Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review

Review information

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Dates

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What's new

Date	Event	Description
13 August 2018	New citation: conclusions not changed	Conclusions are unchanged
13 August 2018	Updated	Searches updated on 13 August 2018; no new trials have been included. We have replaced the term 'partial' by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017)

History

Date	Event	Description
1 November 2016	Updated	Searches updated 1 November 2016; no new trials identified
1 November 2016	New citation: conclusions not changed	Conclusions are unchanged
16 September 2014	Updated	Searches updated 16th September 2014
16 September 2014	New citation: conclusions not changed	Three new studies included; conclusions remain the same
1 November 2010	Updated	Searches updated 1st November 2009; no new trials identified
12 August 2009	Amended	Copyedits made at editorial base
23 September 2008	Amended	Converted to new review format
26 September 2007	Updated	Searches updated 27th July 2007; no new trials identified

Abstract

Background

This is an update of a Cochrane Review first published in 2002 and last updated in 2017. This review is one in a series of Cochrane Reviews investigating pair-wise monotherapy comparisons.

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 go into long-term remission shortly after starting drug therapy with a single antiepileptic drug in monotherapy.

Worldwide, carbamazepine and phenytoin are commonly-used broad spectrum antiepileptic drugs, suitable for most epileptic seizure types. Carbamazepine is a current first-line treatment for focal onset seizures in the USA and Europe. Phenytoin is no longer considered a first-line treatment, due to concerns over adverse events associated with its use, but the drug is still commonly used in low- to middle-income countries because of its low cost. No consistent differences in efficacy have been found between carbamazepine and phenytoin in individual trials; however, the confidence intervals generated by these trials are wide, and therefore, synthesising the data of the individual trials may show differences in efficacy.

Objectives

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

Search methods

For the latest update, we searched the following databases on 13 August 2018: the Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy's Specialised Register and CENTRAL; MEDLINE; the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov); and the World Health Organization International Clinical Trials Registry Platform (ICTRP). We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators, and experts in the field.

Selection criteria

Randomised controlled trials comparing monotherapy with either carbamazepine or phenytoin in children or adults with focal onset seizures or generalised onset (tonic-clonic) seizures.

Data collection and analysis

This was an individual participant data (IPD) review. Our primary outcome was time to treatment failure. Our secondary outcomes were time to first seizure post-randomisation, time to six-month remission, time to 12-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

IPD were available for 595 participants out of 1102 eligible individuals, from four out of 11 trials (i.e. 54% of the potential data). For remission outcomes, a HR greater than 1 indicates an advantage for phenytoin; and for first seizure and withdrawal outcomes, a HR greater than 1 indicates an advantage for carbamazepine. Most participants included in analysis (78%) were classified as experiencing focal onset seizures at baseline and only 22% were classified as experiencing generalised onset seizures; the results of this review are therefore mainly applicable to individuals with focal onset seizures.

Results for the primary outcome of the review were: time to treatment failure for any reason related to treatment (pooled HR adjusted for seizure type for 546 participants: 0.94, 95% CI 0.70 to 1.26, moderate-certainty evidence); time to treatment failure due to lack of efficacy (pooled HR adjusted for seizure type for 546 participants: 0.99, 95% CI 0.69 to 1.41, moderate-certainty evidence); both showing no clear difference between the drugs and time to treatment failure due to adverse events (pooled HR adjusted for seizure type for 546 participants: 1.27, 95% CI 0.87 to 1.86, moderate-certainty evidence), showing that treatment failure due to adverse events may occur earlier on carbamazepine than phenytoin, but we cannot rule out a slight advantage to carbamazepine or no difference between the drugs.

For our secondary outcomes (pooled HRs adjusted for seizure type), we did not find any clear differences between carbamazepine and phenytoin: time to first seizure post-randomisation (582 participants): 1.15, 95% CI 0.94 to 1.40, moderate-certainty evidence); time to 12-month remission (551 participants): 1.00, 95% CI 0.79 to 1.26, moderate-certainty evidence); and time to six-month remission (551 participants): 0.90, 95% CI 0.73 to 1.12, moderate-certainty evidence).

For all outcomes, results for individuals with focal onset seizures were similar to overall results (moderate-certainty evidence), and results for the small subgroup of individuals with generalised onset seizures were imprecise, so we cannot rule out an advantage to either drug, or no difference between drugs (low-certainty evidence). There was also evidence that misclassification of seizure type may have confounded the results of this review, particularly for the outcome 'time to treatment failure'. Heterogeneity was present in analysis of 'time to first seizure' for individuals with generalised onset seizures, which could not be explained by subgroup analysis or sensitivity analyses.

Limited information was available about adverse events in the trials and we could not compare the rates of adverse events between carbamazepine and phenytoin. Some adverse events reported on both drugs were abdominal pain, nausea, and vomiting, drowsiness, motor and cognitive disturbances, dysmorphic side effects (such as rash).

Authors' conclusions

Moderate-certainty evidence provided by this systematic review does not show any differences between carbamazepine and phenytoin in terms of effectiveness (retention) or efficacy (seizure recurrence and seizure remission) for individuals with focal onset or generalised onset seizures.

However, some of the trials contributing to the analyses had methodological inadequacies and inconsistencies, which may have had an impact on the results of this review. We therefore do not suggest that results of this review alone should form the basis of a treatment choice for a person with newly-onset seizures. We did not find any evidence to support or refute current treatment policies. We implore that future trials 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

Carbamazepine versus phenytoin (given as a single drug treatment) for epilepsy

This is an updated version of the Cochrane Review previously published in Issue 2, 2017 of the *Cochrane Database of Systematic Reviews*

Background

Epilepsy is a common neurological disorder in which recurrent seizures are caused by abnormal electrical discharges from the brain. 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 focal onset seizures in which the seizure is generated in and affects only one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain). For around 70% of people with epilepsy, generalised onset or focal onset seizures can be controlled by a single antiepileptic drug. Worldwide, phenytoin and carbamazepine are commonly used antiepileptic drugs, although carbamazepine is used more often in the USA and Europe due to concerns over side effects associated with phenytoin. Phenytoin is still commonly used in low- and middle-income countries in Africa, Asia and South America, because of the low cost of the drug.

Objective

For this updated review, we looked at the evidence from 11 randomised controlled clinical trials comparing phenytoin and carbamazepine, based on how effective the drugs were at controlling seizures (i.e. whether people went back to having seizures or had long periods of freedom from seizures (remission)), and how tolerable any

related side effects of the drugs were.

Methods

We were able to combine data for 595 people from four of the 11 trials; for the remaining 507 people from seven trials, information was not available to use in this review. The evidence is current to August 2018.

Key results

This review of trials found no difference between these two drugs for the seizure types studied for the outcomes of treatment failure (withdrawal from treatment for any reason and also withdrawal from treatment due to continuing seizures or due to side effects) and controlling seizures (recurrence of seizures or achievement of a seizure-free period (remission) of six months or 12 months). Three-quarters of the people recruited in the four trials had focal onset seizures and only one quarter of the people recruited in the four trials had generalised onset seizures, so the results of this review mainly apply to people with focal onset seizures and the results are very limited for people with generalised onset seizures. More information is needed for people with generalised onset seizures.

Some side effects reported by people taking carbamazepine and people taking phenytoin were abdominal pain, nausea, vomiting, tiredness, motor problems (such as poor co-ordination), cognitive problems (poor memory), rashes and other skin problems.

Certainty of the evidence

We judged the certainty of the evidence as moderate to low for the evidence of treatment failure, moderate for remission outcomes and low for seizure outcomes, as it is likely that misclassification of seizure type influenced the results of the review. Within two of the trials providing data for this review, the design of the trial meant that the people and treating clinicians knew which medication they were taking. This design may have influenced the results.

Some of the trials contributing data to the review had methodological problems, which may have introduced bias and inconsistent results into this review, and some individuals over the age of 30 with newly-diagnosed generalised onset seizures may have had their seizure type wrongly diagnosed. These problems may have affected the results of this review and we judged the certainty of the evidence provided by this review as moderate for people with focal onset seizures and of low certainty for people with generalised onset seizures. We do not suggest using the results of this review alone for making a choice between carbamazepine or phenytoin for the treatment of epilepsy.

We suggest that all future trials comparing these drugs or any other antiepileptic drugs should be designed using high-quality methods, and that the seizure types of people included in trials should be classified very carefully to ensure results are also of high quality.

Background

This is an updated version of the Cochrane Review previously published in Issue 2, 2017 of the *Cochrane Database of Systematic Reviews* (Nevitt 2017b).

Description of the condition

Epilepsy is a common neurological condition in which recurrent, unprovoked seizures are caused by abnormal electrical discharges from the brain. Epilepsy is a disorder of many heterogeneous seizure types, with an estimated incidence of 33 to 57 per 100,000 person-years worldwide (Annegers 1999; Hirtz 2007; MacDonald 2000; Olaffsson 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 become seizure-free and go into long-term remission shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), and that around 70% of individuals can achieve seizure freedom using a single antiepileptic drug 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 by 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, or alternative treatments such as epilepsy surgery (Kwan 2000).

We study two seizure types in this review: generalised onset seizures (generalised tonic-clonic seizures with or without other generalised seizure types), in which electrical discharges begin in one part of the brain and move throughout the brain; and focal onset seizures, in which the seizure is generated in and affects only one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain).

Description of the intervention

Carbamazepine and phenytoin are among the most commonly used and earliest drugs licensed for the treatment of epileptic seizures; phenytoin has been used as monotherapy for focal seizures and generalised tonic-clonic seizures for over 50 years (Gruber 1962) and carbamazepine for over 30 years (Shakir

1980). Current NICE guidelines (NICE 2012) for adults and children recommend carbamazepine as a first-line treatment for focal onset seizures and as a second-line treatment for generalised tonic-clonic seizures if first-line treatments sodium valproate and lamotrigine are deemed unsuitable; however, there is evidence that carbamazepine may exacerbate some other generalised seizure types such as myoclonic and absence seizures (Liporace 1994; Shields 1983; Snead 1985). Phenytoin is no longer considered a first-line treatment in the USA and most of Europe, due to concerns over adverse events (Wallace 1997; Wilder 1995), but phenytoin is still used as a first-line drug in low- and middle-income countries (Ogunrin 2005; Pal 1998).

Both carbamazepine and phenytoin have been shown to have teratogenic effects (disturbances to foetal development) (Bromley 2014; Weston 2016), where the risk is estimated to be two to three times that of the general population (Gladstone 1992; Meador 2008; Morrow 2006; Nulman 1997). Carbamazepine is associated particularly with neural tube defects (Matlow 2012) and phenytoin is associated with foetal hydantoin syndrome (Scheinfeld 2003), low folic acid levels and megaloblastic anaemia (Carl 1992). Both carbamazepine and phenytoin are associated with an allergic rash (Tennis 1997) in 5% to 10% of users, which on rare occasions may be life-threatening, and phenytoin is also associated with long-term cosmetic changes including gum hyperplasia, acne and coarsening of the facial features (Mattson 1985; Scheinfeld 2003).

How the intervention might work

Antiepileptic drugs suppress seizures by reducing neuronal excitability. Phenytoin and carbamazepine are broad-spectrum treatments suitable for many seizure types and both have an anticonvulsant mechanism through blocking ion channels, binding with neurotransmitter receptors or through inhibiting the metabolism or reuptake of neurotransmitters (Ragsdale 1991; Willow 1985) and the modulation of gamma-aminobutyric acid-A (GABA-A) receptors (Granger 1995).

Why it is important to do this review

The aim of this review is to summarise efficacy and tolerability data from existing trials comparing carbamazepine and phenytoin when used as monotherapy treatments. The adverse event profiles of the two drugs are well documented (see example references from Description of the intervention), but no consistent differences in efficacy have been found between the two drugs from a number of randomised controlled trials (RCTs) individually (for example: De Silva 1996; Heller 1995; Mattson 1985; Ramsay 1983). Although no clear difference in efficacy has been found from individual studies, the confidence intervals generated by these studies are wide. We cannot exclude important differences in efficacy, which may be shown by synthesising the data of the individual trials.

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 help to overcome these problems. This review is one in a series of Cochrane IPD Reviews investigating pair-wise monotherapy comparisons (Marson 2000; Nevitt 2018a; Nevitt 2018b; Nevitt 2018c; Nevitt 2018d; Nevitt 2019; Nolan 2013b). These data have also been included in IPD network meta-analyses of antiepileptic drug monotherapy (Nevitt 2017a; Tudur Smith 2007).

Objectives

To review the time to treatment failure, remission and first seizure with carbamazepine compared with phenytoin when used as monotherapy in people with focal onset seizures (simple or complex focal 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

- Studies must be randomised controlled trials (RCTs) using either an adequate method of allocation concealment (e.g. sealed opaque envelopes) or a quasi-randomised method of allocation (e.g. allocation by date of birth).
- Studies must be of parallel design; cross-over studies are not an appropriate design for measuring the long-term outcomes of interest in this review (see Types of outcome measures).
- Studies must include a comparison of carbamazepine monotherapy with phenytoin monotherapy in individuals

with epilepsy; cluster-randomised studies are therefore not an eligible design.

We included studies regardless of blinding method (unblinded, single-blind or double-blind).

Types of participants

- We included trials recruiting children or adults with focal onset seizures (simple focal, complex focal, or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures (as a primary generalised seizure type), with or without other generalised seizure types (e.g. absence, myoclonic, etc.).
- We excluded studies that recruited only individuals with other generalised seizure types, without generalised tonic-clonic seizures (such as studies recruiting only individuals with a diagnosis of absence seizures or juvenile myoclonic epilepsy, etc.) due to differences in first-line treatment guidelines (NICE 2012).
- We included individuals who had a new diagnosis of epilepsy or who had experienced a relapse following antiepileptic monotherapy withdrawal only, due to differences in first-line treatment guidelines for individuals with drug-resistant epilepsy (NICE 2012).

Types of interventions

Carbamazepine versus phenytoin (any doses) 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 treatment failure (retention time). This was a combined outcome reflecting both efficacy and tolerability, as the following may have led to failure of treatment: continued seizures, side effects, non-compliance or the initiation of additional add-on treatment. 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).

We consider time to treatment failure according to three definitions:

- Time to treatment failure for any treatment-related reason (continued seizures, side effects, non-compliance or the initiation of additional add-on treatment)
- Time to treatment failure due to adverse events (i.e. side effects)
- Time to treatment failure due to lack of efficacy (i.e. continued seizures)

Secondary outcomes

- Time to first seizure post-randomisation
- Time to achieve 12-month remission (seizure-free period)
- Time to achieve six-month remission (seizure-free period)
- Adverse events (including those relating to treatment withdrawal)

Search methods for identification of studies

Electronic searches

We conducted searches for the original review in 1999, and subsequently in 2001, 2003, 2005, July 2007, November 2009, November 2011, October 2013, September 2014, and November 2016. For the latest update we searched the following databases, applying no language restrictions:

- The Cochrane Register of Studies (CRS Web, 13 August 2018), which includes the Cochrane Epilepsy Group's Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the search strategy outlined in Appendix 1.
- MEDLINE (Ovid, 1946 to August 10 2018), using the search strategy outlined in Appendix 2.
- ClinicalTrials.gov (13 August 2018), using the search strategy outlined in Appendix 3.
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, 13 August 2018), using the search strategy outlined in Appendix 4.

Previously we also searched SCOPUS (1823 to 16th September 2014), using the search strategy outlined in Appendix 5, as an alternative to Embase, but this is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

Searching other resources

In addition, we handsearched relevant journals, reviewed the reference lists of retrieved studies to search for additional reports of relevant studies, contacted Novartis (manufacturers of carbamazepine), Parke-Davis (manufacturers of phenytoin), and experts in the field for information on any ongoing studies, and original investigators of relevant trials found.

Data collection and analysis

Selection of studies

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

discussion.

Data extraction and management

We requested the following IPD 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 failure and reasons for treatment failure
- dose
- dates of dose changes

For each trial for which we did not obtain 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.

In one study (Mattson 1985), seizure data were provided in terms of the number of seizures recorded between each follow-up visit rather than specific dates of seizures. To enable us to calculate time-to-event outcomes, we applied linear interpolation to approximate dates of seizures between follow-up visits, assuming a uniform seizure rate. For example, if four seizures were recorded between two visits which occurred on 1st March 1990 and 1st May 1990 (an interval of 61 days), then the date of first seizure would be approximately 13th March 1990 (i.e. 61 days divided by number of seizures plus 1 rounded to the next day, i.e. 13 days). This allowed us to compute an estimate of the time to six-month remission, 12-month remission, and the time to first seizure.

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

We calculated time to first seizure from the date of randomisation to the date that their first seizure was estimated 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. These methods had been used in the remaining three trials (De Silva 1996; Heller 1995; Ogunrin 2005) for which outcome data (dates of seizures after randomisation) were provided directly.

In one trial (Ogunrin 2005), all participants completed the 12-week trial duration without failing treatment or withdrawing from the study. For three trials (De Silva 1996; Heller 1995; Mattson 1985) we extracted dates and reason for treatment failure or withdrawal from trial case report forms for the original review. Two review authors (SJN and CTS) independently extracted data from all case report forms, resolving disagreements by reconsidering the case report forms at conference. For the analysis of time-to-event data, we defined an 'event' as either the failure of the allocated treatment because of poor seizure control, adverse events, or both. We also classed non-compliance with the treatment regimen or the addition of another antiepileptic drug as 'events' for the outcome 'time to treatment failure.' We censored the outcome if treatment was stopped because the individual achieved a period of remission or if the individual was still on allocated treatment at the end of follow-up.

Assessment of risk of bias in included studies

Two review authors (SJN and CTS) independently assessed all included studies for risks of bias (Higgins 2017), resolving any disagreements by discussion. The domains assessed as being at low, high or unclear risk of bias were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. We took

into account all available information for an included study when making 'Risk of bias' judgements, including multiple publications of the study and additional information provided from study authors with IPD.

Measures of treatment effect

We measured all outcomes in this review as time-to-event outcomes with the hazard ratio (HR) and 95% confidence interval (CI) 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

We did not have any unit of analysis issues. The unit of allocation and analysis was the individual for all included trials, and no trials included in meta-analysis were of a repeated measures (longitudinal) nature or of a cross-over design.

Dealing with missing data

For each trial where IPD were supplied, we reproduced information from trial results where possible, and performed the following 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;
- We reviewed the chronological randomisation sequence, and checked the balance of participant characteristics, 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), 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 CTS) undertook all full quality and 'Risk of bias' assessments. In theory, a review using IPD should overcome issues of reporting biases, as unpublished data can be provided and unpublished outcomes calculated. Any selective reporting bias detected could be assessed with the ORBIT classification system (Kirkham 2010).

Data synthesis

We carried out our analysis on an intention-to-treat basis; i.e. 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', and 'Time to first seizure post-randomisation', we did not censor participants if treatment was withdrawn or failed.

For all outcomes, we investigated the relationship between the time-to-event and treatment effect of the antiepileptic drugs. We used Cox proportional hazards regression models to obtain trial-specific estimates of log (HR), or treatment effect and associated standard errors in Stata Statistical Software, version 14 (Stata 2015). 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 and by visually inspecting survival plots for each outcome of each trial. We evaluated overall estimates of HRs (with 95% confidence intervals (CIs)), using the generic inverse variance method in Data and analyses. We expressed results as a HR and its 95% CI.

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

Subgroup analysis and investigation of heterogeneity

To examine the potential impact of seizure type on results, we stratified all analyses by seizure type (focal onset versus generalised onset), according to the classification of main seizure type at baseline. We classified focal seizures (simple or complex), and focal secondarily generalised seizures as focal epilepsy.

We classified primarily generalised seizures as generalised epilepsy. We conducted a Chi^2 test of interaction between treatment and seizure 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.

Sensitivity analysis

Misclassification of seizure type is a recognised problem in epilepsy, whereby some people with generalised seizures have been mistakenly classed as having focal 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 affected the results of three reviews in our series of pair-wise reviews for monotherapy in epilepsy comparing carbamazepine to phenobarbitone, phenytoin and sodium valproate, in which around 30% to 50% of participants analysed may have had their seizure type misclassified as generalised onset (Marson 2000; Nevitt 2017b; Nevitt 2018b). Given the overlap with studies contributing to this review and the other reviews within the series, we suspected that misclassification of seizure type could also be likely in this review, and so we examined the distribution of age at onset for individuals with generalised seizures.

