-0.21988 (0.10813)		30.0 %	0.80 [0.65, 0.99]
Steinhoff 2005	88	88	-0.222 (0.276)		4.6 %	0.80 [0.47, 1.38]
Subtotal (95% CI)	**1246**	**914**			**53.7 %**	**0.77 [0.66, 0.90]**
Heterogeneity: Chi^2 = 7.51, df = 6 (P = 0.28); I^2 =20%						
Test for overall effect: Z = 3.22 (P = 0.0013)						
Total (95% CI)	**1890**	**1501**			**100.0 %**	**0.69 [0.61, 0.77]**
Heterogeneity: Chi^2 = 16.90, df = 12 (P = 0.15); I^2 =29%						
Test for overall effect: Z = 6.34 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 4.36, df = 1 (P = 0.04), I^2 =77%						

Analysis 1.5. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 5 Time to first seizure.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

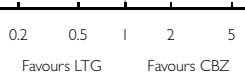
Outcome: 5 Time to first seizure

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brodie 1995 A	70	66	0.36048 (0.24798)		5.3 %	1.43 [0.88, 2.33]
Brodie 1995 B	61	63	0.12822 (0.23634)		5.9 %	1.14 [0.72, 1.81]
Brodie 1999	102	48	-0.15608 (0.23751)		5.8 %	0.86 [0.54, 1.36]
Eun 2012	43	41	-0.26785 (0.36609)		2.4 %	0.77 [0.37, 1.57]
Lee 2011	57	53	0.1156 (0.35958)		2.5 %	1.12 [0.55, 2.27]
Nieto-Barrera 2001	419	202	0.29979 (0.12767)		20.1 %	1.35 [1.05, 1.73]
Reunanen 1996	230	121	0.21504 (0.18849)		9.2 %	1.24 [0.86, 1.79]
SANAD A 2007	377	378	0.20983 (0.08648)		43.7 %	1.23 [1.04, 1.46]
Werhahn 2015	117	116	0.334 (0.25469)		5.0 %	1.40 [0.85, 2.30]
Total (95% CI)	**1476**	**1088**			**100.0 %**	**1.22 [1.09, 1.37]**

Heterogeneity: Chi^2 = 5.35, df = 8 (P = 0.72); I^2 =0.0%

Test for overall effect: Z = 3.54 (P = 0.00040)

Test for subgroup differences: Not applicable



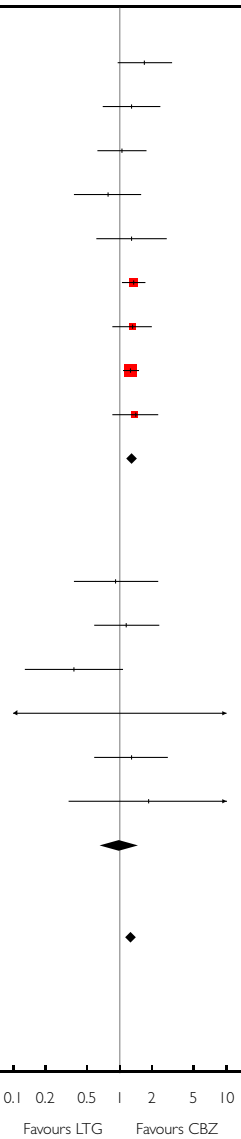
Analysis 1.6. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 6 Time to first seizure by seizure type.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 6 Time to first seizure by seizure type

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Partial						
Brodie 1995 A	44	38	0.53643 (0.2991)		3.8 %	1.71 [0.95, 3.07]
Brodie 1995 B	27	35	0.25662 (0.31735)		3.4 %	1.29 [0.69, 2.41]
Brodie 1999	72	33	0.04267 (0.269)		4.8 %	1.04 [0.62, 1.77]
Eun 2012	43	41	-0.26785 (0.36609)		2.6 %	0.77 [0.37, 1.57]
Lee 2011	51	44	0.2468 (0.38907)		2.3 %	1.28 [0.60, 2.74]
Nieto-Barrera 2001	417	201	0.30024 (0.12774)		21.1 %	1.35 [1.05, 1.73]
Reunanen 1996	150	87	0.27389 (0.21388)		7.5 %	1.32 [0.86, 2.00]
SANAD A 2007	328	333	0.2404 (0.09128)		41.3 %	1.27 [1.06, 1.52]
Werhahn 2015	117	116	0.334 (0.25469)		5.3 %	1.40 [0.85, 2.30]
Subtotal (95% CI)	**1249**	**928**			**92.0 %**	**1.29 [1.14, 1.45]**
Heterogeneity: Chi^2 = 3.80, df = 8 (P = 0.87); I^2 =0.0%						
Test for overall effect: Z = 4.11 (P = 0.000040)						
2 Generalised						
Brodie 1995 A	26	28	-0.08293 (0.4607)		1.6 %	0.92 [0.37, 2.27]
Brodie 1995 B	34	28	0.13928 (0.36114)		2.6 %	1.15 [0.57, 2.33]
Brodie 1999	30	15	-0.99643 (0.54129)		1.2 %	0.37 [0.13, 1.07]
Lee 2011	6	9	-17.8823 (6501)		0.0 %	0.00 [0.0, ∞]
Reunanen 1996	80	34	0.25181 (0.40443)		2.1 %	1.29 [0.58, 2.84]
SANAD A 2007	5	4	0.61633 (0.8761)		0.4 %	1.85 [0.33, 10.31]
Subtotal (95% CI)	**181**	**118**			**8.0 %**	**0.98 [0.65, 1.48]**
Heterogeneity: Chi^2 = 4.45, df = 5 (P = 0.49); I^2 =0.0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)	**1430**	**1046**			**100.0 %**	**1.26 [1.12, 1.41]**
Heterogeneity: Chi^2 = 9.77, df = 14 (P = 0.78); I^2 =0.0%						
Test for overall effect: Z = 3.92 (P = 0.000090)						
Test for subgroup differences: Chi^2 = 1.53, df = 1 (P = 0.22), I^2 =35%						



Analysis 1.7. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 7 Time to first seizure (with aggregate data).