De Silva 1996 was a paediatric study and Mattson 1985 recruited participants with focal seizures only, so there were no participants with new-onset generalised seizures over the age of 30 in these studies. Twenty-nine out of 72 individuals (42%) with generalised onset seizures were over the age of 30 in Heller 1995, and six out of 29 individuals (21%) with generalised onset seizures were over the age of 30 in Ogunrin 2005. Therefore out of 150 participants from the four studies providing IPD, 35 (23%) may have been wrongly classified as having new-onset generalised seizures.

We undertook the following two sensitivity analyses to investigate misclassification for each outcome:

1. We reclassified the 35 individuals with generalised seizure types and age at onset greater than 30 into an 'uncertain seizure type' group.
2. We reclassified the 35 individuals with generalised seizures and age of onset greater than 30 as having focal seizures.

'Summary of findings' tables and certainty of the evidence (GRADE)

For the 2015 update, we 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 table 1 reports the primary outcome of 'Time to treatment failure' in the subgroups of participants with focal onset seizures, generalised onset seizures and overall adjusted by seizure type.

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

We determined the certainty 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 we considered the limitation serious and by two levels for very serious.

Results

Description of studies

Results of the search

For previous versions of the review, we identified 655 records from the databases and search strategies outlined in Electronic searches. We found three further records by handsearching and checking reference lists of included studies. We removed 265 duplicate records and screened 393 records (title and abstract) for inclusion in the review. We excluded 354 records based on title and abstract and assessed 39 full-text articles for inclusion in the review. We excluded 16 studies (reported in 23 full-text articles) from the review (see Excluded studies below) and included 11 trials (reported in 16 full-text articles) in the review (see Included studies below).

For the 2019 update of this review we identified 41 records from the databases.We removed 12 duplicate records and screened 29 records (title and abstract) for inclusion in the review. All 29 records were clearly irrelevant and we excluded them.

See Figure 1 for PRISMA study flow diagram (Moher 2009) for the eligibility screening of all studies identified in searches for all versions of this review (previous searches and the most recent search in August 2018).

Included studies

We included 11 trials in this review (Callaghan 1985; Czapinski 1997; De Silva 1996; Forsythe 1991; Heller 1995; Mattson 1985; Miura 1993; Ogunrin 2005; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995). One trial was available in abstract form only (Czapinski 1997).

One trial recruited individuals of all ages (Callaghan 1985), three trials recruited children only (defined as under the age of 16 in De Silva 1996, and under the age of 14 in Forsythe 1991 and Miura 1993); and the remaining seven trials recruited adults only. Three trials defined adults as individuals above the age of 18 (Czapinski 1997; Mattson 1985; Ramsay 1983), one trial classed adults as older than 13 years (Heller 1995), two trials classed adults as older than 14 years (Ogunrin 2005; Ravi Sudhir 1995) and one trials classed adults as older than 15 years (Pulliainen 1994).

Nine trials recruited individuals with focal onset seizures and generalised onset seizures (Callaghan 1985; De Silva 1996; Forsythe 1991; Heller 1995; Miura 1993; Ogunrin 2005; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995), and two trials recruited individuals with focal onset seizures only (Czapinski 1997; Mattson 1985). Ten trials recruited individuals with new-onset seizures or previously untreated seizures, or both (Callaghan

1985; Czapinski 1997; De Silva 1996; Forsythe 1991; Heller 1995; Miura 1993; Ogunrin 2005; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995). One trial recruited "previously untreated or under treated" individuals (Mattson 1985).

Six trials were conducted in Europe (Callaghan 1985; Czapinski 1997; De Silva 1996; Forsythe 1991; Heller 1995; Pulliainen 1994), two in the USA (Mattson 1985; Ramsay 1983), one in Nigeria (Ogunrin 2005), one in India (Ravi Sudhir 1995), and one in Japan (Miura 1993).

Individual participant data (IPD) could not be supplied for seven trials (Callaghan 1985; Czapinski 1997; Forsythe 1991; Miura 1993; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995), in which 507 individuals had been randomised to either phenytoin or carbamazepine. None of these seven trials reported the specific time-to-event outcomes chosen for this systematic review.

Forsythe 1991 presented times at which the allocated drug was withdrawn and the reason for withdrawal in the trial publication for each individual. Hence, we were able to incorporate this trial into the analysis of 'Time to treatment failure'. For each participant, 'withdrawal and time of occurrence by month' was presented; therefore, to calculate 'Time to treatment failure' we assumed that, for example, if withdrawal occurred during the fifth month, that withdrawal occurred halfway between the fifth and sixth month (i.e. participants spent 167 full days on treatment before withdrawal).

We could not extract sufficient aggregate data from the trial publication in any other trial, and we therefore could not include them in data synthesis. Full details of outcomes considered and a summary of results in each eligible trial for which IPD were not available can be found in Table 1.

IPD were provided by trial authors for the four remaining trials which recruited 595 participants, representing 54% of individuals from 1102 individuals in all eligible trials (De Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005). Two trials (Mattson 1985; Ogunrin 2005) directly provided computerised data, and the authors of the other two trials (Heller 1995; De Silva 1996) supplied a combination of both computerised and paper-based (although mostly computerised) data.

Data were available for the following subject characteristics (percentage of 595 participants with data available): seizure type (100%), sex (99%, missing for two participants in Mattson 1985), age at randomisation (98%, data missing for three participants from Mattson 1985 and Heller 1995), drug randomised (99%, data missing for six participants in De Silva 1996), time since first seizure to randomisation (98%, data missing for eight participants from Mattson 1985 and Heller 1995), number of seizures in six months prior to randomisation (93%, data missing for 41 participants, all 37 participants from Ogunrin 2005 and four participants from Mattson 1985 and Heller 1995). See the Characteristics of included studies table and Table 2 for further details.

The results of neurological examinations were provided for 326 participants (55%) from three trials (De Silva 1996; Heller 1995; Ogunrin 2005), electroencephalographic (EEG) results were provided for 316 participants (53%) from one trial (Mattson 1985) and computerised tomography/magnetic resonance imaging (CT/MRI) results were provided for 324 participants (54%) in two trials (Mattson 1985; Ogunrin 2005).

Excluded studies

We excluded six studies which were not RCTs (Bird 1966; Kuzuya 1993; Rysz 1994; Sabers 1995; Shorvon 1978; Zeng 2010). We excluded seven trials which did not use carbamazepine and phenytoin in monotherapy (Bittencourt 1993; Canadian Study 1998; Hakami 2012; Kosteljanetz 1979; Rajotte 1967; Simonsen 1976; Troupin 1975). We excluded two trials which did not make a randomised comparison between carbamazepine and phenytoin monotherapy (Kaminow 2003; Shakir 1980), and we excluded one trial which had a cross-over design (Cereghino 1974). See Characteristics of excluded studies for further details.

Risk of bias in included studies

For further details see Characteristics of included studies, Figure 2 and Figure 3.

Allocation (selection bias)

Trials for which individual participant data (IPD) were provided

Three trials reported adequate methods of randomisation and allocation concealment; two trials used permuted blocks to generate a random list and concealed allocation by using sealed opaque envelopes (De Silva 1996; Heller 1995), and one trial used number tables to generate a random list and concealed allocation by allocating the randomised drug on a different site from where participants were randomised (Ogunrin 2005). We judged all three trials to be at low risk of selection bias. One trial reported only that participants were randomised with stratification for seizure type (Mattson 1985); no further information was provided in the study publication or from the authors about the methods of generating the random list and concealment of allocation, so we rated this trial at unclear risk of selection bias.

Trials for which no IPD were available

Two trials reported inadequate methods of randomisation and allocation concealment; Forsythe 1991 reported a method of quota allocation and did not report how allocation was concealed, and Callaghan 1985 reported a method of randomisation and allocation concealment based on two Latin squares which

seems to take into account the drug preference of participants (the “drug of first preference” was selected from the randomisation list on a sequential basis); we judged both of these trials to be at high risk of selection bias. The remaining five trials (Czapinski 1997; Miura 1993; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995) reported that the participants were "randomised" or "randomly allocated" etc., but did not provide information on the method of generation of the random list or of allocation concealment, and we judged them to be at unclear risk of selection bias.

Blinding (performance bias and detection bias)

Trials for which IPD were provided

One trial double-blinded participants and personnel using an additional blank tablet (low risk of performance bias; Mattson 1985), but it is unclear if the outcome assessor was blinded in this trial (unclear risk of detection bias). One trial blinded participants and the outcome assessors who performed cognitive testing (low risk of performance and detection bias), but a research assistant recruiting participants and providing counselling on medication adherence was not blinded (Ogunrin 2005). Two trials were unblinded for “practical and ethical reasons” (De Silva 1996; Heller 1995), but it is unclear whether the outcomes of these trials were influenced by the lack of masking.

Trials for which no IPD were available

One trial double-blinded participants and personnel using an additional blank tablet (low risk of performance bias; Ramsay 1983), but it is unclear if the outcome assessor was blinded in this trial (unclear risk of detection bias). Two trials single-blinded the outcome assessor who performed cognitive testing (low risk of detection bias); in one of these trials (Forsythe 1991) the participants and personnel were unblinded (high risk of performance bias), and in the other (Pulliainen 1994) it was unclear if the participants and personnel were blinded or not (unclear risk of performance bias). The remaining four trials (Callaghan 1985; Czapinski 1997; Miura 1993; Ravi Sudhir 1995) did not provide any information on masking of participants, personnel or outcome assessors, so we judged these trials to be at unclear risk of performance bias and detection bias.

Incomplete outcome data (attrition bias)

Trials for which IPD were provided

In theory, a review using IPD 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 four trials (De Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005) provided IPD for all randomised individuals and reported the extent of follow-up for each individual, so we judged all four trials to be at low risk of attrition bias. We queried any missing data with the original study authors. From the information provided by the authors, we deemed the small amount of missing data (Included studies) to be missing at random and that they did not have an effect on our analysis.

Trials for which no IPD were available

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 (Callaghan 1985; Forsythe 1991; Miura 1993). One trial reported attrition rates, but it was unclear if all participants were analysed, so we rated this trial at unclear risk of attrition bias (Czapinski 1997). Three studies excluded between 20% and 35% of participants from the final analysis for “non-compliance”, loss to follow-up or uncontrolled seizures, and included only those who completed the analysis. This approach is not intention-to-treat, so we deemed these three studies to be at high risk of bias (Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995)

Selective reporting (reporting bias)

We requested study protocols in all IPD requests, but protocols were not available for any of the 11 included trials, so we made a judgement of the risks of bias based on the information included in the publications, or from the IPD we received (see Characteristics of included studies for more information).

Trials for which IPD were provided

In theory, a review using IPD should overcome issues of reporting biases, as unpublished data can be provided and unpublished outcomes calculated. We acquired sufficient IPD to calculate the four outcomes ('Time to treatment failure', 'Time to six-month remission','Time to 12-month remission' and 'Time to first seizure') for three of the four trials (De Silva 1996; Heller 1995; Mattson 1985). The study duration of Ogunrin 2005 was 12 weeks and all randomised participants completed the study without withdrawing, so we could only calculate 'Time to first seizure' for this study. We judged all four studies to be at low risk of reporting bias.

Trials for which no IPD were available

Seizure outcomes or adverse events, or both, were fully reported in three trials and we judged these trials to be at low risk of reporting bias (Callaghan 1985; Miura 1993; Ramsay 1983). Two trials reported cognitive outcomes and adverse events, but no seizure outcomes (Forsythe 1991; Pulliainen 1994), and one trial reported cognitive outcomes only, but no adverse events or seizure outcomes (Ravi Sudhir 1995); however, as no protocols were available for these three trials, we do not know whether seizure outcomes or recording of adverse events, or both, were planned a priori. One trial was in abstract form

only and did not provide sufficient information to assess selective reporting bias (Czapinski 1997). We judged all of these trials to be at unclear risk of reporting bias.

Other potential sources of bias

We did not identify any other potential source of bias in any of the 11 included studies.

Effects of interventions

We have provided a summary of the outcomes reported in trials for which no IPD were available in Table 2.

See Table 3 for details about the number of individuals contributing IPD to each analysis, Summary of findings table 1 for a summary of the results for the primary outcome 'Time to treatment failure' (stratified by seizure type), and Summary of findings table 2 for a summary of results for the secondary outcomes 'Time to first seizure' and 'Time to 12-month remission'.

Survival curve plots are shown in Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11; Figure 12; Figure 13; Figure 14 and Figure 15 .

We used Stata software version 14 to produce all survival curve plots using data from all trials providing IPD combined (Stata 2015). We note that participants with event times of zero (i.e. those who experienced treatment failure or experienced seizure recurrence on the day of randomisation) are not included in the 'Numbers at risk' on the graphs and that data are not stratified by trial within these survival curve plots. 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.

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

Primary outcomes

Time to treatment failure (retention time)

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

Time to treatment failure and reason for treatment failure or withdrawal were available for 546 participants from three of the four trials providing IPD: 99% of 558 participants from De Silva 1996, Heller 1995 and Mattson 1985 (see Included studies), and 49.5% of the 1102 participants from the 11 included studies. Although two participants failed treatment (one in each group) in De Silva 1996, a reason for treatment failure was not available and could not be determined from the case notes. Similarly in Heller 1995, for one participant taking carbamazepine, the reason for treatment failure was not available and could not be determined from case notes. Also in Heller 1995, two participants (both on phenytoin) had reasons for treatment failure recorded but no date of treatment failure. We have not included these five participants with missing reasons for treatment failure or treatment failure dates from the two trials in analysis of time to treatment failure. Sufficient IPD were available in the published report for a further 43 participants from one trial (Forsythe 1991). Therefore, 589 participants from four trials were available for the analysis of this outcome (see Table 3). See Table 4 for reasons for premature termination of allocated treatment and how we classified these treatment failures or withdrawals in analysis.

Out of the 592 participants for whom we had reasons for treatment failure or withdrawal (De Silva 1996; Forsythe 1991; Heller 1995; Mattson 1985), 353 participants prematurely withdrew from treatment (60% of total participants): 173 out of 291 participants randomised to carbamazepine (59%), and 180 out of 301 participants randomised to phenytoin (60%).

We deemed 210 participants (59% of total treatment failures) to have withdrawn for reasons related to the trial drug, 103 (60%), on carbamazepine and 107 (59%), on phenytoin, and we classed these reasons as 'events' in analysis. The most common treatment-related reason for treatment failure was a combination of adverse events and lack of efficacy: 81 withdrawals (39% of total treatment failures), 41 (40% of total treatment failures) on carbamazepine and 40 (37% of total treatment failures) on phenytoin. Non-compliance with treatment or participant choice was the treatment-related reason in 21% of total treatment failures, lack of efficacy in 22% of total treatment failures and adverse events in 18% of total treatment failures.

We classed the other 143 reasons (70 on carbamazepine and 73 on phenytoin), which were mostly participants going into remission (43% of other withdrawals) and losses to follow-up (31% of other withdrawals), to be not related to the treatment and censored these participants in the analysis, in addition to the 239 participants (118 on carbamazepine and 121 on phenytoin) who completed the trial without withdrawing or failing treatment.

Considering 'Time to treatment failure for any reason related to the treatment', the overall pooled HR (for 589 participants in four trials) was 0.99 (95% CI 0.76 to 1.31; P = 0.97; moderate-certainty evidence; Analysis 1.1), indicating no clear advantage to either drug. No important heterogeneity was present between trials (I^2 = 3%).

Considering 'Time to treatment failure due to adverse events' (all other reasons for treatment failure or treatment withdrawal censored in analysis), the overall pooled HR (for 589 participants in four trials) was 1.35 (95% CI 0.93

to 1.95; P = 0.12; moderate-certainty evidence; Analysis 1.2), suggesting a potential advantage for phenytoin, which is not statistically significant; in other words, treatment failure due to adverse events may occur earlier on carbamazepine than phenytoin but we cannot rule out a slight advantage to carbamazepine or no difference between the drugs.

A moderate amount of heterogeneity was present between trials (I^2 = 40%). From visual inspection of the forest plot of Analysis 1.2, the HRs of two trials were around 1.15 to 1.16 (De Silva 1996; Mattson 1985) while the HRs of the other two trials were much larger (HRs of 3.83 and 4.57 respectively) and confidence intervals of the HRs were very wide (Forsythe 1991; Heller 1995). Table 4 shows an imbalance between the drugs between the number of participants failing treatment due to adverse events in Forsythe 1991 and Heller 1995; very few participants on phenytoin failed treatment due to adverse events compared to participants on carbamazepine in these trials. This explains the extreme and imprecise HRs for these two trials and may explain the moderate amount of heterogeneity between trials.

Considering 'Time to treatment failure due to lack of efficacy' (all other reasons for treatment failure or treatment withdrawal censored in analysis), the overall pooled HR (for 589 participants in four trials) was 1.02 (95% CI 0.72 to 1.44; P = 0.92; moderate-certainty evidence; Analysis 1.3), indicating no clear advantage to either drug. No heterogeneity was present between trials (I^2 = 0%).

Subgroup analyses: seizure type (focal versus generalised onset)

Treatment failure data for 43 participants extracted from Forsythe 1991 did not distinguish between epilepsy type (focal onset or generalised onset) and we therefore could not include them in the meta-analysis stratified by epilepsy type.

Considering 'Time to treatment failure for any reason related to the treatment', for individuals with focal onset seizures (428 participants from three trials), the pooled HR was 0.83 (95% CI 0.61 to 1.13; P = 0.23; I^2 = 0%; moderate-certainty evidence), suggesting a potential advantage for carbamazepine which is not statistically significant. For individuals with generalised onset seizures (118 participants from two trials), the pooled HR was 2.38 (95% CI 1.04 to 5.47; P = 0.04; I^2 = 0%; low-certainty evidence), indicating a statistically significant advantage for phenytoin; in other words, for individuals with generalised seizures, carbamazepine treatment was withdrawn significantly earlier than phenytoin in the two included trials, but the confidence interval around the pooled HR was wide so we are unsure of the magnitude of the advantage to phenytoin. There was statistically significant evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.02; I^2 = 81.7%; Analysis 1.4).

The overall pooled HR (adjusted by epilepsy type for 546 participants from three trials) was 0.94 (95% CI 0.70 to 1.26; P = 0.68; moderate-certainty evidence; Analysis 1.4). This result is similar to the unadjusted pooled HR (Analysis 1.1), and conclusions remain unchanged following the exclusion of 43 individuals in the stratified analysis (Forsythe 1991). Heterogeneity present within analysis has increased from I^2= 3% to I^2= 35%, probably due to the observed interaction between epilepsy type and treatment effect. This is explored further in the section on 'Sensitivity analysis' (see below).

Considering 'Time to treatment failure due to adverse events', for individuals with focal onset seizures (428 participants from three trials), the pooled HR was 1.19 (95% CI 0.80 to 1.78; P = 0.38; I^2 = 0%; moderate-certainty evidence), suggesting a potential advantage for phenytoin which is not statistically significant. For individuals with generalised onset seizures (118 participants from two trials), the pooled HR was 2.31 (95% CI 0.68 to 7.81; P = 0.18; I^2 = 60%; low-certainty evidence), suggesting a potential advantage for phenytoin, but the confidence interval is wide, so we cannot rule out an advantage to carbamazepine or no difference between drugs. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.31; I^2 = 2.2%; Analysis 1.5).

There was a large amount of heterogeneity between trials (I^2 = 60%) and when we repeated the analysis with a random-effects model, the confidence interval around the pooled HR becomes even wider, at 2.82 (95% CI 0.37 to 21.32; P = 0.32). This heterogeneity is probably due to the imbalance between the drugs between the number of participants failing treatment due to adverse events; very few participants on phenytoin failed treatment due to adverse events compared to participants on carbamazepine in Heller 1995, while the numbers of participants failing each drug in De Silva 1996 were more balanced (see Table 4).

The overall pooled HR (adjusted by epilepsy type for 546 participants from three trials) was 1.27 (95% CI 0.87 to 1.86; P = 0.21; I^2 = 3%; moderate-certainty evidence; Analysis 1.5). This result is similar to the unadjusted pooled HR (Analysis 1.2), and conclusions remain unchanged following the exclusion of participants from Forsythe 1991.