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

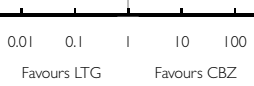
Outcome: 7 Time to first seizure (with aggregate data)

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brodie 1995 A	70	66	0.36048 (0.24798)		4.4 %	1.43 [0.88, 2.33]
Brodie 1995 B	61	63	0.12822 (0.23634)		4.8 %	1.14 [0.72, 1.81]
Brodie 1999	102	48	-0.15608 (0.23751)		4.8 %	0.86 [0.54, 1.36]
Eun 2012	43	41	-0.26785 (0.36609)		2.0 %	0.77 [0.37, 1.57]
Gilad 2007	32	32	-0.7856 (0.4129)		1.6 %	0.46 [0.20, 1.02]
Lee 2011	57	53	0.1156 (0.35958)		2.1 %	1.12 [0.55, 2.27]
Nieto-Barrera 2001	419	202	0.29979 (0.12767)		16.5 %	1.35 [1.05, 1.73]
Reunanen 1996	230	121	0.21504 (0.18849)		7.6 %	1.24 [0.86, 1.79]
Rowan 2005	200	198	0.37 (0.15)		12.0 %	1.45 [1.08, 1.94]
Saetre 2007	93	91	0.41 (0.26)		4.0 %	1.51 [0.91, 2.51]
SANAD A 2007	377	378	0.20983 (0.08648)		36.1 %	1.23 [1.04, 1.46]
Werhahn 2015	118	121	0.334 (0.25469)		4.2 %	1.40 [0.85, 2.30]
Total (95% CI)	**1802**	**1414**			**100.0 %**	**1.24 [1.12, 1.37]**

Heterogeneity: Chi^2 = 12.90, df = 11 (P = 0.30); I^2 =15%

Test for overall effect: Z = 4.15 (P = 0.000034)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 8 Seizure freedom (whole study).

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 8 Seizure freedom (whole study)

Study or subgroup	LTG n/N	CBZ n/N	Risk Ratio(Non-event) M-H,Fixed,95% CI	Weight	Risk Ratio(Non-event) M-H,Fixed,95% CI
Brodie 1995 A	31/70	38/66		3.6 %	1.31 [0.93, 1.86]
Brodie 1995 B	23/61	29/63		4.2 %	1.15 [0.85, 1.56]
Brodie 1999	49/102	21/48		4.6 %	0.92 [0.68, 1.26]
Eun 2012	27/43	25/41		2.1 %	0.95 [0.55, 1.64]
Gilad 2007	23/32	15/32		2.1 %	0.53 [0.28, 1.01]
Lee 2011	41/57	38/53		2.0 %	0.99 [0.55, 1.80]
Nieto-Barrera 2001	191/419	118/202		14.2 %	1.31 [1.09, 1.58]
Reunanen 1996	135/230	81/121		6.6 %	1.25 [0.93, 1.68]
Rowan 2005	57/200	45/198		19.3 %	0.93 [0.82, 1.04]
Saetre 2007	50/93	60/91		3.9 %	1.36 [0.95, 1.95]
SANAD A 2007	95/377	123/378		32.0 %	1.11 [1.01, 1.21]
Steinhoff 2005	62/88	72/88		2.0 %	1.63 [0.94, 2.81]
Werhahn 2015	79/117	90/116		3.3 %	1.45 [0.94, 2.22]
Total (95% CI)	**1889**	**1497**		**100.0 %**	**1.13 [1.06, 1.20]**

Total events: 863 (LTG), 755 (CBZ)

Heterogeneity: Chi^2 = 26.38, df = 12 (P = 0.01); I^2 =55%

Test for overall effect: Z = 3.66 (P = 0.00025)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 9 Time to 6-month remission.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 9 Time to 6-month remission

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brodie 1995 A	70	66	-0.29789 (0.27574)		4.8 %	0.74 [0.43, 1.27]
Brodie 1995 B	61	63	-0.45437 (0.26847)		5.1 %	0.63 [0.38, 1.07]
Eun 2012	43	41	0.02671 (0.28928)		4.4 %	1.03 [0.58, 1.81]
Lee 2011	57	53	0.05511 (0.23827)		6.5 %	1.06 [0.66, 1.69]
Reunanen 1996	230	121	-0.14772 (0.15401)		15.5 %	0.86 [0.64, 1.17]
SANAD A 2007	377	378	-0.1919 (0.08292)		53.5 %	0.83 [0.70, 0.97]
Werhahn 2015	117	116	-0.19551 (0.18937)		10.2 %	0.82 [0.57, 1.19]
Total (95% CI)	**955**	**838**			**100.0 %**	**0.84 [0.74, 0.94]**

Heterogeneity: $Chi^2 = 2.78$, df = 6 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 2.94 (P = 0.0033)

Test for subgroup differences: Not applicable

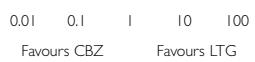
Analysis 1.10. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 10 Time to 6-month remission by seizure type.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 10 Time to 6-month remission by seizure type

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Partial						
Brodie 1995 A	44	38	0.40112 (0.37028)		2.9 %	1.49 [0.72, 3.09]
Brodie 1995 B	27	35	-0.8553 (0.42023)		2.2 %	0.43 [0.19, 0.97]
Eun 2012	43	41	0.02671 (0.28928)		4.7 %	1.03 [0.58, 1.81]
Lee 2011	51	44	0.2466 (0.26055)		5.8 %	1.28 [0.77, 2.13]
Reunanen 1996	150	87	-0.09697 (0.18806)		11.1 %	0.91 [0.63, 1.31]
SANAD A 2007	328	333	-0.18685 (0.08831)		50.3 %	0.83 [0.70, 0.99]
Werhahn 2015	117	116	-0.19551 (0.18937)		10.9 %	0.82 [0.57, 1.19]
Subtotal (95% CI)	**760**	**694**			**87.9 %**	**0.87 [0.77, 1.00]**
Heterogeneity: Chi^2 = 7.98, df = 6 (P = 0.24); I^2 =25%						
Test for overall effect: Z = 2.01 (P = 0.044)						
2 Generalised						
Brodie 1995 A	26	28	-0.06409 (0.41807)		2.2 %	0.94 [0.41, 2.13]
Brodie 1995 B	34	28	-0.20324 (0.36452)		3.0 %	0.82 [0.40, 1.67]
Lee 2011	6	9	-0.84161 (0.69791)		0.8 %	0.43 [0.11, 1.69]
Reunanen 1996	80	34	-0.25098 (0.27001)		5.4 %	0.78 [0.46, 1.32]
SANAD A 2007	5	4	-0.38853 (0.76944)		0.7 %	0.68 [0.15, 3.06]
Subtotal (95% CI)	**151**	**103**			**12.1 %**	**0.78 [0.55, 1.11]**
Heterogeneity: Chi^2 = 0.97, df = 4 (P = 0.92); I^2 =0.0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)	**911**	**797**			**100.0 %**	**0.86 [0.76, 0.97]**
Heterogeneity: Chi^2 = 9.31, df = 11 (P = 0.59); I^2 =0.0%						
Test for overall effect: Z = 2.37 (P = 0.018)						
Test for subgroup differences: Chi^2 = 0.37, df = 1 (P = 0.54), I^2 =0.0%						