Considering 'Time to treatment failure due to lack of efficacy', for individuals with focal onset seizures (428 participants from three trials), the pooled HR was 0.88 (95% CI 0.60 to 1.30; P = 0.52; I^2 = 0%; moderate-certainty evidence), suggesting a potential advantage for carbamazepine which is not statistically significant. For individuals with generalised onset seizures (118 participants from two trials), the pooled HR was 1.86 (95% CI 0.74 to 4.67; P = 0.19; I^2 = 0%; low-certainty evidence), suggesting a potential advantage for phenytoin, but the confidence interval is wide, so we cannot rule out an advantage to carbamazepine or no difference between drugs. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.14; I^2= 53.2%; Analysis 1.6).

The overall pooled HR (adjusted by epilepsy type for 546 participants from three trials) was 0.99 (95% CI 0.69 to 1.41; P = 0.94; I^2 = 0%; moderate-certainty evidence; Analysis 1.6). This result is similar to the unadjusted pooled HR (Analysis 1.3), and conclusions remain unchanged following the exclusion of participants from Forsythe 1991.

Sensitivity analysis

We conducted sensitivity analyses to investigate misclassification of seizure type, reclassifying 29 individuals from Heller 1995 aged 30 or older with new-onset generalised seizures to focal onset seizures or to an uncertain seizure type. The results of the two sensitivity analyses are shown in Table 5. It was not possible to estimate a HR and 95% CI for 'Time to treatment failure due to adverse events' or 'Time to treatment failure due to lack of efficacy' for the 29 participants reclassified as an uncertain seizure type, as none of these participants failed phenytoin treatment due to adverse events or failed carbamazepine treatment due to lack of efficacy.

Considering 'Time to treatment failure for any reason related to the treatment', following reclassification, for the remaining 89 participants with generalised onset seizures the pooled HR was 1.96 (95% CI 0.81 to 4.78; P = 0.14; I^2 = 0%), which still indicates a potential advantage for phenytoin, but this advantage is no longer statistically significant. Reclassifying these 29 participants as having new-onset focal seizures, the pooled HR for 457 participants is 0.88 (95% CI 0.65 to 1.19; P = 0.40; I^2 = 0%), indicating a potential slight advantage for carbamazepine, which is not statistically significant.

Overall, following this reclassification for all participants adjusted for epilepsy type, the numerical result was very similar, indicating no clear difference between the drugs (pooled HR 0.96, 95% CI 0.72 to 1.27; P = 0.76). However, following reclassification, heterogeneity in the analysis of all participants was greatly reduced, from I^2 = 35% to I^2 = 6%, and the observed interaction between seizure type (generalised versus focal onset) and treatment effect is no longer statistically significant (test of subgroup differences: P = 0.09; I^2 = 64.6%).

Overall results for all participants adjusted for epilepsy type were similar when the 29 participants were reclassified as of uncertain seizure type, again indicating no clear difference between the drugs (pooled HR 0.93, 95% CI 0.70 to 1.24; P = 0.63). Again following this reclassification, heterogeneity in the analysis of all participants was greatly reduced, from I^2 = 35% to I^2 = 7%, and the observed interaction between seizure type (generalised versus focal onset) and treatment effect is no longer statistically significant (test of subgroup differences: P = 0.07; I^2 = 61.8%).

Considering time to treatment failure due to adverse events, following reclassification, for the remaining 89 participants with generalised onset seizures, conclusions were unchanged suggesting a potential advantage to phenytoin but the confidence interval is wide, so we cannot rule out an advantage to carbamazepine or no difference between drugs (pooled HR 1.72, 95% CI 0.51 to 5.87). Within the subgroup of participants with generalised onset seizures, heterogeneity was reduced from I^2 = 60% to I^2 = 0% as the reclassification of participants resulted in a more balanced number of participants failing phenytoin or failing carbamazepine treatment in Heller 1995. Reclassifying the 29 participants as having new-onset focal seizures, the pooled HRs for 457 participants with focal onset seizures and for all participants adjusted for epilepsy type were similar to the original analyses, and conclusions were unchanged (see Table 5).

Considering 'Time to treatment failure due to lack of efficacy', following reclassification, the pooled HRs for the remaining 89 participants with generalised onset seizures, for 457 participants with focal onset seizures and for all participants adjusted for epilepsy type were similar to the original analyses and conclusions were unchanged (see Table 5).

Secondary outcomes

Time to first seizure post-randomisation

For this outcome, a HR greater than one indicates a clinical advantage for carbamazepine.

Data for 582 participants (99% of 558 randomised participants from De Silva 1996, Heller 1995 and Mattson 1985 (see Included studies), 100% from Ogunrin 2005, and 53% of the 1102 participants from the 11 included studies) from all four trials providing IPD were available for the analysis of this outcome.

Three hundred and eighty-three out of 582 participants (66%) experienced a recurrence of seizures: 192 out of 297 (64%) on phenytoin and 191 out of 285 on carbamazepine (67%). The overall pooled HR (for 582 participants) was 1.13 (95% CI 0.92 to 1.39; P = 0.23; moderate-certainty evidence; Analysis 1.7), suggesting a potential advantage for phenytoin, which is not statistically significant; in other words, seizure recurrence may occur earlier on carbamazepine than phenytoin but we cannot rule out a slight advantage to carbamazepine or no difference between the drugs. No important heterogeneity was present between trials (I^2 = 34%).

Subgroup analyses: seizure type (focal versus generalised onset)

For the participants with focal onset seizures (432 participants, four trials), the pooled HR was 1.13 (95% CI 0.89 to 1.43; P = 0.32; I^2 = 0%, moderate-certainty evidence), indicating a slight advantage for phenytoin, which is not statistically significant; in other words, seizure recurrence may occur earlier on carbamazepine than on phenytoin, but we cannot rule out a slight advantage to carbamazepine or no difference between drugs.

For the participants with generalised onset seizures (150 participants, three trials), the pooled HR was 1.19 (95% CI 0.81 to 1.75; P = 0.38; I^2 = 0%; moderate-certainty evidence), again indicating a slight advantage for

phenytoin, which is not statistically significant. A moderate amount of statistical heterogeneity was present between trials for generalised onset seizures (I^2 = 45%). This heterogeneity is explored further in the 'Sensitivity analysis' section (see below).

Overall, the pooled HR (adjusted for epilepsy type for 582 participants, four trials) was 1.15 (95% CI 0.94 to 1.40; P = 0.19), suggesting a slight advantage for phenytoin, which is not statistically significant. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.83; I^2 = 0%; Analysis 1.8).

Sensitivity analysis

We conducted sensitivity analyses to investigate misclassification of seizure type, reclassifying 35 individuals from Heller 1995 and Ogunrin 2005 aged 30 or older with new-onset generalised seizures to focal onset seizures or to an uncertain seizure type. The results of the two sensitivity analyses are shown in Table 5.

Following reclassification, the pooled HRs for the remaining 115 participants with generalised onset seizures, for 457 participants with focal onset seizures and for all participants adjusted for epilepsy type were similar to the original analyses and conclusions were unchanged (see Table 5). Following reclassification, heterogeneity in the subgroup of participants with generalised onset seizures is increased from I^2 = 45% to I^2 = 53%, so it does not appear that this heterogeneity is due to misclassification of seizure type.

Considering other potential reasons for the heterogeneity in the subgroup of participants with generalised onset seizures, there is a difference in the direction of effects of the three studies, with De Silva 1996 and Ogunrin 2005 showing a potential advantage for phenytoin and Heller 1995 showing a potential advantage for carbamazepine, yet all study-specific HRs have wide confidence intervals due to small numbers of participants with generalised onset seizures. From correspondence with the study authors, we know that De Silva 1996 and Heller 1995 were conducted under the same protocol and therefore trial characteristics should be homogeneous; the only difference between the two studies is within the age groups recruited (De Silva 1996 recruited children only and Heller 1995 recruited adults only). We therefore performed a further subgroup analysis by adult versus paediatric studies (Ogunrin 2005 also recruited adults only). For 101 adults with generalised onset seizures, the pooled HR was 0.98 (95% CI 0.60 to 1.61; P = 0.94), indicating no clear advantage for either drug, and for 49 children with generalised onset seizures in De Silva 1996 the HR was 1.59 (95% CI 0.86 to 2.94; P = 0.14), indicating a potential advantage for phenytoin, which is not statistically significant. The test for interaction between age groups recruited (adults versus children) and treatment effect was not significant (P = 0.23; I^2 = 30.9%). However, participant numbers with generalised onset seizures are quite limited in this review, so we may not have had the power to detect a difference between age groups.

In Ogunrin 2005 there is an indication that the proportional hazards assumption may be violated (see Data synthesis); the P value of time-varying covariate is 0.02 and visual inspection of the cumulative incidence plot (Figure 16) shows clear crossing of the curves at around 10 days. In other words, up to 10 days seizure recurrence seems to be occurring earlier on phenytoin, but this changes earlier with carbamazepine after 10 days.

As a sensitivity analysis, we fitted a piecewise Cox regression model to investigate any change in treatment effect over time, assuming proportional hazards within each interval. From the visual inspection of Figure 16, the follow-up period of Ogunrin 2005 is split into two intervals; 0 to 10 days and over 10 days (maximum follow-up is 84 days). We can estimate separate HRs for each interval as follows:

- For the interval 0 to 10 days (13 events in 37 participants at risk) the HR is 0.67 (95% CI 0.20 to 2.22; P = 0.51), suggesting a potential advantage for carbamazepine, which is not statistically significant.
- For intervals over 10 days (eight events in 24 participants at risk) the HR is 3.13 (95% CI 1.09 to 9.09; P = 0.03), suggesting a large statistically significant advantage for phenytoin. Visual inspection of Figure 16 also shows a clear advantage for phenytoin after 10 days.

These results suggest some indication of a change in treatment effect over time, with a slight early advantage for carbamazepine, changing to a large statistically significant advantage for phenytoin later in the study, and support the hypothesis of a change in treatment effect over time for Ogunrin 2005. Ogunrin 2005 is by far the shortest of the studies for which we have IPD (maximum follow-up was 84 days in Ogunrin 2005 compared to maximum follow-up of 3995 days in Heller 1995, 4589 days in De Silva 1996 and 1838 days in Mattson 1985), and we did not find statistically significant evidence of a difference between carbamazepine and phenytoin for 'Time to first seizure after randomisation' in any of the three studies with a longer duration (see Analysis 1.7). The apparent large advantage for phenytoin from 10 to 84 days in Ogunrin 2005, may therefore have reduced in size or even changed direction to favour carbamazepine if this study had continued for a longer duration.

Time to achieve 12-month remission

For this outcome, a HR less than one indicates a clinical advantage for phenytoin.

Data for 551 participants (99% of 558 randomised participants from De Silva 1996, Heller 1995 and Mattson 1985 (see Included studies) and 50% of the 1102 participants from the 11 included studies) from three out of four trials providing IPD were available for the analysis of this outcome. Individuals were followed up for a maximum of 12 weeks in Ogunrin 2005, so could not contribute to this outcome.

Two hundred and eighty-nine out of 551 participants (52%) achieved 12-month remission: 155 out of 282 (55%)

on phenytoin and 134 out of 269 (50%) on carbamazepine. The overall pooled HR (for 551 participants) was 1.01 (95% CI 0.80 to 1.27; P = 0.95; moderate-certainty evidence; Analysis 1.9), indicating no clear differences between the drugs. No heterogeneity was present between trials (I^2 = 0%).

Subgroup analyses: seizure type (focal versus generalised onset)

For the participants with focal onset seizures (430 participants, three trials), the pooled HR was 1.06 (95% CI 0.80 to 1.42; P = 0.68; I^2 = 0%; moderate-certainty evidence), indicating no clear advantage for either drug. For the participants with generalised onset seizures (121 participants, two trials), the pooled HR was 0.88 (95% CI 0.58 to 1.33; P = 0.54; I^2 = 73%; moderate-certainty evidence), indicating a potential advantage for phenytoin, which is not statistically significant; in other words, 12-month remission may occur earlier on phenytoin than carbamazepine, but we cannot rule out a slight advantage to carbamazepine or no difference between drugs. There was substantial heterogeneity present between the two trials for individuals with generalised onset seizures (I^2 = 73%). When we repeated the analysis with a random-effects model, the pooled HR was 0.86 (95% CI 0.39 to 1.89; P = 0.70). This heterogeneity is explored further in the 'Sensitivity analysis' section below. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.46; I^2 = 0%; Analysis 1.10).

Overall, the pooled HR (adjusted for epilepsy type for 551 participants in three trials) was 1.00 (95% CI 0.79 to 1.26; P = 0.99; I^2 = 16%; moderate-certainty evidence), indicating no clear advantage for either drug.

Sensitivity analysis

We conducted sensitivity analyses to investigate misclassification of seizure type, reclassifying 29 individuals from Heller 1995 aged 30 or older with new-onset generalised seizures to focal onset seizures or to an uncertain seizure type. The results of the two sensitivity analyses are shown in Table 5.

The pooled HR for 92 participants with generalised onset seizures was 0.69 (95% CI 0.43 to 1.11; P = 0.13; I^2 = 0%), showing that all of the heterogeneity in Analysis 1.10 is explained by misclassification of participants with generalised onset seizures. Reclassifying the 29 participants as having new-onset focal seizures, the pooled HRs for 461 participants with focal onset seizures and for all participants adjusted for epilepsy type were similar to the original analyses and conclusions were unchanged (see Table 5).

In De Silva 1996 there is an indication that the proportional hazards assumption may be violated (see Data synthesis); the P value of time-varying covariate is 0.051 and visual inspection of the cumulative incidence plot (Figure 16) shows crossing of the curves at around 2500 days. In other words, up to 2500 days, participants on phenytoin seem to be achieving 12-month remission quicker than those on carbamazepine, but this changes after 2500 days; however, participant numbers are small (15 participants at risk out of 108 randomised), so small changes may be magnified in this case.

As a sensitivity analysis, we fitted a piecewise Cox regression model to investigate any change in treatment effect over time, assuming proportional hazards within each interval. From the visual inspection of Figure 16, the follow-up period of De Silva 1996 is split into two intervals; 0 to 2500 days and over 2500 days (maximum follow-up was 4163 days). We can estimate separate HRs for each interval as follows:

- For the interval 0 to 2500 days (88 events in 108 participants at risk) the HR is 0.78 (95% CI 0.51 to 1.19; P = 0.23), suggesting a potential advantage for phenytoin, which is not statistically significant.
- For the interval over 2500 days (five events in 15 participants at risk) the HR is 1.59 (95% CI 0.64 to 4.00; P = 0.32), suggesting a potential advantage for carbamazepine, which is not statistically significant.

These results suggest some indication of a change in treatment effect over time, with a potential advantage for phenytoin earlier on in the study, changing to a potential advantage for carbamazepine later in the study. However, CIs of estimates are wide, particularly for the HR after 2500 days, due to small numbers of events and participants at risk, and it is likely that the observed change of direction in effect at around 2500 days is due to small participant numbers after this time.

Time to achieve six-month remission

For this outcome, a HR less than one indicates a clinical advantage for phenytoin.

Data for 551 participants (99% of 558 randomised participants from De Silva 1996, Heller 1995 and Mattson 1985 (see Included studies) and 50% of the 1102 participants from the 11 included studies) from three out of four trials providing IPD were available for the analysis of this outcome. Individuals were followed up for a maximum of 12 weeks in Ogunrin 2005, so could not contribute to this outcome.

Three hundred and thirty-eight out of 551 participants (61%) achieved six-month remission: 179 out of 282 (63%) on phenytoin and 159 out of 269 (59%) on carbamazepine.

The overall pooled HR (for 551 participants) was 0.92 (95% CI 0.74 to 1.14; P = 0.45; moderate-certainty evidence; Analysis 1.11), indicating no clear differences between the drugs. No heterogeneity was present between trials (I^2 = 0%).

Subgroup analyses: seizure type (focal versus generalised onset)

For the participants with focal onset seizures (430 participants, three trials), the pooled HR was 0.98 (95% CI 0.75 to 1.27; P = 0.85; I^2 = 0%; moderate-certainty evidence), indicating no clear advantage for either drug. For

the participants with generalised onset seizures (121, two trials), the pooled HR was 0.77 (95% CI 0.52 to 1.13; P = 0.18; I^2 = 39%; moderate-certainty evidence), indicating a potential advantage for phenytoin, which is not statistically significant; in other words, six-month remission may occur earlier on phenytoin than carbamazepine, but we cannot rule out a slight advantage to carbamazepine or no difference between drugs. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.31; I^2 = 3.2%; Analysis 1.12).

Overall, the pooled HR (adjusted for epilepsy type for 551 participants, three trials) was 0.90 (95% CI 0.73 to 1.12; P = 0.36; I^2 = 0%; moderate-certainty evidence), indicating a potential advantage for phenytoin, which is not statistically significant; in other words, six-month remission may occur earlier on phenytoin than carbamazepine, but we cannot rule out a slight advantage to carbamazepine or no difference between drugs.

Sensitivity analysis

We conducted sensitivity analyses to investigate misclassification of seizure type, reclassifying 29 individuals from Heller 1995 aged 30 or older with new-onset generalised seizures to focal onset seizures or an uncertain seizure type. The results of the two sensitivity analyses are shown in Table 5.

The pooled HR for 92 participants with generalised onset seizures was 0.59 (95% CI 0.37 to 0.93; P = 0.02; I^2 = 0%), indicating that for these individuals, six-month remission occurred significantly earlier on phenytoin than carbamazepine. As observed for 'Time to 12-month remission', all of the heterogeneity in Analysis 1.12 is explained by misclassification of participants with generalised onset seizures. Reclassifying the 29 participants as having new-onset focal seizures, the pooled HRs for 461 participants with focal onset seizures and for all participants adjusted for epilepsy type were similar to the original analyses, and conclusions were unchanged (see Table 5).

In De Silva 1996, there is an indication that the proportional hazards assumption may be violated (see Data synthesis); the P value of time-varying covariate is 0.066 and visual inspection of the cumulative incidence plot (Figure 16) shows crossing of the curves at several points at around 1000 days, 1750 days and 3500 days, suggesting several changes in the direction of treatment effect over time. As in the sensitivity analysis of De Silva 1996 in 'Time to 12-month remission', after 1000 days participant numbers are small (18 participants at risk out of 108 randomised), so small changes may be magnified in the later stages of study follow-up.

As a sensitivity analysis, we fitted a piecewise Cox regression model to investigate any change in treatment effect over time, assuming proportional hazards within each interval. From the visual inspection of Figure 16, the follow-up period of De Silva 1996 is split into three intervals; 0 to 1000 days, 1000 to 1750 days, and over 1750 days (maximum follow-up is 4163 days). We did not consider an interval of 3500 days to the end of the study, due to very small participant numbers at this time (three participants at risk). We can estimate separate HRs for each interval as follows:

- For the interval 0 to 1000 days (87 events in 108 participants at risk) the HR is 0.85 (95% CI 0.55 to 1.30; P = 0.44), suggesting a potential advantage for phenytoin, which is not statistically significant.
- For the interval 1000 to 1750 days (three events in 18 participants at risk) the HR is 0.79 (95% CI 0.24 to 2.70; P = 0.71), again suggesting a potential advantage for phenytoin, which is not statistically significant.
- For intervals over 1750 days (five events in 14 participants at risk) the HR is 1.32 (95% CI 0.72 to 2.44; P = 0.37), suggesting a potential advantage for carbamazepine, which is not statistically significant.

As above, these results suggest some indication of a change in treatment effect over time, with an advantage for phenytoin earlier on in the study, changing to an advantage for carbamazepine later in the study. However, CIs of estimates are again wide, due to small participant numbers in the later two intervals, so we do not have statistically significant evidence to support the hypothesis of a change in treatment effect over time for De Silva 1996, and conclude that the apparent changes of direction in effect at later stages of the study are likely to be due to small participant numbers.