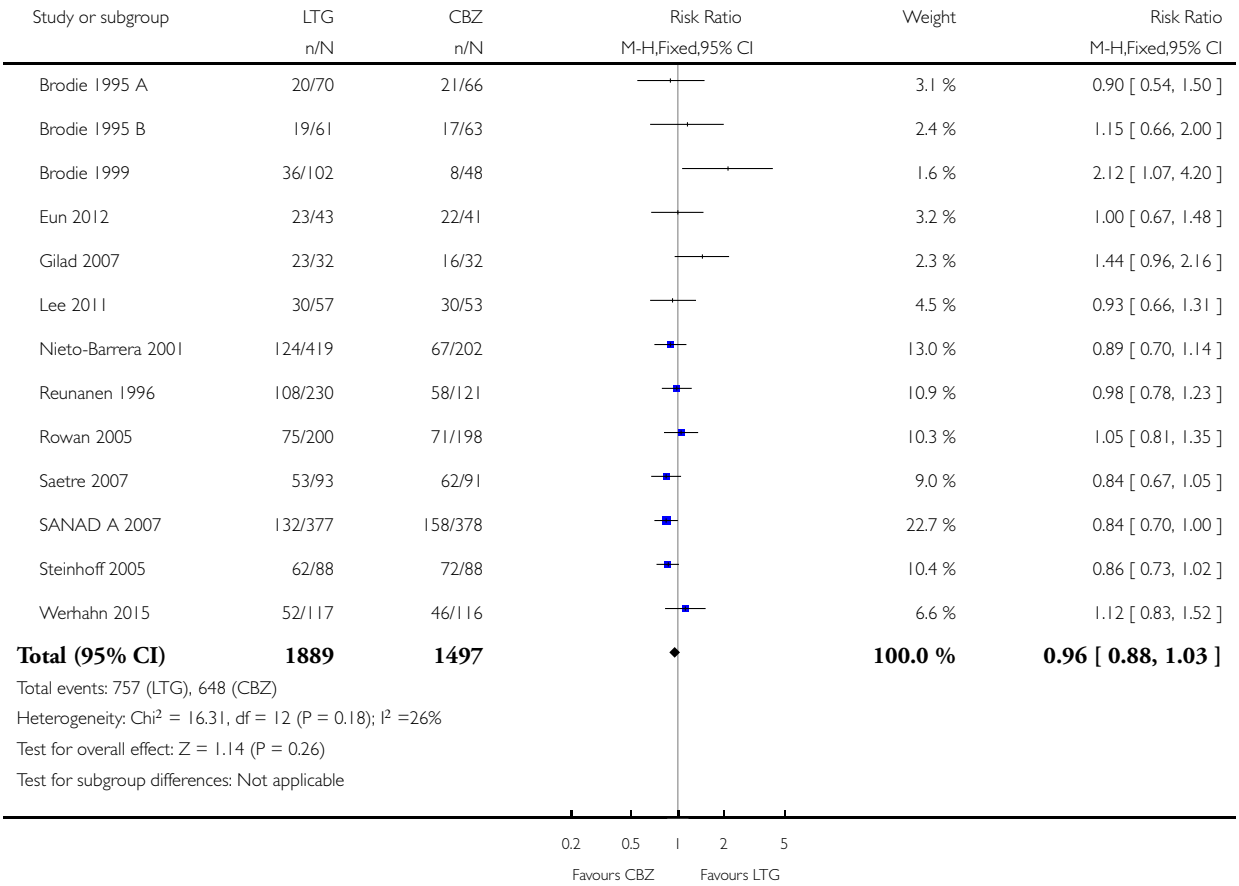


Analysis 1.11. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 11 Seizure freedom at 6 months.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 11 Seizure freedom at 6 months



Analysis 1.12. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 12 Time to 12-month remission.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 12 Time to 12-month remission

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
SANAD A 2007	377	378	-0.10204 (0.0923)		83.5 %	0.90 [0.75, 1.08]
Werhahn 2015	117	116	-0.05938 (0.20772)		16.5 %	0.94 [0.63, 1.42]
Total (95% CI)	**494**	**494**			**100.0 %**	**0.91 [0.77, 1.07]**

Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 13 Time to 12-month remission by seizure type.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 13 Time to 12-month remission by seizure type

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Partial						
SANAD A 2007	328	333	-0.09769 (0.0987)		73.6 %	0.91 [0.75, 1.10]
Werhahn 2015	117	116	-0.05938 (0.20772)		16.6 %	0.94 [0.63, 1.42]
Subtotal (95% CI)	**445**	**449**			**90.2 %**	**0.91 [0.77, 1.09]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
2 Uncertain						
SANAD A 2007	49	45	-0.21512 (0.27024)		9.8 %	0.81 [0.47, 1.37]
Subtotal (95% CI)	**49**	**45**			**9.8 %**	**0.81 [0.47, 1.37]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.80 (P = 0.43)						
Total (95% CI)	**494**	**494**			**100.0 %**	**0.90 [0.76, 1.07]**
Heterogeneity: Chi^2 = 0.22, df = 2 (P = 0.90); I^2 =0.0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
Test for subgroup differences: Chi^2 = 0.19, df = 1 (P = 0.66), I^2 =0.0%						

Analysis 1.14. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 14 Time to 24-month remission.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

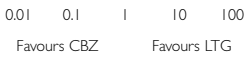
Outcome: 14 Time to 24-month remission

Study or subgroup	LTG N	CBZ N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
SANAD A 2007	377	378	-0.00098 (0.11628)		100.0 %	1.00 [0.80, 1.25]
Total (95% CI)	**377**	**378**			**100.0 %**	**1.00 [0.80, 1.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