Adverse events

We extracted all reported information related to adverse events from the study publications. Miura 1993 and Ravi Sudhir 1995 did not report any information on adverse events and we are uncertain without access to protocols if these data were collected (see Selective reporting (reporting bias)). See Table 6 for details of all adverse event data provided in the other nine studies included in this review. In summary, the adverse events reported by two or more studies in this review are as follows:

For carbamazepine

- Gastrointestinal side effects including abdominal pain, nausea and vomiting: (Forsythe 1991; Mattson 1985; Ramsay 1983).
- Drowsiness/tiredness/fatigue/sedation: (Callaghan 1985; De Silva 1996; Forsythe 1991; Heller 1995; Pulliainen 1994; Ramsay 1983).
- Rash: (Callaghan 1985; Heller 1995; Mattson 1985; Ogunrin 2005).
- Decreased libido, or impotence, or both: (Mattson 1985; Ramsay 1983).
- Headaches: (Forsythe 1991; Heller 1995; Ramsay 1983).
- Motor disturbance (including ataxia, inco-ordination, nystagmus, tremor, slowing of mental function, inattention, psychomotor retardation): (Forsythe 1991; Mattson 1985; Ogunrin 2005; Ramsay 1983).

- Dysmorphic and idiosyncratic side effects (gum hypertrophy, hirsutism, acne, other skin problems): (Mattson 1985; Pulliainen 1994; Ramsay 1983).
- Cognitive side effects and impairments, including depression and memory problems: (Heller 1995; Ogunrin 2005; Pulliainen 1994; Ramsay 1983).

For phenytoin

- Gastrointestinal side effects including abdominal pain, nausea and vomiting: (Mattson 1985; Ramsay 1983).
- Drowsiness/tiredness/fatigue/sedation: (De Silva 1996; Pulliainen 1994; Ramsay 1983).
- Rash: (Callaghan 1985; De Silva 1996; Mattson 1985; Ogunrin 2005).
- Decreased libido, or impotence, or both: (Mattson 1985; Ramsay 1983).
- Motor disturbance (including ataxia, inco-ordination, nystagmus, tremor, slowing of mental function, inattention, psychomotor retardation): (Callaghan 1985; Mattson 1985; Ogunrin 2005; Ramsay 1983).
- Dysmorphic and idiosyncratic side effects (gum hypertrophy, hirsutism, acne, other skin problems): (Callaghan 1985; De Silva 1996; Mattson 1985; Ramsay 1983).
- Cognitive side effects and impairments, including depression and memory problems: (Forsythe 1991; Ogunrin 2005; Ramsay 1983).

Because of the differences in methods of reporting adverse event data across the studies (see Table 6), it is difficult to summarise the 'most common' adverse events overall across the 11 studies, or to deduce whether carbamazepine or phenytoin are most associated with specific adverse events. Adverse event data for individuals were not included in the original IPD requests for earlier versions of this review, but will be sought in all future IPD requests.

Discussion

Summary of main results

The results of this review provide moderate-certainty evidence that for our primary global effectiveness outcome 'Time to treatment failure for any reason related to treatment' (and also for 'Time to treatment failure due to lack of efficacy'), for all individuals, we found no clear differences between the drugs. The results of this review also provide moderate-certainty evidence that for all individuals, treatment failure due to adverse events may occur earlier on carbamazepine than phenytoin, but we cannot rule out a slight advantage to carbamazepine or no difference between the drugs.

Considering differences between the subgroups of individuals with focal onset seizures and generalised onset seizures for 'Time to treatment failure for any reason related to treatment', given that subgroup sizes are unbalanced (118 with generalised seizures (22%) and 428 with focal seizures (78%) as classified by the studies) and that results may be confounded by misclassification of seizure type in up to 29 participants, we cannot draw any firm conclusions about an association between treatment and seizure type (i.e. an advantage for carbamazepine for individuals with focal onset seizures and an advantage for phenytoin for individuals with generalised onset seizures). We require more evidence, particularly from individuals with correctly classified generalised onset seizures, to inform this analysis. Furthermore, due to small numbers of participants within the two seizure-type subgroups failing treatment due to adverse events or due to lack of efficacy, we cannot draw any firm conclusions about any differences between the drugs in the two seizure-type subgroups for 'Time to treatment failure due to adverse events' or 'Time to treatment failure due to lack of efficacy'.

Similarly for the secondary outcomes 'Time to first seizure', 'Time to 12-month remission', 'Time to six-month remission', we found no consistent or statistically significant differences between phenytoin and carbamazepine for participants overall or by seizure type. Evidence for these outcomes was of moderate to low certainty. However, subgroups of participants by seizure type are again unbalanced in size, and misclassification of seizure types may have confounded analyses. More evidence is needed, particularly from individuals with correctly classified generalised seizures, to inform all of the outcomes of this review.

Limited information was available about adverse events in the trials and we could not compare the rates of adverse events between carbamazepine and phenytoin. Some adverse events reported on both drugs were abdominal pain, nausea, and vomiting, drowsiness, motor and cognitive disturbances, dysmorphic side effects (such as rash).

For all outcomes in this review, for all individuals and for the subgroups of participants with focal onset seizures and generalised onset seizures, we therefore encourage caution in the interpretation of the results and we would not encourage basing a choice between these two drugs on the results of this review alone.

Overall completeness and applicability of evidence

We believe our systematic electronic searches identified all relevant evidence for this review. We have gratefully received individual participant data (IPD) for 595 individuals (54% of individuals from all eligible trials) from the authors of four trials (De Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005), which included a comparison of phenytoin versus carbamazepine for the treatment of epilepsy. However, 484 individuals (44%) from six relevant trials (Callaghan 1985; Czapinski 1997; Miura 1993; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995) could not be included in any analysis as IPD were not available and outcomes of

interest were not reported in the published reports. Sufficient data for 23 individuals (2%) were published in one trial (Forsythe 1991) to contribute to analysis for the primary outcome 'Time to treatment failure', but insufficient data were available to include these individuals in the analyses by seizure type and the analyses of other outcomes. Having to exclude data from half of eligible participants due to lack of IPD and insufficient reporting in study publications is likely to have impacted on the applicability of the evidence, but it is difficult to quantify exactly how large this impact was on the results of this review (see Potential biases in the review process).

Three trials contributing around 80% of the participant data to this review recruited adults only (Heller 1995; Mattson 1985; Ogunrin 2005); the remaining study was a paediatric trial (De Silva 1996). Also, the largest single trial contributing over half of the participant data to this review (Mattson 1985) recruited individuals with focal onset seizures only, so that only around 25% of participants included in this review were experiencing generalised onset seizures. Furthermore, there is evidence within this review to suggest that up to 23% of individuals with new-onset generalised seizures may have had their seizure type misclassified. For these reasons, the results of this review may not be fully generalisable to children or to individuals with generalised onset seizures, and more evidence is required from participants with generalised seizure types.

Quality of the evidence

The four trials for which IPD were available were generally at low risk of bias (see Figure 3). Three of the trials contributing around half of the participant data to this review described adequate methods of randomisation and allocation concealment (De Silva 1996; Heller 1995; Ogunrin 2005), but the largest single trial, contributing 54% of participant data (Mattson 1985), did not describe the method of randomisation and allocation concealment used, and this information was not available from study authors. We are uncertain whether this lack of information has impacted on the results of this review. Two of the trials providing IPD blinded participants and outcome assessors (Mattson 1985; Ogunrin 2005) and the other two trials (De Silva 1996; Heller 1995) were designed as pragmatic open-label trials, as masking of treatment would not be "practicable or ethical", would "undermine compliance" and would have "introduced bias due to a very large drop-out rate." For the three trials providing treatment failure information, the treatment failure or withdrawal rate in the double-blinded trial (Mattson 1985) was 40%, and the treatment failure or withdrawal rates were 36% and 24% in De Silva 1996 and Heller 1995 respectively (29.5% treatment failure/withdrawal rate overall in the two open-label studies, which is statistically significantly lower than the treatment failure/withdrawal rate in the double-blind study; P = 0.009). It is therefore debatable whether a double-blind design is the most appropriate for trials of monotherapy in epilepsy of long duration and whether such a design does have an impact upon the dropout rate and therefore on the results of the trial. Further differences between the studies were in the population recruited (age of participants and seizure types). We discuss these differences below in Overall completeness and applicability of evidence.

Trials for which no IPD were available were generally of poorer quality than those for which we had IPD, with two studies describing inadequate methods of randomisation or allocation concealment (Callaghan 1985; Forsythe 1991), three trials presenting incomplete outcome data following exclusion of participants (Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995) and two trials providing very limited information on trial methodology, available only in abstract or summary form (Czapinski 1997; Miura 1993).

Overall, due to the documented methodological issues that may have introduced heterogeneity, biases and imprecision into our meta-analyses, we rated the evidence provided in this review as of moderate certainty for all individuals and for individuals with focal onset seizures, and of low certainty for individuals with generalised onset seizures according to GRADE criteria (see Summary of findings table 1; Summary of findings table 2). We would not encourage basing a choice between these two drugs on the results of this review alone.

Potential biases in the review process

We were provided with IPD for 595 out of 1102 eligible participants (54%) from four out of 11 studies included; we conducted all analyses as IPD analyses. Such an approach has many advantages, such as allowing us to standardise definitions of outcomes across trials, and attrition and reporting biases being reduced as we can perform additional analyses and calculate additional outcomes from unpublished data. For the outcomes we used in this review which are of a time-to-event nature, an IPD approach is considered to be the 'gold standard' approach to analysis (Parmar 1998).

However, despite the advantages of this approach, for reasons out of our control we were not able to obtain IPD for 507 participants from seven eligible studies and except for one study of 43 participants reporting data which could contribute to our primary outcome 'Time to treatment failure' (Forsythe 1991), no aggregate data were available for our outcomes of interest in study publications. We therefore had to exclude around half of eligible participants from our analyses, which may have introduced bias into the review.

From the results reported in these seven studies (see Table 1 for narrative description of the results of each study), only one study showed a statistically significant difference in efficacy between carbamazepine and phenytoin for participants with generalised onset seizures (73% seizure-free with phenytoin versus 39% seizure-free with carbamazepine (Callaghan 1985)). There was no difference between treatments for participants with focal onset seizures (P = 0.006). Some significant differences between carbamazepine and phenytoin in terms of specific adverse events and cognitive adverse events were also

reported (see Table 1). However, no consistent differences in efficacy or tolerability were reported in these seven studies, so it is unclear whether the exclusion of these studies from our meta-analysis has impacted upon our results and conclusions. Furthermore, five of the seven studies that we could not include in meta-analysis were at high risk of bias for at least one methodological aspect (see Figure 3), so inclusion of these data may have introduced bias into our results.

We have evidence from previous reviews conducted by the Cochrane Epilepsy Group (Marson 2000; Nevitt 2017b; Nevitt 2018b) that misclassification of seizure type is an important issue in epilepsy trials. We believe that the results of the original trials and hence the results of this meta-analysis may have been confounded by classification bias, particularly the 35 individuals from two trials (Heller 1995; Ogunrin 2005) classified with new-onset generalised seizures over the age of 30 (Malafosse 1994). Sensitivity analysis to investigate potential misclassification of these individuals may impact upon our conclusion for two outcomes ('Time to treatment failure' and 'Time to six-month remission'), and explains all heterogeneity among individuals with generalised onset seizures for the outcomes 'Time to 12-month remission' and 'Time to six-month remission'. Both studies with potentially misclassified participants used the International League Against Epilepsy (ILAE) classification of 1981 (Commission 1981) to classify generalised onset and focal onset seizures. Heller 1995 was initiated before the publication of the revised ILAE classification in 1989 (Commission 1989), so some individuals in Heller 1995 may have been classified correctly according to Commission 1981 but misclassified by the revised Commission 1989. Ogunrin 2005 was initiated around 10 years after the publication of Commission 1989, but this study was conducted in Nigeria, a low-income country without access to the same facilities as trials conducted in the USA and Europe; seizure types were therefore classified clinically, and electroencephalographs (EEGs)/magnetic resonance imaging (MRI) were not required for diagnosis of epilepsy. Clinical classification may have contributed to potential misclassification in this study.

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 seizure times. We are aware that an individual's seizure patterns may be non-linear; we therefore recommend caution when interpreting the numerical results of the seizure-related outcomes. We also made an assumption that the treatment effect for each outcome did not change over time (proportional hazards assumption, see Data synthesis). For three of the outcomes, there was evidence that this assumption may have been violated for one of the trials. Sensitivity analysis showed that changes in treatment effect tended to occur in the later stages of the studies when small participant numbers were being followed up, so small changes in treatment effect would be magnified. Furthermore, we are aware that in trials of long duration (e.g. De Silva 1996, Heller 1995 and Mattson 1985 followed up participants for between three and 10 years), the assumption of treatment effect remaining constant over time may not be appropriate. For example, there is likely to be a difference between participants who achieve immediate remission compared with participants who achieve later remission, and we encourage that results should be interpreted with this limitation in mind.

Agreements and disagreements with other studies or reviews

No single trial included in this review has found convincing differences between phenytoin and carbamazepine with respect to seizure control or seizure type. To our knowledge, together with previous versions of this review, this is the only systematic review and meta-analysis that compares carbamazepine and phenytoin monotherapy for focal onset seizures and generalised onset tonic-clonic seizures. A network meta-analysis has been published (Nevitt 2017a), comparing all direct and indirect evidence from carbamazepine, phenytoin and other standard and new antiepileptic drugs licensed for monotherapy. It also found no differences between carbamazepine and phenytoin for the outcomes specified in this review.

Authors' conclusions

Implications for practice

Moderate-certainty evidence provided by this systematic review does not show any differences between carbamazepine and phenytoin in terms of effectiveness (retention) or efficacy (seizure recurrence and seizure remission) for individuals with focal onset or generalised onset seizures.

However, some of the trials contributing to the analyses had methodological inadequacies and inconsistencies, which may have had an impact on the results of this review. We therefore do not suggest that the results of this review alone should form the basis of a treatment choice for a patient with newly-onset seizures.

Current guidelines recommend carbamazepine or lamotrigine as first-line treatment for adults and children with new-onset focal seizures, and sodium valproate for adults and children with new-onset generalised seizures (NICE 2012); the results of this review do not inform current treatment policy.

Implications for research

We found no consistent differences in efficacy between these two commonly used antiepileptic drugs in individual trials. The methodological quality of trials comparing these two drugs has been variable, producing variable individual trial results and introducing heterogeneity into the pooled results of this review, which makes the pooled results difficult to interpret. If there are differences in efficacy and tolerability across heterogeneous populations of individuals such as those studied here, it is likely that

these differences are small. It has been argued that future comparative antiepileptic drug trials should be powered to establish equivalence (Jones 1996), and therefore be capable of detecting what is considered to be the smallest important clinical difference.

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 about 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 drugs with documented adverse event profiles, such as phenytoin, masking of treatment may be important to avoid preconceptions of the drug being more likely to be associated with serious adverse events, which the results of this review did not show.

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 most 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 (IPD) available for analysis, we are left with no choice but to exclude a proportion of relevant evidence from the review, which will impact upon the interpretation of the results of the review and 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 treatment failure (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 IPD approach.

A network meta-analysis has also been published (Nevitt 2017a), comparing all direct and indirect evidence from carbamazepine, phenytoin and other standard and new antiepileptic drugs licensed for monotherapy. This network meta-analysis will be updated as more information becomes available; however, we acknowledge that as phenytoin is no longer considered to be a first-line agent for newly-diagnosed individuals, in favour of newer agents, such as lamotrigine and levetiracetam, it is unlikely that a substantial amount of new evidence will become available for this review.

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We are greatly indebted to all of the original trialists that have provided individual participant data (IPD) and input into this review.

We are grateful to the Cochrane Epilepsy Group Information Specialist, Graham Chan, for performing all electronic searches.

We acknowledge Jennifer Weston, Paula Williamson and Helen Clough for contributions to the original review and previous versions of the review.

Contributions of authors

SJN assessed trials for inclusion in the review update, obtained individual participant data from trial investigators for the review update, assessed risks of bias in all included trials, performed analyses in Stata version 14, added survival plots and a 'Summary of findings' table, and updated the text of the review.

CTS was the lead investigator on the original review, assessed eligibility and methodological quality of original individual trials, organised and cleaned the IPD sets, performed data validation checks and statistical analyses, and co-wrote the original review.

AGM obtained IPD from trial investigators, provided guidance with the clinical interpretation of results, assessed eligibility and methodological quality of individual trials, and co-wrote the original review.

Declarations of interest

SJN: none known

AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).
CTS: none known

Differences between protocol and review

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

Update 2015: we added sensitivity analyses following identification of potential misclassification of seizure type. The existence of misclassification in the individual studies could not have been known at the time of writing the original protocol.

Update 2015: we added the outcomes 'Time to six-month remission' and 'Adverse events' for consistency with the other reviews in the series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons.

Update 2015: we added 'Summary of findings' tables to the update in 2015 and added text in the Methods section for 'Summary of findings' tables in August 2016.

Update 2018: 'Time to withdrawal of allocated treatment' was re-defined as 'Time to treatment failure', due to feedback received from the Cochrane Editorial Unit regarding potential confusion regarding 'withdrawal' as a positive or negative outcome of anti-epileptic monotherapy.

Additional analyses of 'Time to treatment failure' (due to lack of efficacy and due to adverse events), following feedback on published anti-epileptic drug monotherapy reviews that these sub-outcomes would be useful for clinical practice.

The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

We exclude cross-over designs, as this design is not appropriate for measuring the long-term outcomes of the review; previously included cross-over studies are now excluded from the review.

Published notes

Sarah J Nolan (lead author of 2015 update) is now Sarah J Nevitt

Characteristics of studies

Characteristics of included studies

Callaghan 1985

Methods	Single-centre, randomised, parallel-group trial of people referred for assessment at Cork Regional Hospital, Ireland 3 treatment arms: carbamazepine, phenytoin, sodium valproate Dates conducted: Not stated
Participants	Adults and children with a minimum of 2 untreated generalised or focal seizures in the 6 months preceding the study Number randomised: PHT = 58, CBZ = 59 52 participants (44%) with focal epilepsy. 61 (52%) men Age range: 4 to 75 years. Duration of treatment (range in months): 3 to 47
Interventions	Monotherapy with PHT or CBZ Mean daily dose achieved: PHT = 5.4 mg/kg, CBZ = 10.9 mg/kg
Outcomes	Seizure control: excellent (complete freedom of seizures) good (> 50% reduction in seizure frequency) poor (< 50% reduction in seizure frequency or no response) Side effects
Notes	Outcomes chosen for this review were not reported. IPD not available Funding: Grants provided by Labaz, Geigy, and Warner-Lambert. Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation based on 2 Latin squares without stratification. The first, second and third preference of drug for the participant appears to have been taken into account in the process. Unclear if assignment was completely random
Allocation concealment (selection bias)	High risk	An independent person (department secretary) selected the “drug of first preference” from randomisation list on a sequential basis. Allocation not adequately concealed
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported. Intention-to-treat approach taken, all randomised participants analysed
Selective reporting (reporting bias)	Low risk	Primary outcomes (seizure control) and secondary outcomes (side effects) reported sufficiently
Other bias	Low risk	No other bias detected

Czapinski 1997

Methods	36-month randomised, comparative study 4 treatment arms: carbamazepine, sodium valproate, phenytoin, phenobarbitone Dates conducted and country: Not stated (assumed conducted in Poland due to author affiliations)
Participants	Adults with newly-diagnosed epilepsy Number randomised: CBZ = 30, PHT = 30 100% focal epilepsy, Age range: 18 to 40 years Percentage men and range of follow-up not mentioned (outcome recorded at 3 years)
Interventions	Monotherapy with PHT or CBZ Starting doses CBZ = 400 mg/day, PHT = 200 mg/day. Dose achieved not stated
Outcomes	Proportion achieving 24-month remission at 3 years and exclusions after randomisation due to adverse effects or no efficacy
Notes	Abstract only. Outcomes chosen for this review were not reported, IPD pledged but not received Funding: Not stated Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study randomised but no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Unclear risk	"Exclusion rates" reported for all treatment groups, no further information provided
Selective reporting (reporting bias)	Unclear risk	No protocol available, study available in abstract format only. Outcomes for this review not available
Other bias	Low risk	No other bias detected

De Silva 1996

Methods	Randomised, parallel-group, open-label paediatric study conducted in 2 centres in the United Kingdom Trial conducted between 1981 and 1987 4 treatment arms: carbamazepine, sodium valproate, phenytoin, phenobarbitone
Participants	Children with newly-diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the study) Number randomised: CBZ = 54, PHT = 54 64 children (59%) with focal epilepsy. 59 (55%) boys. Mean age (range): 9 (3 to 16) years Range of follow-up: 3 to 88 (months)
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 175 mg/day, CBZ = 400 mg/day
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse effects and withdrawals due to adverse events
Notes	IPD provided for all randomised participants. All outcomes in this review calculated from IPD Funding: support provided by the Medical Research Council, the Health Promotion Trust, Ciba-Geigy, Parke-Davis, and Sanofi Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed by 4 batches of concealed opaque envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Unblinded; authors state masking of treatment would not be “practicable or ethical” and would “undermine compliance.” Unclear if lack of masking influenced outcome
Blinding of outcome assessment (detection bias)	Unclear risk	Unblinded; authors state masking of treatment would not be “practicable or ethical” and would “undermine compliance.” Unclear if lack of masking influenced outcome
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided[1]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[1]
Other bias	Low risk	No other bias detected

Forsythe 1991

Methods	Single-centre, randomised, parallel-group trial. 3 treatment arms: carbamazepine, phenytoin, sodium valproate Dates conducted and country: Not stated (assumed conducted in United Kingdom due to author affiliations)
Participants	Children with at least 3 newly-diagnosed generalised or focal seizures within a period of 6 months Number randomised: PHT = 20, CBZ = 23 No information on epilepsy type, sex or range of follow-up Age range: 5 to 14 years. Study duration: 12 months
Interventions	Monotherapy with PHT or CBZ Mean dose: PHT = 6.1 mg/day, CBZ = 17.9 mg/day
Outcomes	Cognitive assessments Summary of withdrawals from randomised drug
Notes	Outcomes chosen for this review were not reported IPD not available, but could be constructed from the publication for the outcome 'Time to treatment failure' Funding: A grant was obtained from the Yorkshire Regional Health Authority, support for measuring serum levels provided by Ciba-Geigy PLC and Sanofi PLC. Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quota allocation by sex, age, seizure type and current treatment is an inadequate randomisation method
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	High risk	Personnel and participants (and parents) unblinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors single-blinded for cognitive testing
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, results reported and analysed for all participants randomised and all who completed various stages of follow-up ¬
Selective reporting (reporting bias)	Unclear risk	1 of 4 outcomes for this review reported. Cognitive outcomes described in Methods section well reported in Results section. Adverse effects reported, no seizure outcomes reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	Low risk	No other bias detected

Heller 1995

Methods	Randomised, parallel-group, open-label paediatric study conducted in 2 centres in the United Kingdom Trial conducted between 1981 and 1987 4 treatment arms: carbamazepine, sodium valproate, phenytoin, phenobarbitone
Participants	Adults with newly-diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the study) Number randomised: CBZ = 61, PHT = 63 52 participants (42%) with focal epilepsy. 64 (52%) men. Mean age (range): 31 (13 to 72) years Range of follow-up (months): 1 to 91
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 300 mg/day, CBZ = 600 mg/day
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse effects and withdrawals due to adverse events
Notes	IPD provided for all randomised participants. All outcomes in this review calculated from IPD Funding: support provided by the Medical Research Council, the Health Promotion Trust, Ciba-Geigy, Parke-Davis, and Sanofi Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed by 4 batches of concealed opaque envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Unblinded; authors state masking of treatment would not be “practical” and would have “introduced bias due to a very large drop-out rate.” Unclear if outcome was influenced
Blinding of outcome assessment (detection bias)	Unclear risk	Unblinded; authors state masking of treatment would not be “practical” and would have “introduced bias due to a very large drop-out rate.” Unclear if outcome was influenced
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided[1]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[1]
Other bias	Low risk	No other bias detected

Mattson 1985

Methods	Multicentre, randomised, parallel-group, double-blinded study over 10 centres in the USA with separate randomisation schemes used for each seizure type 4 treatment arms: carbamazepine, phenytoin, phenobarbitone, primidone Dates conducted: Not stated
Participants	Adults with previously untreated or under-treated simple or complex focal or secondary generalised tonic-clonic seizures Number randomised: PHT = 165, CBZ = 155 100% focal epilepsy. 278 (87%) men. Mean age (range): 41 (18 to 82) years Range of follow-up: 0 to 66 months
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 400 mg/day, CBZ = 800 mg/day
Outcomes	Participant retention/time to drug failure (length of time participant continued to take randomised drug) Composite scores of seizure frequency (seizure rates and total seizure control) and toxicity Incidence of side effects
Notes	IPD provided for all randomised participants. All outcomes in this review calculated from IPD Funding: supported by the Veterans Adminstration Medical Research Service Cooperative Studies Program (CS 118) Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised with stratification for seizure type. Method of randomisation not stated and not provided by authors
Allocation concealment (selection bias)	Unclear risk	No information provided in the publication or by study authors
Blinding of participants and personnel (performance bias)	Low risk	Double-blind (participants and personnel) achieved using an additional blank tablet
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessment was blinded, no information provided
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided[1]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[1]
Other bias	Low risk	No other bias detected

Miura 1993

Methods	Prospective randomised study. 3 treatment arms: carbamazepine, phenytoin, sodium valproate Dates conducted and country: Not stated (assumed conducted in Japan due to author affiliation)
Participants	Children aged 1 to 14 with previously untreated focal seizures or generalised tonic-clonic seizures, or both Number randomised: PHT = 51, CBZ = 66. 84 (72%) with focal seizures. No information on gender Range of follow-up: 6 to 66 months, mean follow-up: 37 months in PHT group, 34 in CBZ group
Interventions	Monotherapy with PHT or CBZ. Initial daily dose: PHT = 7.2 ± 1.4 mg/kg/day, CBZ = 13.0 ± 1.6 mg/kg/day
Outcomes	Proportion of all randomised participants with seizure recurrence (by seizure type) Proportion of participants with optimum plasma levels with seizure recurrence (by seizure type)
Notes	Very limited information available.The study is reported in a summary publication of 3 different studies (other 2 studies are not CBZ vs PHT) Outcomes chosen for this review were not reported, and IPD not available Funding: Not stated Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study is described as "randomised" but no further details are provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided; unclear if the study was blinded or not
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided; unclear if the study was blinded or not
Incomplete outcome data (attrition bias)	Low risk	Ranges of follow-up given for both treatment groups. Results reported "at the end of follow up," no withdrawals or exclusions mentioned, all participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Seizure recurrence outcomes described and well reported. No adverse events reported; no protocol available so unclear if adverse events were planned a priori. Outcomes for this review not available
Other bias	Low risk	No other bias detected

Ogunrin 2005

Methods	Double-blinded, parallel-group, randomised study conducted in a single centre in Nigeria between October 2000 and October 2002 3 treatment arms: carbamazepine, phenytoin, phenobarbitone
Participants	Consecutive newly-diagnosed people aged 14 or over presenting at the outpatient neurology clinic of the University Teaching Hopsital, Benin City, Nigeria with recurrent, untreated afebrile seizures Number randomised: PHT = 19, CBZ = 19 8 participants with focal seizures (22%), 23 men (62%). Mean age (range): 29.8 years (14 to 38 years) All participants followed up for 12 weeks
Interventions	Monotherapy with PHT or CBZ. Median daily dose (range): PHT = 200 mg (100 to 300 mg), CBZ = 600 mg (400 to 1200 mg)
Outcomes	Cognitive measures (reaction times, mental speed, memory, attention)
Notes	IPD provided for all randomised participants. Study duration was 12 weeks; all participants completed the study without withdrawing, so outcomes 'Time to treatment failure', 'Time to six-month remission' and 'Time to 12-month remission' could not be calculated. 'Time to first seizure' calculated from IPD provided Funding: Not stated Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study randomised using simple randomisation. Each participant was asked to pick 1 from a table of numbers (1 - 60), numbers corresponded to allocation of 1 of 3 drugs (information provided by author)
Allocation concealment (selection bias)	Low risk	Recruitment/randomisation of participants and allocation of treatments took place on different sites (information provided by author)
Blinding of participants and personnel (performance bias)	Low risk	Participants single-blinded. Research assistant recruiting participants and counselling on medication adherence was not blinded
Blinding of outcome assessment (detection bias)	Low risk	Investigators performing cognitive assessments were single-blinded
Incomplete outcome data (attrition bias)	Low risk	All randomised participants completed the study. All randomised participants analysed from IPD provided[1]
Selective reporting (reporting bias)	Low risk	1 outcome for this review calculated from IPD provided[1]. Other outcomes for this review not available due to short study length. All cognitive outcomes from the study well reported
Other bias	Low risk	No other bias detected

Pulliainen 1994

Methods	Single-centre, randomised, parallel-group trial of participants, referrals to the outpatient department of neurology of the Central Hospital of Paijat-Hame, Finland 2 treatment arms: carbamazepine and phenytoin Dates conducted: Not stated
Participants	Adults (eligible age range 15 to 57) with newly-diagnosed epilepsy Number randomised: PHT = 20, CBZ = 23* 10 (23%) participants with focal epilepsy. 20 (47%) men Mean age (SD) years: PHT = 31.5 (11.3), CBZ = 26.8 (13.2)
Interventions	Monotherapy with PHT or CBZ. Dose information not reported
Outcomes	Cognitive assessments (visual motor speed, co-ordination, attention and concentration, verbal and visuospatial learning, visual and recognition memory, reasoning, mood, handedness) Harmful side effects
Notes	*59 participants were randomised but 16 were subsequently excluded. Results were presented only for the 43 participants who completed the entire study Outcomes chosen for this review were not reported. IPD not available Funding: Not stated Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to treatment groups, method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided; unclear if participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Cognitive outcome assessor was blinded
Incomplete outcome data (attrition bias)	High risk	16/59 (27%) of participants excluded from analysis. Results presented only for 43 participants who completed the study
Selective reporting (reporting bias)	Unclear risk	Cognitive outcomes described in Methods section well reported in Results section. Adverse effects reported, no seizure outcomes reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	Low risk	No other bias detected

Ramsay 1983

Methods	Randomised, 'two compartment' parallel study, conducted in the USA 2 treatment arms: carbamazepine, phenytoin Dates conducted: Not stated
Participants	Adults, previously untreated, with at least 2 seizures or at least 1 seizure and an EEG with paroxysmal features Number randomised: PHT = 45, CBZ = 42 55 participants (63%) with focal epilepsy. 60 (69%) men. Overall mean age (range) 37.4 (18 to 77) years Study duration: 2 years. Range of follow-up not reported
Interventions	Monotherapy with PHT or CBZ Mean daily dose achieved (for the 54 participants with no major side effects): PHT = 5.35 mg/kg/day, CBZ = 9.32 mg/kg/day
Outcomes	Laboratory measures Side effects (major and minor) Seizure control/treatment failure
Notes	7 participants on CBZ and 10 participants on PHT were “dropped for non-compliance” and excluded from analysis Outcomes chosen for this review were not reported. IPD not available Funding: Supported in part by the Southern Foundation for Brain Research Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned to treatment groups; method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Low risk	Double-blind (participants and personnel) achieved with additional blank tablet
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	High risk	17/87 (19.5%) of participants excluded from analysis for "non-compliance". Results presented only for participants who completed the study
Selective reporting (reporting bias)	Low risk	All efficacy and tolerability outcomes specified in the Methods sections reported well in the Results section. No protocol available. Outcomes chosen for this review were not reported
Other bias	Low risk	No other bias detected

Ravi Sudhir 1995

Methods	Single-centre, randomised, parallel-group study of participants referred to the Neurology Clinic of Nehru Hospital, Chandigarh, India 2 treatment arms: carbamazepine, phenytoin Dates conducted: Not stated
Participants	Newly-diagnosed and drug naïve adults over the age of 14 attending the Neurology Clinic of Nehru Hospital, Chandigarh, India Number randomised: PHT = 20, CBZ = 20 11 participants with focal epilepsy (27.5%), 28 men (70%) Mean age (range): PHT group 23.4 (14 to 44 years), CBZ 24.4 (14 to 45 years) Study duration 10 to 12 weeks. Range of follow-up not reported
Interventions	Monotherapy with PHT or CBZ. Initial daily dose: PHT = 5 mg/kg/day, CBZ = 10 mg/kg/day
Outcomes	Cognitive measures before and after treatments (verbal, performance, memory, visuomotor, perceptomotor organisation, visual organisation, dysfunction)
Notes	6 participants on CBZ and 8 participants on PHT were excluded from final analysis of cognitive assessments who were lost to follow-up or who had uncontrolled seizures Outcomes chosen for this review were not reported. IPD not available Funding: Not stated Conflicts of interest: None stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were randomised to one of the two study groups", no further information given on methods of randomisation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided; unclear if study was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided; unclear if study was blinded
Incomplete outcome data (attrition bias)	High risk	14/40 (35%) of participants excluded from analysis who were lost to follow-up or experienced uncontrolled seizures. Results presented only for participants who completed the study
Selective reporting (reporting bias)	Unclear risk	Cognitive outcomes described in Methods section well reported in Results section. No seizure outcomes or adverse events reported and outcomes chosen for this review not reported. No protocol available, so unclear if seizure outcomes were planned a priori
Other bias	Low risk	No other bias detected

Footnotes

[1]For studies in which IPD were provided (De Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005) attrition and reporting bias are reduced as attrition rates and unpublished outcome data are requested.

CBZ: carbamazepine

EEG: electroencephalograph
IPD: individual participant data
PHT: phenytoin

Characteristics of excluded studies

Bird 1966

Reason for exclusion	Unclear whether trial is randomised and unclear whether participants received either CBZ or PHT as monotherapy. Authors could not be contacted to clarify, so trial excluded due to uncertainties.

Bittencourt 1993

Reason for exclusion	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. Participants were given phenobarbital initially which was later withdrawn whilst either CBZ or PHT was also introduced

Canadian Study 1998

Reason for exclusion	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. No randomised monotherapy comparison between CBZ and PHT. Participants were separated into 2 treatment arms (based on previous drug failure) and randomised to CBZ and clobazam in 1 arm and PHT or clobazam in the other arm

Cereghino 1974

Reason for exclusion	Cross-over design; cross-over studies are not an appropriate design for measuring the long-term outcomes of interest in this review

Hakami 2012

Reason for exclusion	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. Participants who failed CBZ or PHT monotherapy were randomised to levetiracetam or VPS monotherapy

Kaminow 2003

Reason for exclusion	Participants were randomised to lamotrigine or 'standard therapy' (PHT, CBZ or VPA at the choice of the investigator). No randomised comparison can be made of CBZ and PHT

Kosteljanetz 1979

Reason for exclusion	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. All medication except phenobarbital and primidone were discontinued gradually, whilst dose of randomised drug CBZ or PHT was increased

Kuzuya 1993

Reason for exclusion	Study is not randomised; participants were already on CBZ or PHT monotherapy on entry into the study

Rajotte 1967

Reason for exclusion	Unclear if the study was randomised. Comparison between CBZ monotherapy and PHT monotherapy cannot be made. The trial has a cross-over design with a 2-week washout period in which both drugs were taken to make a gradual transition

Rysz 1994

Reason for exclusion	Unclear whether trial is randomised and unclear whether participants received either CBZ or PHT as monotherapy. Authors could not be contacted to clarify therefore trial excluded due to uncertainties.

Sabers 1995

Reason for exclusion	Not fully randomised: "The treatment was chosen at random unless the individual diagnoses required a specific drug"

Shakir 1980

Reason for exclusion	Direct comparison between CBZ and PHT not available. The publication reports 2 separate randomised studies, the first compares VPS and PHT and the second compares VPS and CBZ

Shorvon 1978

Reason for exclusion	Study is not randomised

Simonsen 1976

Reason for exclusion	Randomised participants were slowly withdrawn from their previous treatment as part of the trial and therefore a comparison between CBZ and PHT monotherapy cannot be made

Troupin 1975

Reason for exclusion	All participants received PHT for 2 months prior to entering a randomised cross-over period. It is unclear whether a comparison between CBZ and PHT monotherapy could be made

Zeng 2010

Reason for exclusion	The study is not randomised - the investigator made the choice of treatment for each participant

Footnotes

CBZ: carbamazepine; PHT: phenytoin; VPS: sodium valproate

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Carbamazepine compared with phenytoin (time to treatment failure)

Carbamazepine compared with phenytoin for epilepsy						
Patient or population: adults and children with new-onset focal or generalised epilepsy **Settings:** outpatients **Intervention:** carbamazepine **Comparison:** phenytoin						
	Illustrative comparative risks* (95% CI)		**Relative effect (95% CI)[a]**	**No. of Participants (studies)**	**Certainty (quality) of the evidence (GRADE)**	
	Assumed risk	**Corresponding risk**				
Outcomes	**Phenytoin**	**Carbamazepine**				**Comments**

Time to treatment failure (any reason related to treatment) *All participants* Range of follow-up:1 day to 4403 days	The median time to treatment failure was 2135 days in the phenytoin group	The median time to treatment failure was 2422 days (307 days longer) in the carbamazepine group	**HR 0.94** (0.70 to 1.26)[a]	546 (3 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for carbamazepine There was also no statistically significant difference between drugs in treatment failure due to adverse events (HR 1.27, 95% CI 0.87 to 1.86; P = 0.21; I^2 = 3%), or treatment failure due to lack of efficacy: HR 0.99 (95% CI 0.69 to 1.41; P = 0.94; I^2 = 0%)
Time to treatment failure (any reason related to treatment) *Subgroup: focal onset seizures* Range of follow-up: 1 day to 4064 days	The median time to treatment failure was 1300 days in the phenytoin group	The median time to treatment failure was 2422 days (1122 days longer) in the carbamazepine group	**HR 0.83** (0.61 to 1.13)	428 (3 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for carbamazepine There was also no statistically significant difference between drugs in treatment failure due to adverse events (HR 1.19, 95% CI 0.80 to 1.78; P = 0.38, I^2 = 0%), or treatment failure due to lack of efficacy: HR 0.88 (95% CI 0.60 to 1.40, P = 0.52, I^2 = 0%)
Time to treatment failure (any reason related to treatment) *Subgroup: generalised onset tonic clonic seizures* Range of follow-up:1 day to 4403 days	The 10th percentile[c] of time to treatment failure was 778 days in the phenytoin group	The 10th percentile[c] of time to treatment failure was 108 days (670 days shorter) in the carbamazepine group	**HR 2.38** (1.04 to 5.47)	118 (2 studies)	⊕⊕⊖⊖ **low**[b,d]	HR < 1 indicates a clinical advantage for carbamazepine There was no statistically significant difference between drugs in treatment failure due to adverse events (HR 2.31, 95% CI 0.68 to 7.81; P = 0.18; I^2 = 60% , or treatment failure due to lack of efficacy: HR 1.86 (95% CI 0.74 to 4.67; P = 0.19; I^2 = 0%) but confidence intervals are wide so we cannot rule out an advantage to either drug or no difference between the drugs

*Illustrative risks in the carbamazepine and phenytoin groups are calculated at the median time to treatment failure (i.e. the time to 50% of participants failing or withdrawing from allocated treatment) within each group across all trials. The relative effect (pooled hazard ratio) shows the comparison of 'Time to treatment failure' between the treatment groups.

CI: 95% confidence interval; **HR**: hazard ratio

GRADE Working Group grades of evidence

High certainty (quality): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty (quality): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty (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 certainty (quality): We are very uncertain about the estimate.

Footnotes

[a]Pooled HR for all participants adjusted for seizure type. All pooled HRs presented calculated with fixed-effect model.

[b]Downgraded once for risk of bias: risk of bias unclear for one element of all of the three studies included in the analysis. Additionally, 29 adult participants may have had their seizure type wrongly classified as generalised onset; sensitivity analyses show misclassification may have had an impact on results and conclusions about an

association between treatment and seizure type.
[c]The 10th percentile of time to treatment failure (i.e. the time to 50% of participants failing or withdrawing from allocated treatment) is presented for the subgroup with generalised seizures, as fewer than 50% of participants failed/withdrew from treatment, so we could not calculate median time.
[d]Downgraded once for imprecision: the subgroup of participants with generalised onset tonic–clonic seizures is relatively small (22% of total participants) and confidence intervals around pooled results are fairly wide.