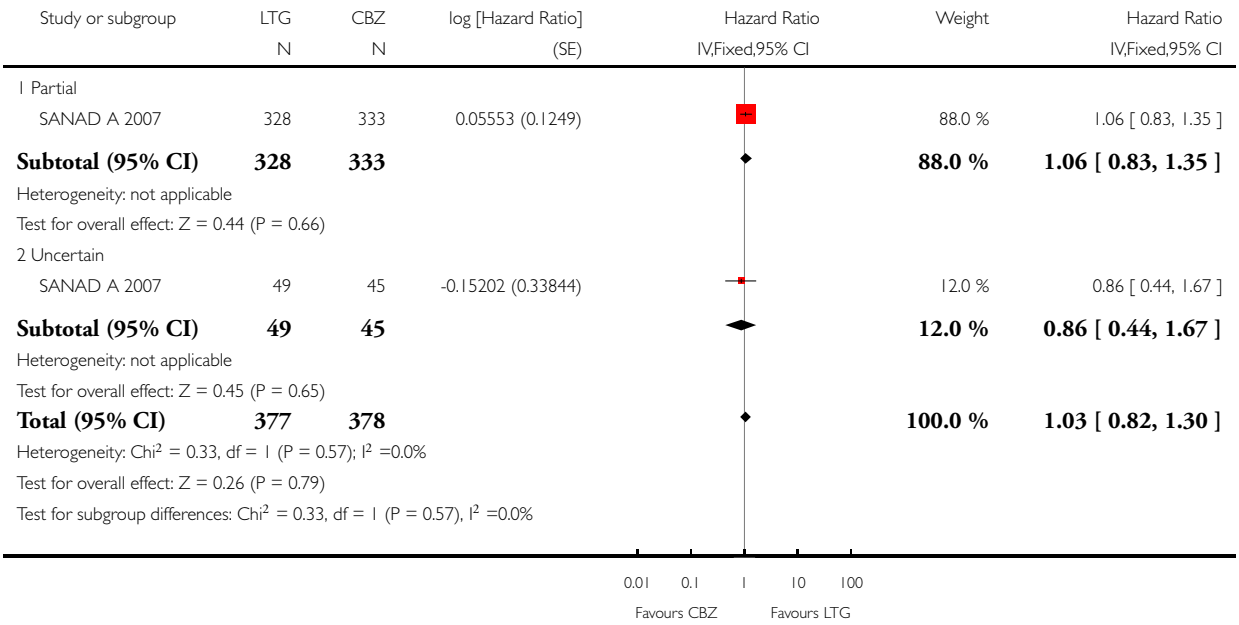


Analysis 1.15. Comparison 1 Lamotrigine (LTG) versus carbamazepine (CBZ), Outcome 15 Time to 24-month remission by seizure type.

Review: Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review

Comparison: 1 Lamotrigine (LTG) versus carbamazepine (CBZ)

Outcome: 15 Time to 24-month remission by seizure type



ADDITIONAL TABLES

Table 1. Demographic characteristics of trial participants (trials providing individual participant data)

	Partial seizures: n (%)			Male gender: n (%)			Age at entry (years): Mean (SD), range			Aged > 30 and generalised seizures: n (%)			Epilepsy duration (years): Mean (SD), range			Number of seizures in prior 6 months: median (range)		
	LTG	CBZ	Missing	LTG	CBZ	Missing	LTG	CBZ	Missing	LTG	CBZ	Missing	LTG	CBZ	Missing	LTG	CBZ	Missing
Brodie 1995A	44 (63%)	38 (58%)	0	28 (40%)	28 (42%)	0	35.3 (17.1), 15	32.5 (14.4), 13	0	11	9	0	2.2 (3.3), 0 to	1.8 (2.3), 0.	0	4 (1 to 490)	3 (1 to 960)	0

Table 1. Demographic characteristics of trial participants (trials providing individual participant data) (*Continued*)

							to 71	to 69					17.9	3 to 11.0			
Brodie 1995B	27 (44%)	35 (56%)	0	26 (43%)	30 (48%)	0	30.9 (14.5), 14 to 86	29.1 (13.9), 14 to 81	0	12	11	0	1.4 (3.2), 0 to 19.4	1.2 (1.8), 0 to 7.1	0	3 (1 to 1020)	3 (2 to 122)	0
Brodie 1999	72 (71%)	33 (69%)	0	55 (54%)	28 (58%)	0	77.3 (6.1), 65 to 94	76.2 (5.9), 66 to 88	0	30	15	0	NA	NA	150	3 (1 to 163)	4.5 (1 to 108)	0
Eun 2012	43 (100%	41 (100%	0	24 (56%)	24 (59%)	0	9.2 (2.0), 6 to 13	8.3 (2.1), 5 to 12	0	0	0	0	0.6 (0.9), 0 to 4.5	0.5 (0.3), 0 to 1.4	1	3 (2 to 11)	3 (2 to 11)	0
Lee 2011	51 (89%)	44 (83%)	0	24 (42%)	33 (62%)	0	33.6 (12.6), 16 to 60	38.3 (11.5), 16 to 60	0	2	7	0	NA	NA	110	2 (0 to 60)	2 (0 to 200)	0
Nieto-Barrera 2001	418 (99.5%)	201 (99.5%)	0	222 (53%)	107 (53%)	0	27.1 (21.7), 2 to 84	27.5 (21.0), 2 to 77	1	1	1	0	NA	NA	622	4 (1 to 9000)	3 (1 to 3600)	0
Reunanen 1996	150 (65%)	87 (72%)	0	127 (55%)	61 (50%)	0	31.8 (14.0), 12 to 71	32.7 (14.6), 13 to 71	2	31	12	0	2.2 (3.2), 0 to 17.1	2.2 (3.7), 0.26 to 8	3	3 (1 to 133)	3 (1 to 145)	1
SANAA 2007	329 (99%)	333 (99%)	85	205 (55%)	204 (55%)	18	36.8 (18.4), 6 to 83	39.3 (18.4), 5 to 82	18	46	42	0	NA	NA	727	2(0 to 1185)	4 (0 to 466)	19

Table 1. Demographic characteristics of trial participants (trials providing individual participant data) (*Continued*)

Werhahn 2015	118 (100%	121 (100%	0	69 (59%)	65 (54%)	0	70.8 (7.5), 60 to 88	71.8 (6.7), 60 to 89	0	0	0	0	NA	NA	239	2 (1 to 20)	2 (1 to 90)	6

CBZ = carbamazepine, LTG = lamotrigine; n = number of participants; NA = not applicable; SD = standard deviation

Table 2. Baseline neurologic characteristics of participants (trials providing individual participant data)

	EEG normal: n (%)			CT scan normal: n (%)			Neurological exam normal: n (%)		
	LTG	CBZ	Missing	LTG	CBZ	Missing	LTG	CBZ	Missing
Brodie 1995 A	32 (46%)	30 (46%)	2	38 (84%)	44 (90%)	42	62 (89%)	61 (92%)	0
Brodie 1995 B	42 (73%)	34 (56%)	6	34 (77%)	38 (79%)	32	56 (92%)	52 (83%)	0
Brodie 1999	NA	NA	150	39 (39%)	23 (48%)	1	59 (58%)	31 (65%)	0
Eun 2012	3 (7%)	3 (7%)	0	38 (88%)	37(90%)	0	43 (100%)	40 (98%)	0
Lee 2011	31 (54%)	27 (51%)	0	36 (63%)	38 (72%)	0	57 (100%)	53 (100%)	0
Nieto-Barrera 2001	NA	NA	622	NA	NA	622	NA	NA	622
Reunanen 1996	9 (53%)	4 (44%)	325	11 (73%)	5 (83%)	330	202 (89%)	103 (85%)	0
SANAD A 2007	NA	NA	756	NA	NA	756	277 (75%)	281 (76%)	18
Werhahn 2015	45 (38%)	37 (31%)	1	26 (22%)	26 (21%)	1	NA	NA	239

CBZ = carbamazepine; CT = computerised tomography; EEG = electroencephalogram; LTG = lamotrigine; n = number of participants; NA = not applicable

Table 3. Number of participants included in analyses (trials providing individual participant data)

	Number randomised			Time to withdrawal of allocated treatment			Time to first seizure			Time to 6-month remission[1]			Time to 12-month remission			Time to 24-month remission		
	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	Total
Brodie 1995A	70	66	136	70	66	136	70	66	136	70	66	136	NA	NA	NA	NA	NA	NA
Brodie 1995B	61	63	124	61	63	124	61	63	124	61	63	124	NA	NA	NA	NA	NA	NA
Brodie 1999[1]	102	48	150	102	48	150	102	48	150	102	48	150	NA	NA	NA	NA	NA	NA
Eun 2012	43	41	84	43	41	84	43	41	84	43	41	84	NA	NA	NA	NA	NA	NA
Lee 2011	57	53	110	57	53	110	57	53	110	57	53	110	NA	NA	NA	NA	NA	NA
Nieto-Barrera 2001[1,2]	420	202	622	419	202	621	419	202	621	419	202	621	NA	NA	NA	NA	NA	NA
Reunanen 1996	230	121	351	230	121	351	230	121	351	230	121	351	NA	NA	NA	NA	NA	NA
SANAA 2007[3]	378	378	756	377	377	754	377	378	755	377	378	755	377	378	755	377	378	755

Table 3. Number of participants included in analyses (trials providing individual participant data) (*Continued*)

Werhahn 2015[4]	118	121	239	118	121	239	117	116	233	117	116	233	117	116	233	NA	NA	NA
Total	**1479**	**1093**	**2572**	**1477**	**1092**	**2569**	**1476**	**1088**	**2564**	**1476**	**1088**	**2564**	**494**	**494**	**988**	**377**	**378**	**755**

CBZ = carbamazepine; LTG = lamotrigine; NA: not applicable (trial duration not sufficient to measure the outcome).
[1]Brodie 1999 and Nieto-Barrera 2001 are of 24 weeks duration (approximately six months). The two trials are not included in the analyses of time to six-month remission but are included in sensitivity analysis of seizure freedom at six months.
[2]Follow-up data are missing for one participant in Nieto-Barrera 2001,
[3]Withdrawal time missing for two participants and seizure data after follow-up missing for one participant in SANAD A 2007.
[4]Seizure data after follow-up missing for six participants in Werhahn 2015.

Table 4. Reasons for premature discontinuation (withdrawal of allocated treatment)

Reason for early termination[1]		Adverse events	Inadequate response/ seizure recurrence	Both adverse events and inadequate response	Protocol violation/ non-compliance	Withdrew consent/ participant choice[3]	Other (treatment-related)[4]	Illness or death (not treatment-related)	Remission of seizures	Lost to follow-up	Other (not treatment-related)[5]	Completed trial	Total
Classification in time-to-event analyses		**Event**	**Event**	**Event**	**Event**	**Event**	**Event**	**Censored**	**Censored**	**Censored**	**Censored**	**Censored**	
Brodie 1995 A	**LTG**	14	1	0	5	4	0	2	0	0	2	42	70
	CBZ	19	2	0	9	4	0	0	0	0	0	32	66
Brodie 1995 B	**LTG**	4	2	0	8	3	0	0	0	1	0	43	61
	CBZ	16	1	0	9	2	0	0	0	1	0	34	63
Brodie 1999	**LTG**	18	0	0	7	3	0	0	0	2	0	72	102
	CBZ	20	0	0	3	2	0	2	0	1	0	20	48
Eun 2012	**LTG**	3	4	0	0	0	0	0	0	4	0	32	43

Table 4. Reasons for premature discontinuation (withdrawal of allocated treatment) (*Continued*)

	CBZ	3	0	0	0	1	0	0	0	3	0	34	41
Gilad 2007[2]	**LTG**	1	0	0	0	0	0	0	0	0	0	31	32
	CBZ	10	0	0	0	0	0	1	0	0	0	21	32
Lee 2011	**LTG**	4	3	0	2	7	0	0	0	2	0	39	57
	CBZ	7	0	0	3	2	0	0	0	7	0	34	53
Nieto-Barrera 2001[6]	**LTG**	34	12	0	6	12	0	4	0	12	0	339	419
	CBZ	26	4	0	11	1	0	1	0	3	0	156	202
Reunanen 1996	**LTG**	10	1	0	17	3	0	7	0	0	0	192	230
	CBZ	12	0	0	11	6	0	2	0	0	0	90	121
Rowan 2005[2]	**LTG**	20	7	0	15	24	0	7	0	10	5	112	200
	CBZ	54	3	0	14	28	0	14	0	4	10	71	198
Saetre 2007[2]	**LTG**	13	0	0	2	0	10	0	0	0	0	68	93
	CBZ	23	0	0	1	0	6	0	0	0	0	61	91
SANADA 2007[7]	**LTG**	61	60	11	1	8	20	5	23	0	8	181	378
	CBZ	104	43	20	2	7	7	10	25	0	9	151	378
Steinhoff 2005[2]	**LTG**	7	1	0	0	13	3	0	0	0	0	64	88
	CBZ	17	0	0	0	7	5	0	0	0	0	59	88
Werhahn 2015	**LTG**	30	2	0	6	13	1	0	0	0	0	66	118
	CBZ	39	3	0	3	20	0	0	0	0	0	56	121
Total		569	149	31	135	170	52	55	48	50	34	2100	3393
Total LTG		219	93	11	69	90	34	25	23	31	15	1281	1891
Total CBZ		350	56	20	66	80	18	30	25	19	19	819	1502

[1]Primary reason for discontinuation specified - participants may have withdrawn from allocated treatment for a combination of reasons.
[2]Reasons for withdrawal of allocated treatment extracted from trial publications for Gilad 2007, Rowan 2005, Saetre 2007 and Steinhoff 2005. Individual participant data for reasons for treatment withdrawal provided for other trials.

[3]Withdrawal of consent/participant choice classified as an event in this review but censored in included trial (SANAD A 2007). Sensitivity analysis classifying withdrawal of consent as a censored observation did not change the conclusions (results available on request).
[4]Other treatment-related withdrawals: investigator choice (Werhahn 2015), drug-related death, pregnancy or perceived remission (SANAD A 2007). Specified only as 'other reason' for Saetre 2007 and Steinhoff 2005.
[5]Other withdrawals (not treatment-related): epilepsy diagnosis changed (Brodie 1995 A; SANAD A 2007). Specified only as 'other reason' for Rowan 2005 and for seven participants in SANAD A 2007.
[6]One participant (randomised to LTG) with date and reason for withdrawal missing.
[7]Two participants with date of withdrawal missing so not included in analysis of time to treatment withdrawal but with reasons for withdrawal provided (both censored: one withdrew from LTG due to remission of seizures, one withdrew from CBZ due to 'other' non-treatment-related reason).