2 Carbamazepine compared with phenytoin (secondary outcomes)

Carbamazepine compared with phenytoin for epilepsy						
Patient or population: adults and children with new-onset focal or generalised epilepsy **Settings:** outpatients **Intervention:** carbamazepine **Comparison:** phenytoin						
Outcomes	**Illustrative comparative risks* (95% CI)** **Assumed risk** **Phenytoin**	**Corresponding risk** **Carbamazepine**	**Relative effect (95% CI)[a]**	**No. of Participants (studies)**	**Certainty (quality) of the evidence (GRADE)**	**Comments**
Time to first seizure after randomisation *All participants* Range of follow-up: 0 days to 4589 days	The median time to first seizure was 124 days in the phenytoin group	The median time to first seizure was 79 days (45 days shorter) in the carbamazepine group	**HR 1.15** (0.94 to 1.40)	582 (4 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for carbamazepine
Time to first seizure after randomisation *Subgroup: focal onset seizures* Range of follow-up: 0 days to 4589 days	The median time to first seizure was 78 days in the phenytoin group	The median time to first seizure was 62 days (16 days shorter) in the carbamazepine group	**HR 1.13** (0.89 to 1.43)	432 (4 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for carbamazepine
Time to first seizure after randomisation *Subgroup: generalised onset tonic clonic seizures* Range of follow-up: 2 days to 4070 days	The median time to first seizure was 323 days in the phenytoin group	The median time to first seizure was 142 days (181 days shorter) in the carbamazepine group	**HR 1.19** (0.81 to 1.75)	150 (3 studies)	⊕⊕⊖⊖ **low**[b,c]	HR < 1 indicates a clinical advantage for carbamazepine
Time to achieve 12-month remission *All participants* Range of follow-up: 0 days to 4222 days	The median time to 12-month remission was 472 days in the phenytoin group	The median time to 12-month remission was 481 days (9 days longer) in the carbamazepine group	**HR 1.00** (0.79 to 1.26)	551 (3 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenytoin
Time to achieve 12-month remission *Subgroup: focal onset seizures* Range of follow-up: 0 days to 4222 days	The median time to 12-month remission was 531 days in the phenytoin group	The median time to 12-month remission was 515 days (16 days shorter) in the carbamazepine group	**HR 1.06** (0.80 to 1.42)	430 (3 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenytoin

Time to achieve 12-month remission *Subgroup: generalised onset tonic clonic seizures* Range of follow-up: 7 days to 4163 days	The median time to 12-month remission was 366 days in the phenytoin group	The median time to 12-month remission was 375 days (9 days longer) in the carbamazepine group	**HR 0.88** (0.58 to 1.33)	121 (2 studies)	⊕⊕⊖⊖ **low**[b,d]	HR < 1 indicates a clinical advantage for phenytoin

*Illustrative risks in the carbamazepine and phenytoin groups are calculated at the median time to first seizure or time to 12-month remission (i.e. the time to 50% of participants experiencing a first seizure or 12-months of remission) within each group across all trials. The relative effect (pooled hazard ratio) shows the comparison of 'Time to first seizure' or 'Time to 12-month remission' between the treatment groups.

CI: 95% confidence interval; **HR**: hazard ratio

GRADE Working Group grades of evidence

High certainty (quality): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty (quality): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty (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 certainty (quality): We are very uncertain about the estimate.

Footnotes

[a]Pooled HR for all participants adjusted for seizure type. All pooled HRs presented calculated with a fixed-effect model.
[b]Downgraded once due to risk of bias: risk of bias unclear for one element of three studies included in the analysis.
[c]Downgraded once due to inconsistency: heterogeneity was present between trials (I^2 = 45%) which could not be explained by sensitivity analyses examining misclassification of seizure type, or age groups recruited within the studies.
[d]Downgraded once due to inconsistency: substantial heterogeneity present between trials (I^2 = 73%). This heterogeneity is likely to be due to misclassification of seizure type of 29 adult participants.

Additional tables

1 Outcomes considered and summary of results for trials with no IPD

Trial	Outcomes reported	Summary of results
Callaghan 1985	1. Seizure control: excellent (seizure-free) good (> 50% reduction) poor (< 50% reduction) 2. Side effects	1. PHT (n = 58); CBZ (n = 59) PHT: 39 (67%); CBZ: 22 (37%) PHT: 7 (12%); CBZ: 22 (37%) PHT: 12 (21%); CBZ: 15 (25%) PHT: 6 (10%); CBZ: 5 (8%)
Czapinski 1997	1. Proportion achieving 24-month remission at 3 years 2. Proportion excluded after randomisation due to adverse effects or no efficacy	1. PHT: 59%; CBZ: 62% 2. PHT: 23%; CBZ: 30%
Forsythe 1991	1. Cognitive assessments 2. Withdrawals from randomised drug	1. No significant differences between the two treatment groups on any cognitive tests 2. PHT: 6 withdrawals out of 20 participants (30%); CBZ: 9 withdrawals out of 23 participants (39%)
Miura 1993	1. Proportion of all randomised participants with seizure recurrence (by seizure type) 2. Proportion of participants with optimum plasma levels with seizure recurrence (by seizure type)	PHT (n = 51); CBZ (n = 66) 1. PHT (focal): 10/31 (32%); PHT (generalised): 7/20 (35%); CBZ (focal): 21/53 (40%); CBZ (generalised): 2/13 (15%) 2. PHT (focal): 4/17 (24%); PHT (generalised): 1/8 (13%); CBZ (focal): 4/17 (24%); CBZ (generalised): 0/7 (0%)
Pulliainen 1994	1. Cognitive assessments (visual motor speed, co-ordination, attention and concentration, verbal and visual-spatial learning, visual and recognition memory, reasoning, mood, handedness) 2. Harmful side effects	1. Compared to CBZ, participants on PHT became slower (motor speed of the hand) and their visual memory decreased. There was an equal decrease in negative mood (helplessness, irritability, depression) on PHT and CBZ 2. 3 participants taking PHT complained of tiredness, and 1 participant taking CBZ complained of facial skin problems, another tiredness and memory problems
Ramsay 1983	1. Side effects (major and minor) 2. Treatment failure/seizure control 3. Laboratory results	1. Incidence of: 1. major side effects (among analysed participants): PHT 8/35 participants (23%); CBZ 8/35 participants (23%) 2. minor side effects: cognitive impairment and sedation twice as likely on CBZ as PHT 3. other minor side effects similar between groups 2.¬Treatment failures among analysed participants: PHT 4/35 (11%); CBZ: 5/35 (14%) Seizure control (among analysed participants with no major side effects): PHT: 23/27 participants (86%); CBZ: 22/27 participants (82%) 3. Significantly lower mean LDH level at 24 weeks in CBZ participants than PHT participants (P < 0.01). Other laboratory results similar across treatment groups
Ravi Sudhir 1995	1. Cognitive measures (verbal, performance, memory, visual-motor, perceptomotor organisation, visual organisation, dysfunction)	1. No significant differences between any tests of cognitive function taken before treatment and after 10 - 12 weeks for both treatment groups

Footnotes

CBZ = carbamazepine; LDH = lactate dehydrogenase; PHT= phenytoin

2 Demographic characteristics of trial participants (trials providing individual participant data)

Trial	Focal seizures: n (%)		Male participants: n (%)[a]		Age at entry (years): Mean (SD), range[b]		Epilepsy duration (years): mean (SD), range[c]		Number of seizures in prior 6 months, median (range)[d]	
	CBZ	PHT	CBZ	PHT	CBZ	PHT	CBZ	PHT	CBZ	PHT
De Silva 1996[e]	29 (54%)	30 (56%)	30 (56%)	34 (63%)	9.2 (3.8) 2 to 15	9.5 (3.4) (3 to 16)	1.7 (2.6), 0 to 12	1.0 (2.1) (0 to 14)	3 (1 to 500)	3 (1 to 404)
Heller 1995	24 (39%)	28 (44%)	30 (49%)	34 (54%)	29.3 (14.1) 13 to 69	33.5 (14.3) (14 to 72)	4.4 (7.4), 0.1 to 40	3.8 (5.4) (0 to 24)	2 (1 to 354)	2 (1 to 575)
Mattson 1985	155 (100%)	165 (100%)	133 (87%)	145 (88%)	42.1 (15.9) 18 to 82	40.8 (15.3) (18 to 81)	5.9 (9.1), 0.5 to 55	6.6 (9.1) (0.5 to 59)	1 (1 to 100)	1 (1 to 26)
Ogunrin 2005	5 (26%)	3 (17%)	12 (63%)	11 (61%)	28.2 (5.8) 14 to 38	18.8 (2.6) (15 to 26)	NA	NA	18 (6 to 36)	12 (6 to 18)

Footnotes

n: number of participants; CBZ: carbamazepine; NA: not available; PHT:phenytoin SD: standard deviation

[a]Sex was missing for two participants on CBZ from Mattson 1985.
[b]Age at randomisation was missing for two participants on CBZ from Mattson 1985 and one participant on CBZ from Heller 1995.
[c]Epilepsy duration was missing for 41 participants; all 37 participants from Ogunrin 2005, three participants on CBZ from Mattson 1985, one participant on CBZ from Heller 1995.
[d]Number of seizures in the prior six months was missing for eight participants, seven participants from Mattson 1985 (three participants on PHT and four on CBZ), one participant on CBZ from Heller 1995.

[e]Randomised drug missing for six participants in De Silva 1996.

3 Number of participants contributing to each analysis

Trial	Number randomised			Time to treatment failure (any reason, adverse events, lack of efficacy)			Time to 12-month remission			Time to 6-month remission			Time to first seizure		
	PHT	CBZ	Total	PHT	CBZ	Total	PHT	CBZ	Total	PHT	CBZ	Total	PHT	CBZ	Total
De Silva 1996[a]	54	54	108	53	53	106	54	54	108	54	54	108	54	54	108
Heller 1995[b]	63	61	124	61	60	121	63	61	124	63	61	124	63	61	124
Mattson 1985[c]	165	155	320	165	154	319	165	154	319	165	154	319	162	151	313
Forsythe 1991[d]	20	23	43	20	23	43	Information not available			Information not available			Information not available		
Ogunrin 2005[e]	18	19	37	Information not available			Information not available			Information not available			18	19	37
Total	320	312	632	299	290	589	282	269	551	282	269	551	297	285	582

Footnotes

CBZ = carbamazepine, PHT= phenytoin

[a]Individual participant data (IPD) supplied for 114 participants recruited in De Silva 1996; randomised drug not recorded in six participants. Reasons for treatment failure not available for two participants (one randomised to

CBZ and one to PHT); these participants are not included in analysis of time to treatment failure.
[b]Reasons for treatment failure not available for three participants (one randomised to CBZ and two to PHT) in Heller 1995; these participants are not included in analysis of time to treatment failure.
[c]No follow-up data after randomisation available for one participant randomised to CBZ in Mattson 1985. Data on seizure recurrence not available for six additional participants (three randomised to CBZ and three to PHT); these participants are not included in the analysis of Time to first seizure.
[d]IPD for 'Time to treatment failure' available in the study publication of Forsythe 1991. Data for other outcomes not available.
[e]Study duration of Ogunrin 2005 is 12 weeks, so six- and 12-month remission of seizures could not be achieved and cannot therefore be calculated. All randomised participants completed the study without withdrawing from treatment, so time to treatment failure cannot be analysed.

4 Reasons for premature discontinuation

	De Silva 1996[a]		Forsythe 1991		Heller 1995[a,b]		Mattson 1985		Total[c]		
Reason for early termination	CBZ	PHT	CBZ	PHT	CBZ	PHT	CBZ	PHT	CBZ	PHT	Total
Adverse events (Event)	3	2	4	1	8	1	11	8	26	12	38
Seizure recurrence (Event)	12	10	2	1	5	8	3	6	22	25	47
Both seizure recurrence and adverse events (Event)	6	5	0	0	4	2	31	33	31	40	81
Non-compliance/participant choice (Event)	0	0	3	4	0	0	11	26	14	30	44
Participant went into remission (Censored)	18	24	0	0	6	14	0	0	24	38	62
Lost to follow-up (Censored)	0	0	0	0	0	0	26	19	26	19	45
Death (Censored)[d]	0	0	0	0	0	0	4	5	4	5	9
Other (Censored)[e]	0	0	0	0	0	0	16	11	16	11	27
Completed the study (did not withdraw) (Censored)	14	12	14	14	37	38	53	57	118	121	239
Total	53	53	23	20	60	63	155	165	281	301	592

Footnotes

n = number of individuals contributing to the outcome 'Time to treatment failure'

[a]One participant for Heller 1995 (CBZ) and two for De Silva 1996 (one PHT and one CBZ) have missing reasons for treatment failure.
[b]Two participants from Heller 1995 (both PHT) had missing treatment failure times and did not contribute to analysis, but reasons for treatment failure are given.
[c]All participants in Ogunrin 2005 completed the study without withdrawing, so this study did not contribute to 'Time to treatment failure'.
[d]Death due to reasons not related to the study drug.
[e]Other reasons from Mattson 1985: participants developed other medical disorders including neurological and psychiatric disorders.

5 Sensitivity analysis - Epilepsy type misclassification, fixed-effect analysis

	Original analysis		Generalised onset and age at onset > 30 years classified as focal onset		Generalised onset and age at onset > 30 years classified as uncertain seizure type	
Outcome	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences

Outcome	Original analysis		Generalised onset and age at onset > 30 years classified as focal onset		Generalised onset and age at onset > 30 years classified as uncertain seizure type	
	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences
Time to treatment failure (for any reason related to treatment)[a]	F: 0.83 (0.61 to 1.13), I^2 = 0% G: 2.38 (1.04 to 5.47), I^2 = 0% O: 0.94 (0.70 to 1.26), I^2 = 35%	Chi^2 = 5.45, df = 1, P = 0.02, I^2 = 81.7%	F: 0.88 (0.65 to 1.19), I^2 = 0% G: 1.96 (0.81 to 4.78), I^2 = 0% O: 0.96 (0.72 to 1.27), I^2 = 6%	Chi^2 = 2.83, df = 1, P = 0.09, I^2 = 64.6%	F: 0.83 (0.61 to 1.13), I^2 = 0% G: 1.96 (0.81 to 4.78), I^2 = 0% U: 5.23 (0.47 to 58.71), I^2 = NA O: 0.93 (0.70 to 1.24), I^2 = 7%	Chi^2 = 5.24, df = 2, P = 0.07, I^2 = 61.8%
Time to treatment failure due to adverse events[a]	F: 1.19 (0.80 to 1.78), I^2 = 0% G: 2.31 (0.68 to 7.81), I^2 = 60% O: 1.27 (0.87 to 1.86), I^2 = 3%	Chi^2 = 1.02, df = 1, P = 0.31, I^2 = 2.2%	F: 1.25 (0.84 to 1.86), I^2 = 22% G: 1.72 (0.51 to 5.87), I^2 = 0% O: 1.29 (0.88 to 1.88), I^2 = 0%	Chi^2 = 0.24, df = 1, P = 0.62, I^2 = 0%	F: 1.19 (0.80 to 1.78), I^2 = 0% G: 1.72 (0.51 to 5.87), I^2 = 0% U: Not estimable[c] O: 1.24 (0.85 to 1.81), I^2 = 0%	Chi^2 = 0.31, df = 2, P = 0.86, I^2 = 0%
Time to treatment failure due to lack of efficacy[a]	F: 0.88 (0.60 to 1.30), I^2 = 0% G: 1.86 (0.74 to 4.67), I^2 = 0% O: 0.99 (0.69 to 1.41), I^2 = 0%	Chi^2 = 2.14, df = 1, P = 0.14, I^2 = 53.2%	F: 0.91 (0.62 to 1.34), I^2 = 0% G: 1.81 (0.68 to 4.82), I^2 = 0% O: 1.00 (0.70 to 1.43), I^2 = 0%	Chi^2 = 1.64, df = 1, P = 0.20, I^2 = 38.9%	F: 0.88 (0.60 to 1.30), I^2 = 0% G: 1.81 (0.68 to 4.82), I^2 = 0% U: Not estimable[c] O: 0.97 (0.68 to 1.40), I^2 = 0%	Chi^2 = 1.78, df = 2, P = 0.41, I^2 = 0%
Time to first seizure[b]	F: 1.13 (0.89 to 1.43), I^2 = 0% G: 1.19 (0.81 to 1.75), I^2 = 45% O: 1.15 (0.94 to 1.40), I^2 = 0%	Chi^2 = 0.05, df = 1, P = 0.83, I^2 = 0%	F: 1.15 (0.91 to 1.44), I^2 = 0% G: 1.19 (0.77 to 1.84), I^2 = 53% O: 1.16 (0.94 to 1.42), I^2 = 0%	Chi^2 = 0.02, df = 1, P = 0.88, I^2 = 0%	F: 1.13 (0.89 to 1.43), I^2 = 0% G: 1.19 (0.77 to 1.84), I^2 = 53% U: 0.82 (0.29 to 2.34), I^2 = NA O: 1.13 (0.92 to 1.39), I^2 = 0%	Chi^2 = 0.41, df = 2, P = 0.82, I^2 = 0%

Outcome	Original analysis		Generalised onset and age at onset > 30 years classified as focal onset		Generalised onset and age at onset > 30 years classified as uncertain seizure type	
	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences	Pooled HR (95% CI) fixed-effect model	Test of subgroup differences
Time to 12-month remission[a]	F: 1.06 (0.80 to 1.42), I^2 = 0% G: 0.88 (0.58 to 1.33), I^2 = 73% O: 1.00 (0.79 to 1.26), I^2 = 16%	Chi^2 = 0.54, df = 1, P = 0.46, I^2 = 0%	F: 1.10 (0.84 to 1.45), I^2 = 0% G: 0.69 (0.43 to 1.11), I^2 = 0% O: 0.98 (0.77 to 1.24), I^2 = 0%	Chi^2 = 2.79, df = 1, P = 0.09, I^2 = 64.2%	F: 1.06 (0.80 to 1.42), I^2 = 0% G: 0.69 (0.43 to 1.11), I^2 = 0% U: 1.91 (0.74 to 4.90), I^2 = NA O: 0.99 (0.78 to 1.25), I^2 = 15%	Chi^2 = 4.32, df = 2, P = 0.12, I^2 = 53.7%
Time to 6-month remission[a]	F: 0.98 (0.75 to 1.27), I^2 = 0% G: 0.77 (0.52 to 1.13), I^2 = 39% O: 0.90 (0.73 to 1.12), I^2 = 0%	Chi^2 = 1.03, df = 1, P = 0.31, I^2 = 3.2%	F: 0.98 (0.76 to 1.26), I^2 = 0% G: 0.59 (0.37 to 0.93), I^2 = 0% O: 0.87 (0.70 to 1.09), I^2 = 15%	Chi^2 = 3.63, df = 1, P = 0.06, I^2 = 72.5%	F: 0.98 (0.75 to 1.27), I^2 = 0% G: 0.59 (0.37 to 0.93), I^2 = 0% U: 1.20 (0.51 to 2.83), I^2 = NA O: 0.88 (0.71 to 1.10), I^2 = 2%	Chi^2 = 4.01, df = 2, P = 0.13, I^2 = 50.1%

Footnotes

Chi^2: Chi^2 statistic; CI: confidence interval; df: degrees of freedom of Chi^2 distribution; F: focal epilepsy; G: generalised epilepsy; HR: Hazard Ratio; O: overall (all participants); U: uncertain epilepsy; P: P value (< 0.05 are classified as statistically significant)

[a]29 participants reclassified to focal epilepsy or uncertain epilepsy type from Heller 1995.
[b]35 participants reclassified to focal epilepsy or uncertain epilepsy type from Heller 1995 and Ogunrin 2005.
[c]HR and 95% CI not estimable as no participants with uncertainty epilepsy type failed carbamazepine treatment due to lack of efficacy or failed phenytoin treatment due to adverse events in Heller 1995.