Table 5. Sensitivity analysis - Reunanen 1996

Treatment	N	Comparator	N	Total	Time to treatment withdrawal		Time to first seizure		Time to 6-month remission	
					HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Lamotrigine (both arms)	230	Carbamazepine	121	351	0.58 (0.35 to 0.92)	0.02	1.24 (0.86 to 1.79)	0.25	0.84 (0.36 to 1.95)	0.68
Lamotrigine 200 mg	115	Lamotrigine 100 mg + carbamazepine	236	351	0.47 (0.25 to 0.86)	0.02	0.96 (0.67 to 1.36)	0.8	0.62 (0.24 to 1.58)	0.32
Lamotrigine 100 mg	115	Lamotrigine 200 mg + carbamazepine	236	351	1.05 (0.63 to 1.75)	0.85	1.29 (0.91 to 1.83)	0.15	1.33 (0.56 to 3.17)	0.52
Lamotrigine 200 mg	115	Carbamazepine	121	236	0.41 (0.21 to 0.78)	0.007	1.12 (0.73 to 1.72)	0.59	0.63 (0.22 to 1.78)	0.39
Lamotrigine 100 mg	115	Carbamazepine	121	236	0.73 (0.43 to 1.26)	0.26	1.37 (0.90 to 2.07)	0.14	1.10 (0.41 to 2.92)	0.86

mg= milligrams per day; HR = hazard ratio; 95% CI = 95% confidence interval

Table 6. Sensitivity analysis - misclassification of seizure type

	Time to treatment withdrawal	Time to first seizure	Time to 6-month remission
Original analysis	P: HR 0.75, 95% CI (0.64 to 0.86) G: HR 0.46, 95% CI (0.30 to 0.71) O: HR 0.71, 95% CI (0.62 to 0.81)	P: HR 1.29, 95% CI (1.14 to 1.45) G: HR 0.98, 95% CI (0.65 to 1.48) O: HR 1.26, 95% CI (1.12 to 1.41)	P: HR 0.87, 95% CI (0.77 to 1.00) G: HR 0.78, 95% CI (0.55 to 1.11) O: HR 0.86, 95% CI (0.76 to 0.97)
Test of subgroup differences	Chi^2 = 4.36, df = 1 (P value = 0.04), I^2 = 77.1%	Chi^2 = 1.53, df = 1 (P value = 0.22), I^2 = 34.5%	Chi^2 = 0.37, df = 1 (P value = 0.54), I^2 = 0%
Generalised onset and age at onset > 30 reclassified as partial onset	P: HR 0.72, 95% CI (0.62 to 0.83) G: HR 0.58, 95% CI (0.32 to 1.06) O: HR 0.71, 95% CI (0.62 to 0.82)	P: HR 1.25, 95% CI (1.11 to 1.41) G: HR 1.17, 95% CI (0.67 to 2.04) O: HR 1.25, 95% CI (1.11 to 1.40)	P: HR 0.85, 95% CI (0.75 to 0.97) G: HR 0.69, 95% CI (0.44 to 1.08) O: HR 0.84, 95% CI (0.74 to 0.95)
Test of subgroup differences	Chi^2 = 0.45, df = 1 (P value = 0.50), I^2 = 0%	Chi^2 = 0.06, df = 1 (P value = 0.81), I^2 = 0%	Chi^2 = 0.80, df = 1 (P value = 0.37), I^2 = 0%
Generalised onset and age at onset > 30 reclassified as uncertain seizure type	P: HR 0.75, 95% CI (0.64 to 0.86) G: HR 0.58, 95% CI (0.32 to 1.06) U: HR 0.62, 95% CI (0.39 to 0.97) O: HR 0.72, 95% CI (0.63 to 0.83)	P: HR 1.29, 95% CI (1.14 to 1.45) G: HR 1.17, 95% CI (0.67 to 2.04) U: HR 0.88, 95% CI (0.58 to 1.33) O: HR 1.24, 95% CI (1.11 to 1.39)	P: HR 0.87, 95% CI (0.77 to 1.00) G: HR 0.69, 95% CI (0.44 to 1.08) U: HR 0.89, 95% CI (0.60 to 1.31) O: HR 0.86, 95% CI (0.76 to 0.97)
Test of subgroup differences	Chi^2 = 1.15, df = 2 (P value = 0.56), I^2 = 0%	Chi^2 = 3.03, df = 2 (P value = 0.22), I^2 = 33.9%	Chi^2 = 1.02, df = 2 (P value = 0.60), I^2 = 0%

CI = confidence interval; G = generalised onset seizures; HR = hazard ratio; O = overall pooled result adjusted by seizure type; P = partial onset seizures; U = uncertain seizure type.

Table 7. Summary of adverse events experienced (seven trials providing detailed individual participant data)

Trial	Number experiencing adverse events			Number of adverse events			Number of adverse events per person (range)		Number of drug-related adverse events[1]			Number of adverse events requiring action/ treatment change			Number of patients needing a treatment change/dose change		
	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	LTG	CBZ	Total	LTG	CBZ	Total	LTG	CBZ	Total
Brodie 1995A	62	58	120	388	322	710	1 to 30	1 to 17	94	124	218	167	111	278	22	32	54
Brodie 1995B	54	58	112	285	291	576	1 to 14	1 to 18	81	125	206	98	81	179	20	40	60
Brodie 1999	91	41	132	338	173	511	1 to 12	1 to 10	109	73	182	92	66	158	39	27	66
Eun 2012	3	6	9	5	8	13	1 to 30	1 to 2	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lee 2011	4	6	10	NA	NA	NA	NA	NA	4	5	9	NA	NA	NA	NA	NA	NA
Nieto-Barrera 2001	218	120	338	524	277	801	1 to 10	1 to 11	238	152	390	116	82	198	70	54	124
Reunanen 1996	124	77	201	451	243	694	1 to 14	1 to 8	138	169	307	156	52	208	23	36	59
SANAA 2007	229	260	489	1038	1339	2377	1 to 25	1 to 37	NA	NA	NA	447	665	1112	120	173	293

Table 7. Summary of adverse events experienced (seven trials providing detailed individual participant data) (*Continued*)

Werhahn 2015	120	110	230	779	770	1549	1 to 53	1 to 30	291	382	673	147	159	306	64	65	129

CBZ = carbamazepine; LTG = lamotrigine; NA = information not available.
[1]In Brodie 1995 A, Brodie 1995 B and Reunanen 1996 adverse events that are "definitely related", in Brodie 1999 and Nieto-Barrera 2001 "a reasonable possibility" that adverse events are treatment-related and in Werhahn 2015 adverse events are "related, probably related or possibility related".