6 Adverse event data (narrative report)

Trial	Adverse event data[a]	Summary of reported results	
		Carbamazepine (CBZ)	Phenytoin (PHT)
Callaghan 1985[b]	All adverse events according to drug (note: no participants withdrew due to adverse events)	CBZ (n = 59): drowsiness (n = 2), rash (n = 3)	PHT (n = 58): gum hypertrophy (n = 2), rash (n = 2), ataxia (n = 2)
Czapinski 1997[c]	"Exclusions" due to adverse events or no efficacy"	Proportion "excluded": CBZ: 30% (out of 30 randomised to CBZ)	Proportion "excluded": PHT: 23.3% (out of 30 randomised to PHT)
De Silva 1996	"Unacceptable" adverse events leading to drug withdrawal[d]	CBZ (n = 54): drowsiness (n = 1), blood dyscrasia (n = 1)	PHT (n = 54): drowsiness (n = 2), skin rash (n = 1), blood dyscrasia (n = 1), hirsutism (n = 1)

Trial	Adverse event data[a]	Summary of reported results	
		Carbamazepine (CBZ)	Phenytoin (PHT)
Forsythe 1991	Withdrawal due to adverse events (no other adverse event data reported)	4 participants out of 23 randomised to CBZ withdrew for the following reasons (some withdrew for more than adverse event): slowing of mental function, headache, anorexia, nausea, abdominal pain, fatigue and drowsiness[2]	1 participant out of 20 randomised to PHT withdrew from the study due to depression and anorexia
Heller 1995	"Unacceptable" adverse events leading to drug withdrawal[d]	CBZ (n = 61): drowsiness (n = 3), rash (n = 2), headache (n = 1), depression (n = 1)	PHT (n = 63): myalgia (n = 1), irritability (n = 1)
Mattson 1985[b]	Narrative report of 'Adverse effects' and 'Serious side effects'	CBZ (n = 155): motor disturbance (ataxia, incoordination, nystagmus, tremor: 33%); dysmorphic and idiosyncratic side effects (gum hypertrophy, hirsutism, acne and rash: 14%); gastrointestinal problems (27%); decreased libido or impotence (13%); No serious side effects	PHT (n = 165); motor disturbance (ataxia, inco-ordination, nystagmus, tremor: 28%); dysmorphic and idiosyncratic side effects (gum hypertrophy, hirsutism, acne and rash: 22 %); gastrointestinal problems (24%); decreased libido or impotence (11%) 1 serious side effect - 1 participant has confirmed lymphoma, rash improved rapidly following discontinuation of PHT
Miura 1993	No adverse events reported	N/A	N/A
Ogunrin 2005[b]	Participant reported symptomatic complaints (provided as IPD)	CBZ (n = 19): memory impairment (n = 9) psychomotor retardation (n = 1) inattention (n = 1) transient rash (n = 1) CBZ-induced cough (n = 1)	PHT (n = 18): memory impairment (n = 7) psychomotor retardation (n = 1) inattention (n = 2) transient rash (n = 1)
Pulliainen 1994	Participant-reported adverse events	1 participant on CBZ complained of facial skin problems; 1 participant on CBZ complained of tiredness and memory problems	3 participants on PHT complained of tiredness
Ramsay 1983[b]	Major and minor side effects	CBZ (n = 35): Major side effects: rash (n = 1), pruritus (n = 1), impotence (n = 2), dizziness (n = 1), headaches (n = 1), impaired cognition (n = 1), elevated liver enzymes (n = 1) Mild side effects: nausea (33%), headaches (24%), cognitive impairment (33%), nystagmus (52%), sedation (33%), fine tremor (20%)	PHT (n = 35): Major side effects: rash (n = 4), exfoliative dermatitis (n = 1), impotence (n = 1), dizziness (n = 1), nausea/vomiting (n = 1) Mild side effects: nausea (38%), gingival hyperplasia (12%), headaches (32%), cognitive impairment (15%), nystagmus (40%), sedation (15%), fine tremor (28%)

Trial	Adverse event data[a]	Summary of reported results	
		Carbamazepine (CBZ)	Phenytoin (PHT)
Ravi Sudhir 1995	No adverse events reported	N/A	N/A

Footnotes

CBZ = carbamazepine, N/A = not available, PHT= phenytoin

[a]Adverse event data are recorded as reported narratively in the publications, so exact definition of a symptom may vary. Adverse event data supplied as IPD for Ogunrin 2005. Adverse event data were not requested in original IPD requests (De Silva 1996; Heller 1995; Mattson 1985) but will be for all future IPD requests. For numbers of treatment withdrawals due to adverse events in studies for which IPD were provided (De Silva 1996; Heller 1995; Mattson 1985) see Table 4.
[b]Participants may report more than one adverse event.
[c]Czapinski 1997 is an abstract only, so very little information is reported.
[d]Participants may have withdrawn due to adverse event alone or a combination of adverse events and poor efficacy (seizures).

References to studies

Included studies

Callaghan 1985

[CRSSTD: 3369541]

Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A comparative study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. British Journal of Clinical Practice 1983;27:7-9. [CRSREF: 5281720]

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Goggin T, Casey C, Callaghan N. Serum levels of sodium valproate, phenytoin and carbamazepine and seizure control in epilepsy. Irish Medical Journal 1986;79(6):150-6. [CRSREF: 5281721]

Czapinski 1997

[CRSSTD: 3369545]

Czapinski P, Terczynski A, Czapinska E. Randomised 36-month comparative study of valproic acid, phenytoin, phenobarbital and carbamazepine efficacy in patients with newly diagnosed epilepsy with focal complex seizures. Epilepsia 1997;38 Suppl(3):42. [CRSREF: 3369546]

De Silva 1996

Published and unpublished data [CRSSTD: 3369547]

De Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996;347(9003):709-13. [CRSREF: 3369548]

Forsythe 1991

[CRSSTD: 3369549]

Berg I, Butler A, Ellis M, Foster J. Psychiatric aspects of epilepsy in childhood treated with carbamazepine, phenytoin or sodium valproate: a random trial. Developmental Medicine and Child Neurology 1993;35(2):149-57. [CRSREF: 5281723]

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Heller 1995

Published and unpublished data [CRSSTD: 3369551]

Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AL, et al. Phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. Journal of Neurology, Neurosurgery, and Psychiatry 1995;58(1):44-50. [CRSREF: 3369552]

Mattson 1985

Published and unpublished data [CRSSTD: 3369553]

Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, et al. Comparison of carbamazepine, phenobarbital, phenytoin and primidone in focal and secondary generalized tonic-clonic seizures. New England Journal of Medicine 1985;313(3):145-51. [CRSREF: 3369554]

Miura 1993

[CRSSTD: 3369555]

Miura H. Developmental and therapeutic pharmacology of antiepileptic drugs. Japanese Journal of Psychiatry and Neurology 1993;47(2):169-74. [CRSREF: 3369556]

Ogunrin 2005

Published and unpublished data [CRSSTD: 3369557]

Ogunrin O, Adamolekun B, Ogunniyi A. Cognitive effects of anti-epileptic drugs in Nigerians with epilepsy. African Journal of Neurological Sciences 2005;24:18-24. [CRSREF: 3369558]

Pulliainen 1994

[CRSSTD: 3369559]

Pulliainen V, Jokelainen M. Comparing the cognitive effects of phenytoin and carbamazepine in long-term monotherapy: a two-year follow-up. Epilepsia 1995;36(12):1195-202. [CRSREF: 5281724]

* Pulliainen V, Jokelainen M. Effects of phenytoin and carbamazepine on cognitive functions in newly diagnosed epileptic patients. Acta Neurologica Scandinavica 1994;89(2):81-6. [CRSREF: 3369560]

Ramsay 1983

[CRSSTD: 3369561]

Berger JR, Ramsay RE, Wilder BJ, Bruni J. A double-blind study comparing carbamazepine to phenytoin as initial seizure therapy. Neurology 1981;31(4 Pt 2):159. [CRSREF: 5281725]

* Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. Neurology 1983;33(7):904-10. [CRSREF: 3369562]

Ravi Sudhir 1995

[CRSSTD: 3369563]

Ravi Sudhir RV, Sawhney IM, Prabhakar S, Pershad D, Nain CK. Comparative cognitive effects of phenytoin and carbamazepine in adult epileptics. Neurology India 1995;43(4):186-92. [CRSREF: 3369564]

Excluded studies

Bird 1966

[CRSSTD: 3369571]

Bird CA, Griffin BP, Miklaszewska JM, Galbraith AW. Tegretol (carbamazepine): a controlled trial of new anti-convulsant. British Journal of Psychiatry 1966;112:737-42. [CRSREF: 3369572]

Bittencourt 1993

[CRSSTD: 3369573]

Bittencourt PR, Antoniuk SA, Bigarella MM, Da Costa JC, Doro MP, Ferreira AS, et al. Carbamazepine and phenytoin in epilepsies refractory to barbiturates: efficacy, toxicity and mental function. Epilepsy Research 1993; 16(2):147-55. [CRSREF: 3369574]

Canadian Study 1998

[CRSSTD: 3369577]

Bawden HN, Camfield CS, Camfield PR, Cunningham C, Darwish H, Dooley JM, et al. The cognitive and behavioural effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy. Epilepsy Research 1999;33(2-3):133-43. [CRSREF: 5281726]

* Canadian Study Group for Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Epilepsia 1998;39(9):952-9. [CRSREF: 3369578]

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Data and analyses

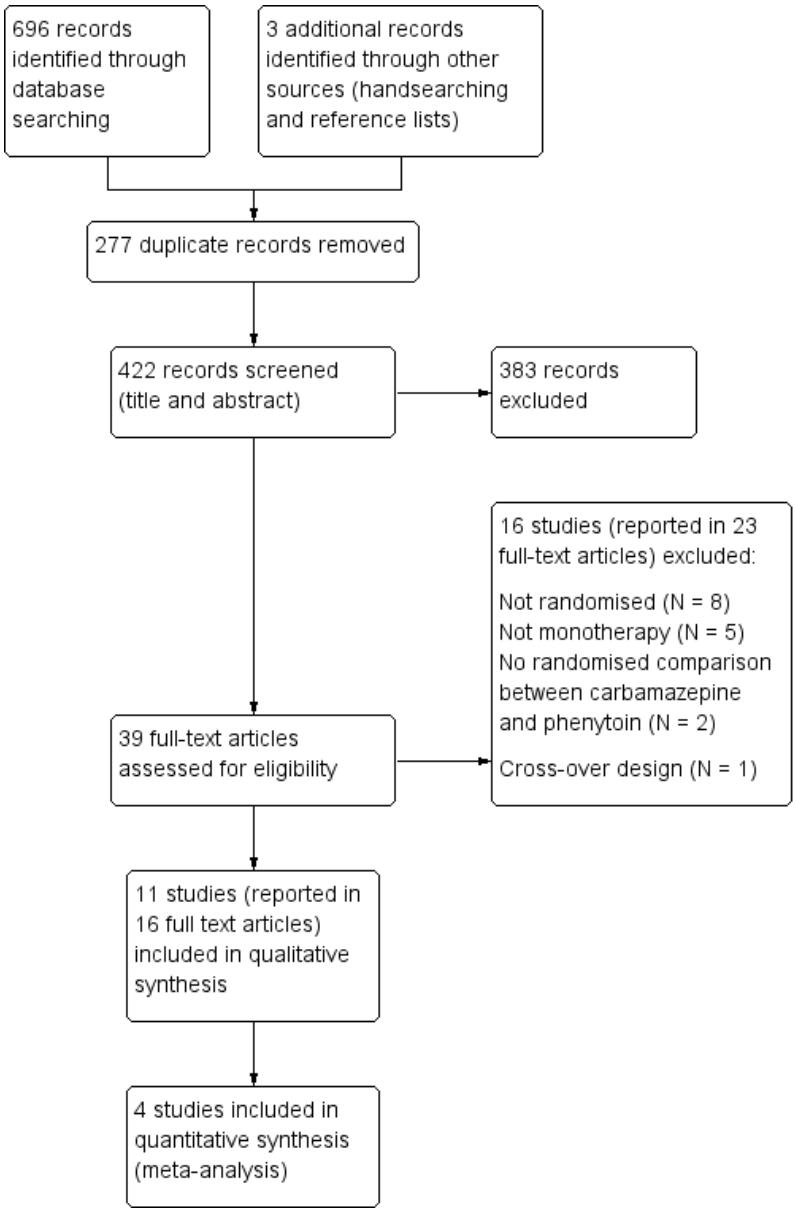
1 Carbamazepine (CBZ) versus phenytoin (PHT) monotherapy

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Time to treatment failure (any reason related to the treatment)	4	589	Hazard Ratio(IV, Fixed, 95% CI)	0.99 [0.76, 1.31]
1.2 Time to treatment failure due to adverse events	4	589	Hazard Ratio(IV, Fixed, 95% CI)	1.35 [0.93, 1.95]
1.3 Time to treatment failure due to lack of efficacy	4	589	Hazard Ratio(IV, Fixed, 95% CI)	1.02 [0.72, 1.44]
1.4 Time to treatment failure (any reason related to the treatment) - by epilepsy type	3	546	Hazard Ratio(IV, Fixed, 95% CI)	0.94 [0.70, 1.26]
1.4.1 Focal onset seizures	3	428	Hazard Ratio(IV, Fixed, 95% CI)	0.83 [0.61, 1.13]
1.4.2 Generalised onset seizures	2	118	Hazard Ratio(IV, Fixed, 95% CI)	2.38 [1.04, 5.47]
1.5 Time to treatment failure due to adverse events - by epilepsy type	3	546	Hazard Ratio(IV, Fixed, 95% CI)	1.27 [0.87, 1.86]
1.5.1 Generalised onset seizures	2	118	Hazard Ratio(IV, Fixed, 95% CI)	2.31 [0.68, 7.81]
1.5.2 Focal onset seizures	3	428	Hazard Ratio(IV, Fixed, 95% CI)	1.19 [0.80, 1.78]
1.6 Time to treatment failure due to lack of efficacy - by epilepsy type	3	546	Hazard Ratio(IV, Fixed, 95% CI)	0.99 [0.69, 1.41]
1.6.1 Focal onset seizures	3	428	Hazard Ratio(IV, Fixed, 95% CI)	0.88 [0.60, 1.30]
1.6.2 Generalised onset seizures	2	118	Hazard Ratio(IV, Fixed, 95% CI)	1.86 [0.74, 4.67]

1.7 Time to first seizure post-randomisation	4	582	Hazard Ratio(IV, Fixed, 95% CI)	1.13 [0.92, 1.39]
1.8 Time to first seizure post-randomisation - by epilepsy type	4	582	Hazard Ratio(IV, Fixed, 95% CI)	1.15 [0.94, 1.40]
1.8.1 Focal onset seizures	4	432	Hazard Ratio(IV, Fixed, 95% CI)	1.13 [0.89, 1.43]
1.8.2 Generalised onset seizures	3	150	Hazard Ratio(IV, Fixed, 95% CI)	1.19 [0.81, 1.75]
1.9 Time to achieve 12-month remission	3	551	Hazard Ratio(IV, Fixed, 95% CI)	1.01 [0.80, 1.27]
1.10 Time to achieve 12-month remission - by epilepsy type	3	551	Hazard Ratio(IV, Fixed, 95% CI)	1.00 [0.79, 1.26]
1.10.1 Focal onset seizures	3	430	Hazard Ratio(IV, Fixed, 95% CI)	1.06 [0.80, 1.42]
1.10.2 Generalised onset seizures	2	121	Hazard Ratio(IV, Fixed, 95% CI)	0.88 [0.58, 1.33]
1.11 Time to achieve six-month remission	3	551	Hazard Ratio(IV, Fixed, 95% CI)	0.92 [0.74, 1.14]
1.12 Time to achieve six-month remission - by epilepsy type	3	551	Hazard Ratio(IV, Fixed, 95% CI)	0.90 [0.73, 1.12]
1.12.1 Focal onset seizures	3	430	Hazard Ratio(IV, Fixed, 95% CI)	0.98 [0.75, 1.27]
1.12.2 Generalised onset seizures	2	121	Hazard Ratio(IV, Fixed, 95% CI)	0.77 [0.52, 1.13]

Figures

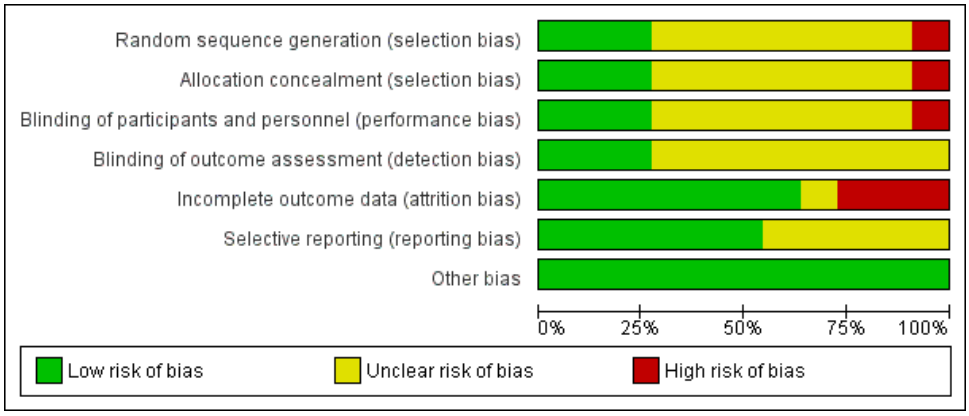
Figure 1



Caption

Study flow diagram.