Table 8. Most commonly occurring adverse events (trials providing detailed individual participant data)

Most commonly occurring adverse events	Brodie 1995 A				Brodie 1995 B				Brodie 1999				Nieto-Barrera 2001			
	LTG		CBZ		LTG		CBZ		LTG		CBZ		LTG		CBZ	
	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts
Accidental injury/fracture	2	2	1	1	3	3	2	2	19	12	4	3	7	7	1	1
Aggression	8	6	2	2	0	0	0	0	2	2	0	0	3	3	2	2
Anorex weight loss	2	2	0	0	6	4	0	0	2	2	1	1	6	5	0	0
Anxiety/depression	12	5	7	5	6	3	10	7	3	3	0	0	8	8	2	2
Aphasia	0	0	3	3	0	0	0	0	1	1	2	2	1	1	0	0

Table 8. Most commonly occurring adverse events (trials providing detailed individual participant data) (*Continued*)

Ataxia	2	2	6	5	0	0	0	0	0	0	0	0	2	2	3	3
Chest infection/ bronchitis	11	6	12	8	3	3	1	1	16	12	4	4	18	15	8	8
Cold/ influenza	17	15	4	4	8	8	10	9	7	7	1	1	25	19	11	11
Concentration	0	0	1	1	0	0	1	1	0	0	0	0	4	4	1	1
Confusion	1	1	0	0	0	0	0	0	2	2	1	1	0	0	0	0
Cough wheeze	5	5	5	5	2	2	1	1	6	5	1	1	6	5	6	5
Dental	3	3	2	2	1	1	1	1	1	1	1	1	6	6	3	3
Dizzy/ faint	16	9	16	11	12	9	22	14	26	18	16	14	43	34	16	15
Drowsy fatigued	32	21	52	31	34	20	49	36	25	17	21	15	36	34	45	40
Gastrointestinal disturbances	14	7	10	8	6	6	7	5	29	22	14	11	36	28	17	17

Table 8. Most commonly occurring adverse events (trials providing detailed individual participant data) (*Continued*)

Hair loss	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1	1
Headac mi-graine	77	27	31	17	48	24	52	22	14	10	8	8	56	46	16	14
Im-po-tence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
In-creased wors-ened seizure	1	1	2	2	1	1	0	0	4	4	2	2	14	12	4	4
Kid-ney/ uri-nary prob-lems	3	2	2	2	4	4	1	1	12	10	4	4	4	4	1	1
Mem-ory prob-lems	7	5	2	2	5	3	3	2	4	4	0	0	2	2	1	1
Men-strual prob-lems	3	3	16	12	0	0	4	4	0	0	1	1	0	0	0	0
Mood/ be-haviou change	9	5	6	5	1	1	6	6	5	4	0	0	7	7	4	4
Nau-sea/ vom-iting	17	13	15	11	26	18	21	9	21	17	8	6	26	23	13	11
Pain	19	13	9	6	23	13	7	5	20	17	7	7	13	8	4	2

Table 8. Most commonly occurring adverse events (trials providing detailed individual participant data) (*Continued*)

Pins and needles/ tingling	2	1	3	2	3	3	0	0	1	1	0	0	1	1	0	0
Rash/ skin problems	25	21	20	13	32	15	32	23	31	19	30	14	49	46	32	30
Sleep problems/ dreams	4	3	4	4	8	5	12	5	9	8	0	0	19	19	1	1
Throat tonsil infection	11	7	7	6	6	5	3	3	1	1	0	0	15	14	7	7
Tremor twitch	1	1	2	1	0	0	0	0	1	1	0	0	0	0	2	2
Visual disturbance/ nystagmus	8	4	6	5	2	2	9	6	1	1	4	3	7	7	3	2
Weight gain	3	3	1	1	2	1	0	0	0	0	0	0	3	3	3	3

Table of most commonly occurring adverse events split into two for formatting reasons.
Events = number of adverse events reported; Ppts = number of participants reporting the adverse event (a participant could report the same type of adverse event multiple times).
LTG = lamotrigine; CBZ = carbamazepine
Most common adverse events are defined as events reported 10 or more times in at least one of the seven trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015). Less commonly reported adverse events are not summarised in this table but details are available on request from the review authors. General terminology for the type of adverse events was defined by the review authors based on the individual participant data provided.

Table 9. Most commonly occurring adverse events continued (trials providing detailed individual participant data)

Most commonly occurring adverse events	Reunanen 1996				SANAD A 2007				Werhahn 2015				Total (across seven studies)			
	LTG		CBZ		LTG		CBZ		LTG		CBZ		LTG		CBZ	
	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts	Events	Ppts
Accidental injury/fracture	2	2	0	0	29	19	10	10	16	15	14	7	78	60	32	24
Aggression	1	1	0	0	25	18	41	21	1	1	1	1	40	31	46	26
Anorexia/weight loss	3	2	0	0	12	11	16	13	1	1	0	0	32	27	17	14
Anxiety/depression	4	4	2	2	48	34	46	34	17	14	17	10	98	71	84	60
Aphasia	1	1	0	0	7	4	11	8	1	1	7	5	11	8	23	18
Ataxia	0	0	3	3	38	20	30	22	1	1	0	0	43	25	42	33
Chest infection/bronchitis	3	3	1	1	2	1	6	5	8	8	3	3	61	48	35	30

Table 9. Most commonly occurring adverse events continued (trials providing detailed individual participant data) (*Continued*)

Cold/influenza	9	8	2	2	1	1	3	3	11	9	20	15	78	67	51	45
Concentration	3	3	4	3	8	7	11	11	5	5	3	3	20	19	21	20
Confusion	0	0	0	0	30	19	33	22	4	4	5	5	37	26	39	28
Cough wheeze	3	3	0	0	4	4	1	1	14	11	13	11	40	35	27	24
Dental	6	5	0	0	7	7	16	11	3	2	2	2	27	25	25	20
Dizzy/faint	17	13	20	13	55	32	64	37	74	46	62	41	243	161	216	145
Drowsy fatigued	56	40	77	47	125	72	267	123	30	24	51	46	338	228	562	338
Gastrointestinal disturbances	21	17	10	8	48	31	49	35	45	34	65	42	199	145	172	126
Hair loss	0	0	0	0	6	4	15	6	3	3	3	3	10	8	20	11
Headac migraine	74	42	20	13	95	49	97	43	48	31	40	29	412	229	264	146
Impotence	1	1	0	0	5	4	17	5	0	0	0	0	6	5	17	5

Table 9. Most commonly occurring adverse events continued (trials providing detailed individual participant data) (*Continued*)

Increased worsened seizures	1	1	0	0	29	21	41	25	86	35	58	27	136	75	107	60
Kidney/urinary problems	4	3	2	2	4	3	10	8	16	16	18	17	47	42	38	35
Memory problems	4	4	3	3	38	23	71	34	7	6	7	7	67	47	87	49
Menstrual problems	15	9	13	7	4	4	3	2	0	0	0	0	22	16	37	26
Mood/behaviour change	5	5	4	1	32	22	56	34	2	2	6	5	61	46	82	55
Nausea/vomiting	21	15	15	11	38	23	54	35	30	23	37	24	179	132	163	107
Pain	18	15	1	1	14	9	15	12	55	28	28	20	162	103	71	53
Pins and needles/tingling	3	2	0	0	13	13	23	13	4	4	3	3	27	25	29	18
Rash/skin problems	33	26	17	14	65	36	99	65	23	20	39	32	258	183	269	191

Table 9. Most commonly occurring adverse events continued (trials providing detailed individual participant data) (*Continued*)

Sleep problems/ dreams	27	19	3	2	46	32	24	12	19	18	10	9	132	104	54	33
Throat tonsil infection	13	10	1	1	2	2	1	1	6	4	4	3	54	43	23	21
Tremor twitch	7	6	0	0	28	12	13	10	16	8	10	9	53	28	27	22
Visual disturbance/ nystagmus	6	4	7	5	34	22	33	22	13	10	8	4	71	50	70	47
Weight gain	1	1	0	0	21	13	42	21	4	4	3	3	34	25	49	28

Table of most commonly occurring adverse events split into two for formatting reasons.
Events = number of adverse events reported; Ppts = number of participants reporting the adverse event (a participant could report the same type of adverse event multiple times).
LTG = lamotrigine; CBZ = carbamazepine
Most common adverse events are defined as events reported 10 or more times in at least one of the seven trials (Brodie 1995 A; Brodie 1995 B; Brodie 1999; Nieto-Barrera 2001; Reunanen 1996; SANAD A 2007; Werhahn 2015). Less commonly reported adverse events are not summarised in this table but details are available on request from the review authors. General terminology for the type of adverse events was defined by the review authors based on the individual participant data provided.

APPENDICES

Appendix 1. Epilepsy Specialized Register search strategy

The following was used for the latest update.
#1 lamotrigine or lamictal
#2 MeSH DESCRIPTOR Carbamazepine Explode All
#3 carbamazepine or tegretol
#4 #2 OR #3
#5 #1 AND #4 AND INREGISTER
#6 ((adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*)):TI
#7 (#5 NOT #6) AND >03/12/2015:CRSCREATED

Appendix 2. CENTRAL via CRSO search strategy

For the latest update, the following was used to search CENTRAL via the Cochrane Register of Studies Online (CRSO).
#1 epilepax OR lamictal OR lamotrigin*
#2 MESH DESCRIPTOR Carbamazepine EXPLODE ALL TREES
#3 biston OR carbamazepin* OR carbatrol OR cbz OR epitol OR equetro OR neurotop OR tegretol OR teril OR timonil
#4 #2 OR #3
#5 #1 AND #4
#6 (epilep* OR seizure* OR convuls*):TI,AB,KY
#7 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#8 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#9 #6 OR #7 OR #8
#10 eclampsia:TI
#11 #9 NOT #10
#12 #5 AND #11
#13 ((adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*) NOT (monotherap* or alone or singl*)):TI
#14 #12 NOT #13
#15 ("Conference Abstract"):PT AND INEMBASE
#16 #14 NOT #15
#17 * NOT INMEDLINE AND 03/12/2015 TO 17/10/2016:CD
#18 #16 AND #17
Earlier versions of this review used the following to search CENTRAL in the *Cochrane Library*.
#1 (lamotrigine OR lamictal)
#2 MeSH descriptor Carbamazepine explode all trees
#3 carbamazepine or tegretol
#4 (#1 AND (#2 OR #3))
#5 MeSH descriptor Epilepsy explode all trees
#6 MeSH descriptor Seizures explode all trees
#7 epilep* or seizure* or convulsion*
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)

Appendix 3. MEDLINE search strategy

The following was used for the latest update. It is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011).

1. (lamotrigine or lamictal).tw.
2. carbamazepine/ or carbamazepine.tw. or tegretol.tw.
3. 1 and 2
4. exp Epilepsy/
5. exp Seizures/
6. (epilep$ or seizure$ or convuls$).tw.
7. 4 or 5 or 6
8. exp *Pre-Eclampsia/ or exp *Eclampsia/
9. 7 not 8
10. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
11. clinical trials as topic.sh.
12. trial.ti.
13. 10 or 11 or 12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 3 and 9 and 15
17. ((adjunct$ or “add-on” or “add on” or adjuvant$ or combination$ or polytherap$) not (monotherap$ or alone or singl$)).ti.
18. 16 not 17
19. remove duplicates from 18
20. limit 19 to ed=20151203-20161017

Earlier versions of this review used the following search strategy, based on the previous Cochrane Highly Sensitive Search Strategy for MEDLINE as set out in Appendix 5b of the *Cochrane Handbook for Systematic Reviews of Interventions* (version 4.2.5, updated May 2005) (Higgins 2005).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trials/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. clinical trial.pt.
8. Clinical Trial/
9. (clin$ adj trial$).ab,ti.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ab,ti.
11. exp PLACEBOS/
12. placebo$.ab,ti.
13. random$.ab,ti.
14. exp Research Design/
15. or/1-14
16. (animals not humans).sh.
17. 15 not 16
18. lamotrigine.tw.
19. carbamazepine/ or carbamazepine.tw.
20. exp epilepsy/ or epilep$.tw.
21. exp seizures/ or seizure$.tw.
22. convulsion$.tw.
23. 18 and 19
24. 20 or 21 or 22
25. 23 and 24 and 17

WHAT'S NEW

Last assessed as up-to-date: 17 October 2016.

Date	Event	Description
17 October 2016	New search has been performed	Searches updated 17 October 2016; eight new studies have been included
17 October 2016	New citation required but conclusions have not changed	Conclusions are unchanged.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2006

Date	Event	Description
11 August 2009	Amended	Contact details updated.
27 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

SJ Nolan assessed studies for inclusion in the review update, obtained individual participant data from trial investigators for the review update, assessed risk of bias in all included studies, performed analyses in SAS version 9.3, Stata version 11.2, added survival plots and a 'Summary of findings' table, and updated the text of the review.

C Tudur Smith provided statistical supervision and was involved with data analysis in the original review.

AG Marson independently assessed studies for inclusion, obtained individual participant data from trial investigators, provided guidance with the clinical interpretation of results, assessed eligibility and methodological quality of individual studies, and co-wrote the original review.

J Weston independently assessed risk of bias in all included studies.

DECLARATIONS OF INTEREST

SJ Nolan: none known.

J Weston: none known.

AG Marson was Chief Investigator of SANAD A 2007.

C Tudur Smith was involved in the statistical analysis of SANAD A 2007.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK.

External sources

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

December 2014: the title was changed to specify that the review uses individual participant data.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Carbamazepine [*therapeutic use]; Epilepsies, Partial [drug therapy]; Epilepsy [*drug therapy]; Epilepsy, Generalized [drug therapy]; Randomized Controlled Trials as Topic; Triazines [*therapeutic use]

MeSH check words

Adult; Child; Humans