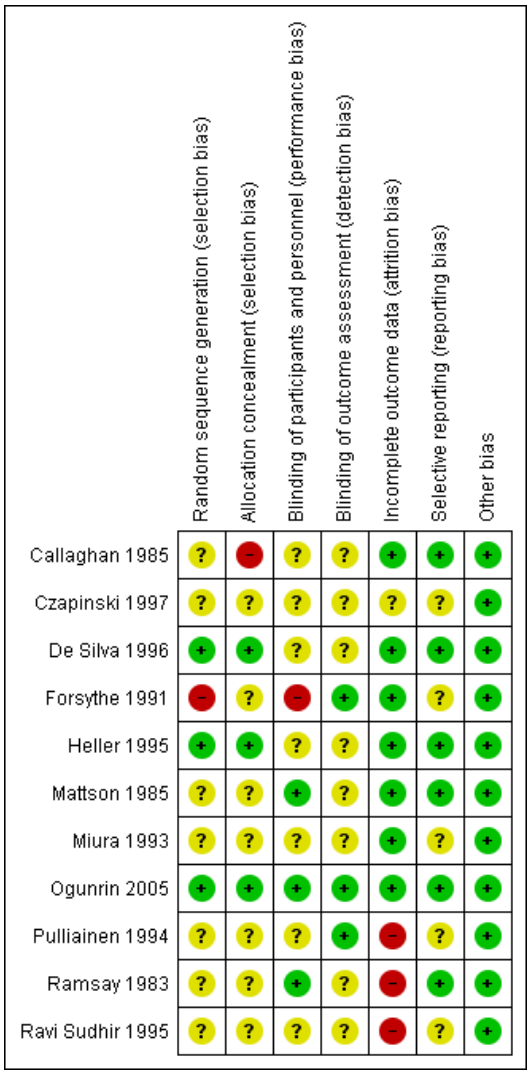
Figure 2



Caption

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

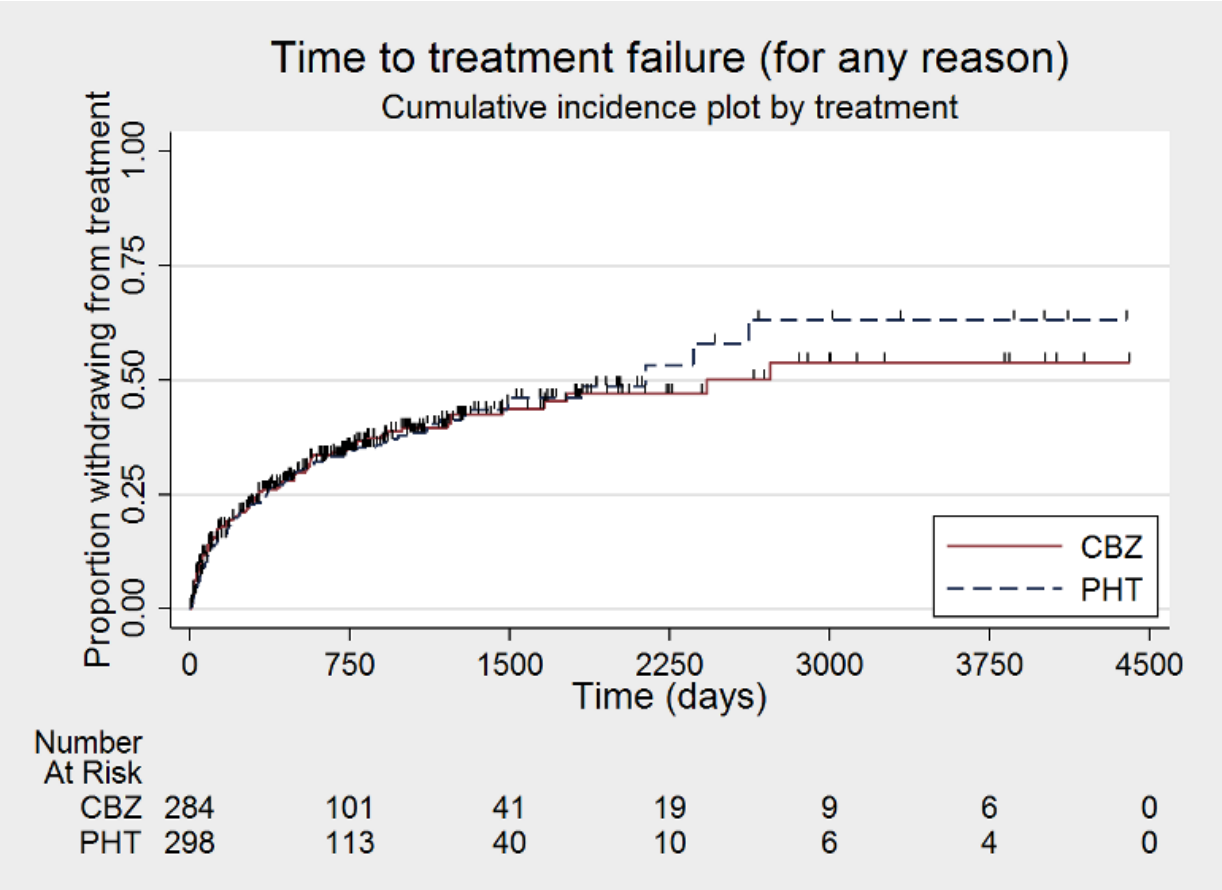
Figure 3



Caption

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

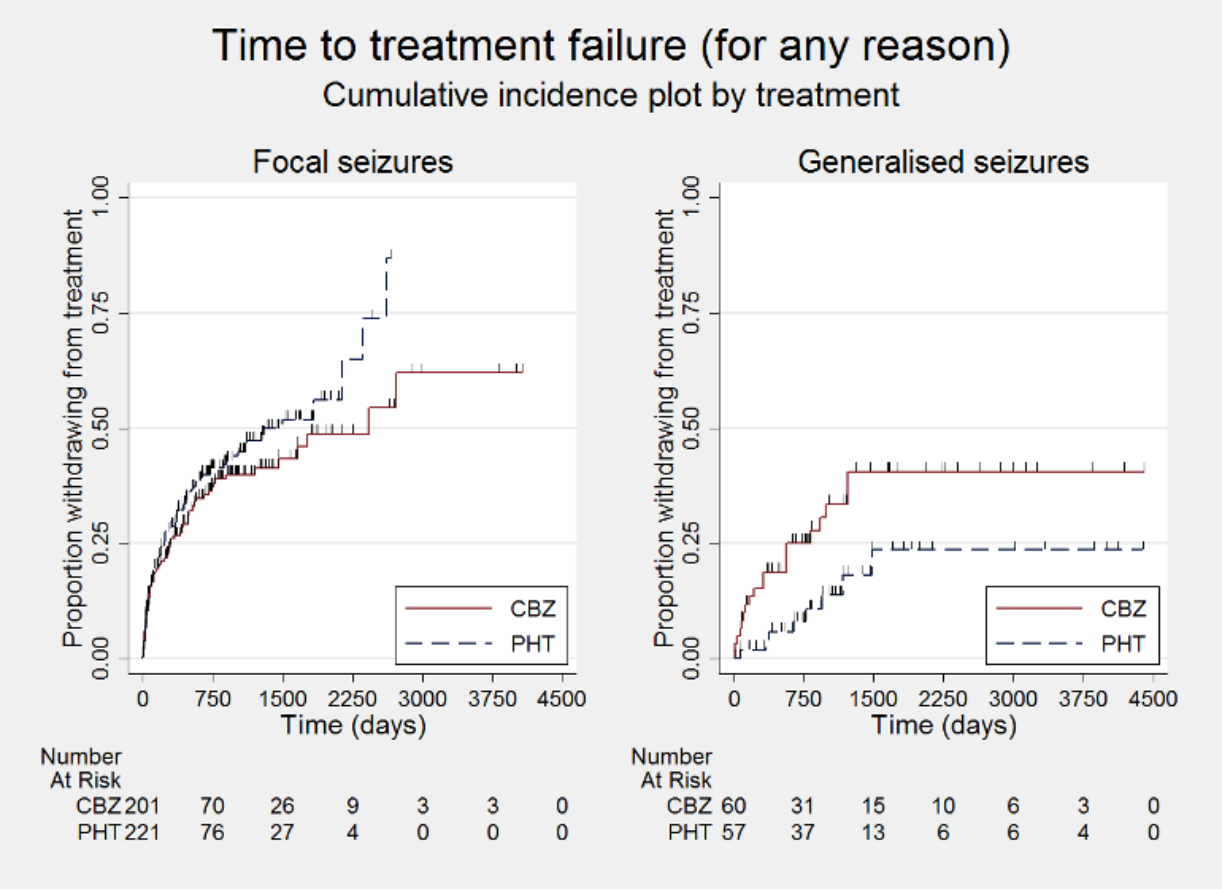
Figure 4



Caption

Time to treatment failure – any reason related to the treatment (CBZ: carbamazepine; PHT: phenytoin)

Figure 5

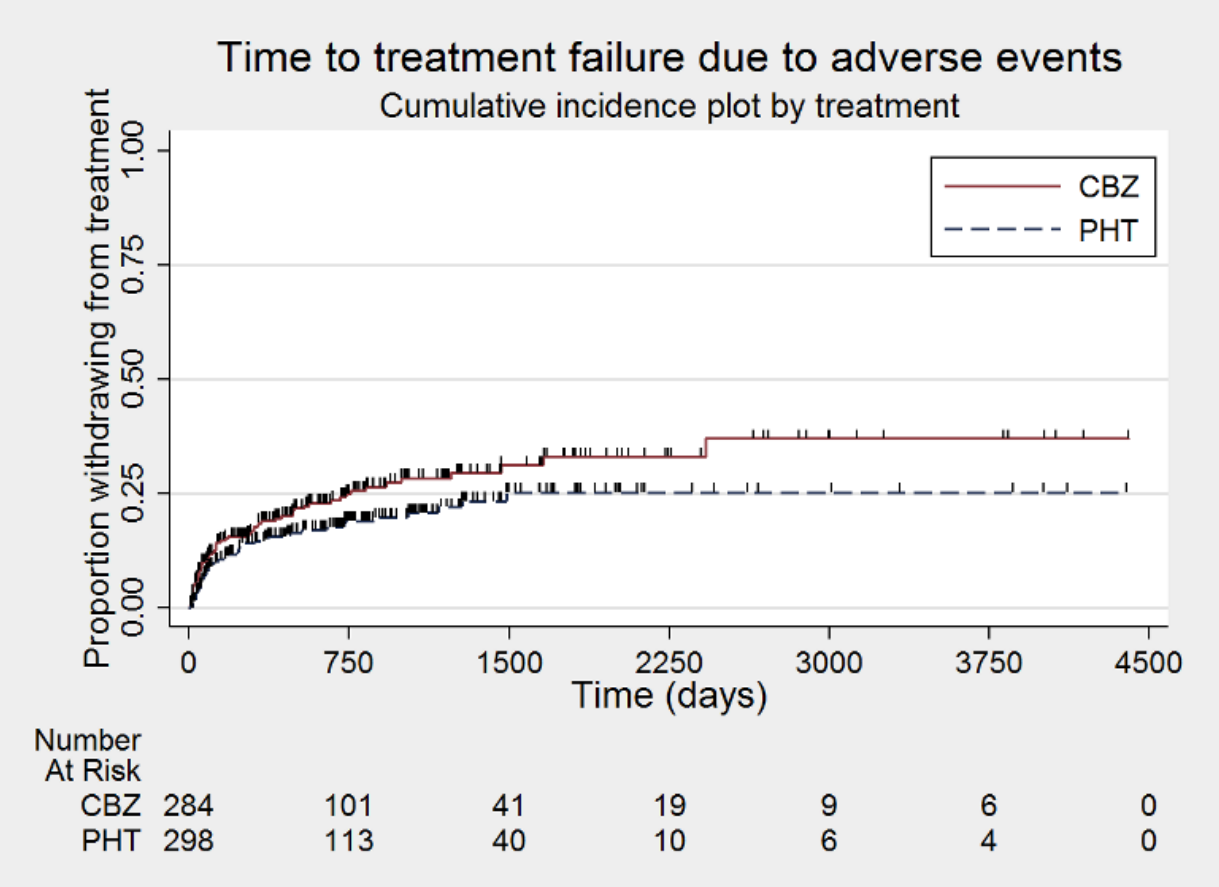


Caption

Time to treatment failure – any reason related to the treatment, by epilepsy type (CBZ: carbamazepine; PHT:

phenytoin)

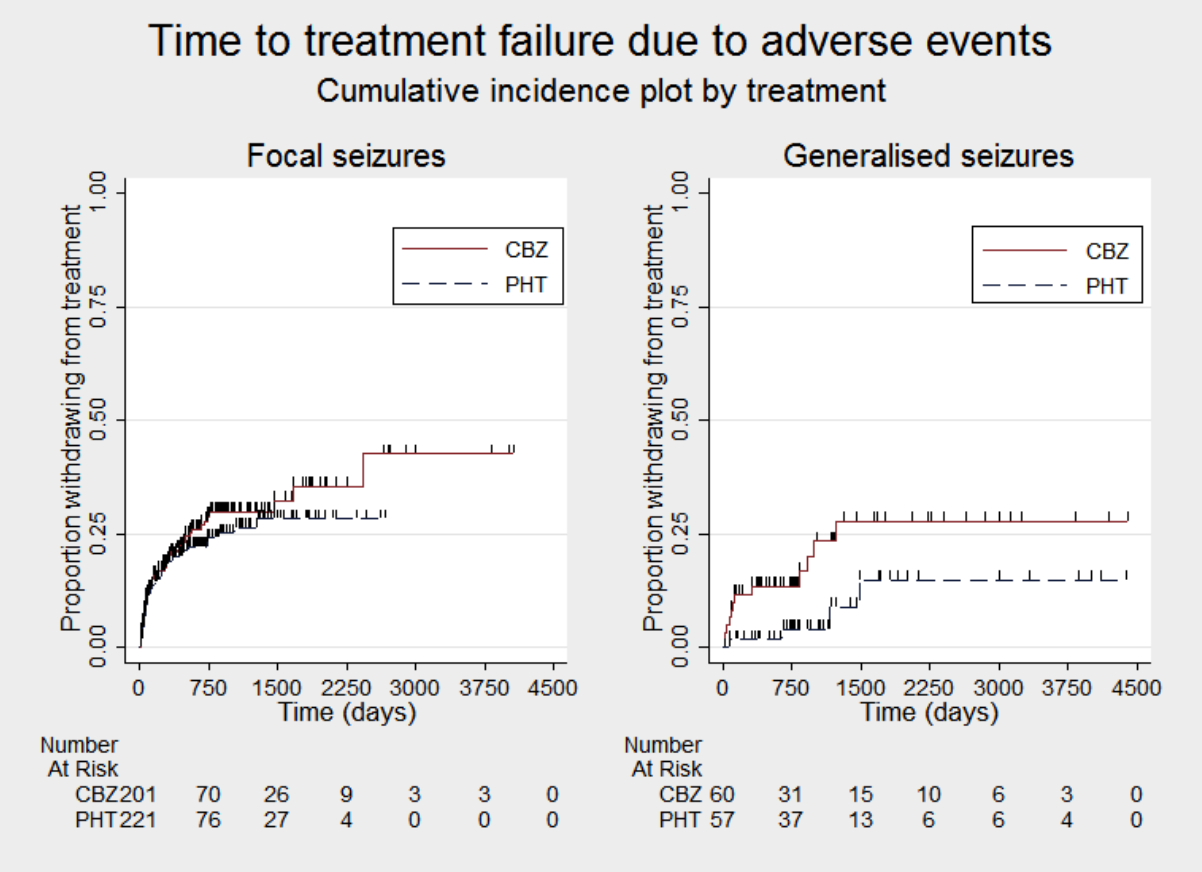
Figure 6



Caption

Time to treatment failure due to adverse events (CBZ: carbamazepine; PHT: phenytoin)

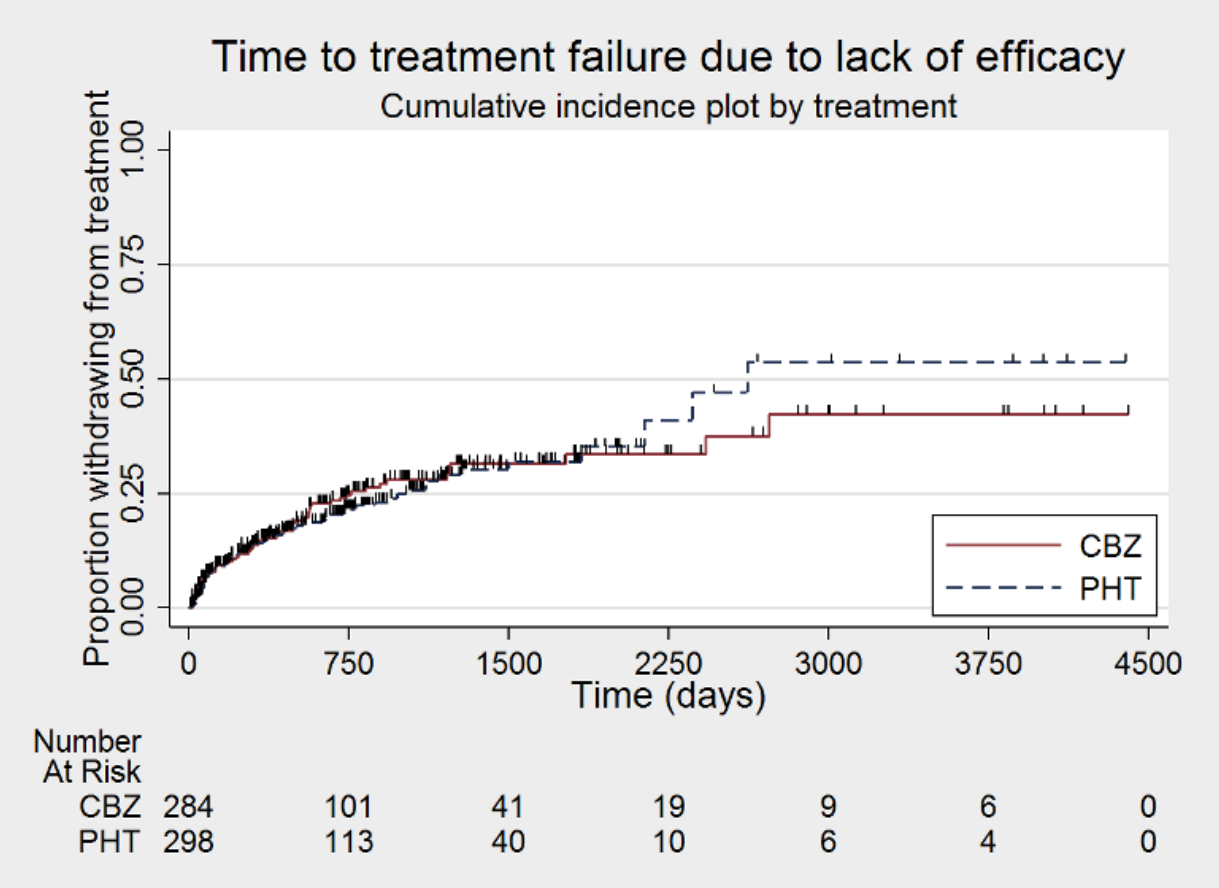
Figure 7



Caption

Time to treatment failure due to adverse events, by epilepsy type (CBZ: carbamazepine; PHT: phenytoin)

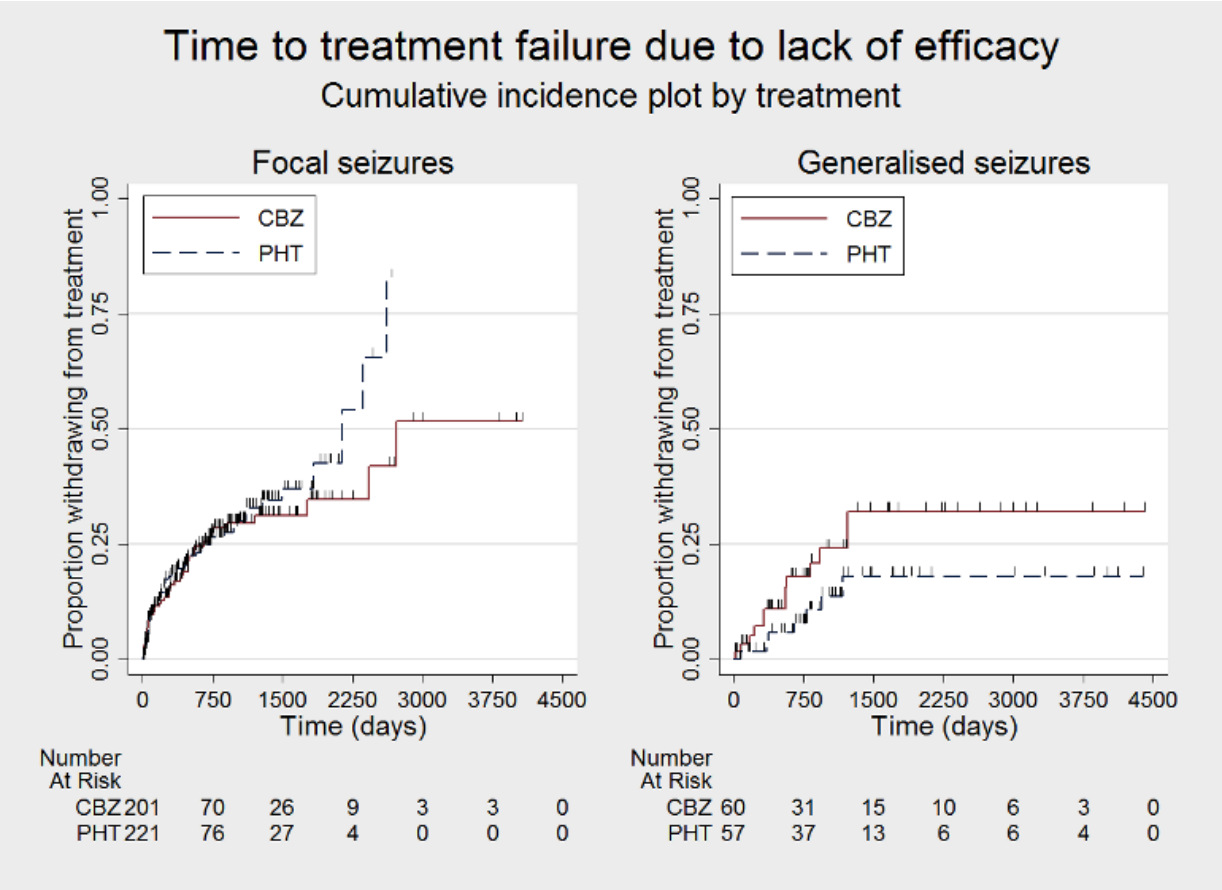
Figure 8



Caption

Time to treatment failure due to lack of efficacy (CBZ: carbamazepine; PHT: phenytoin)

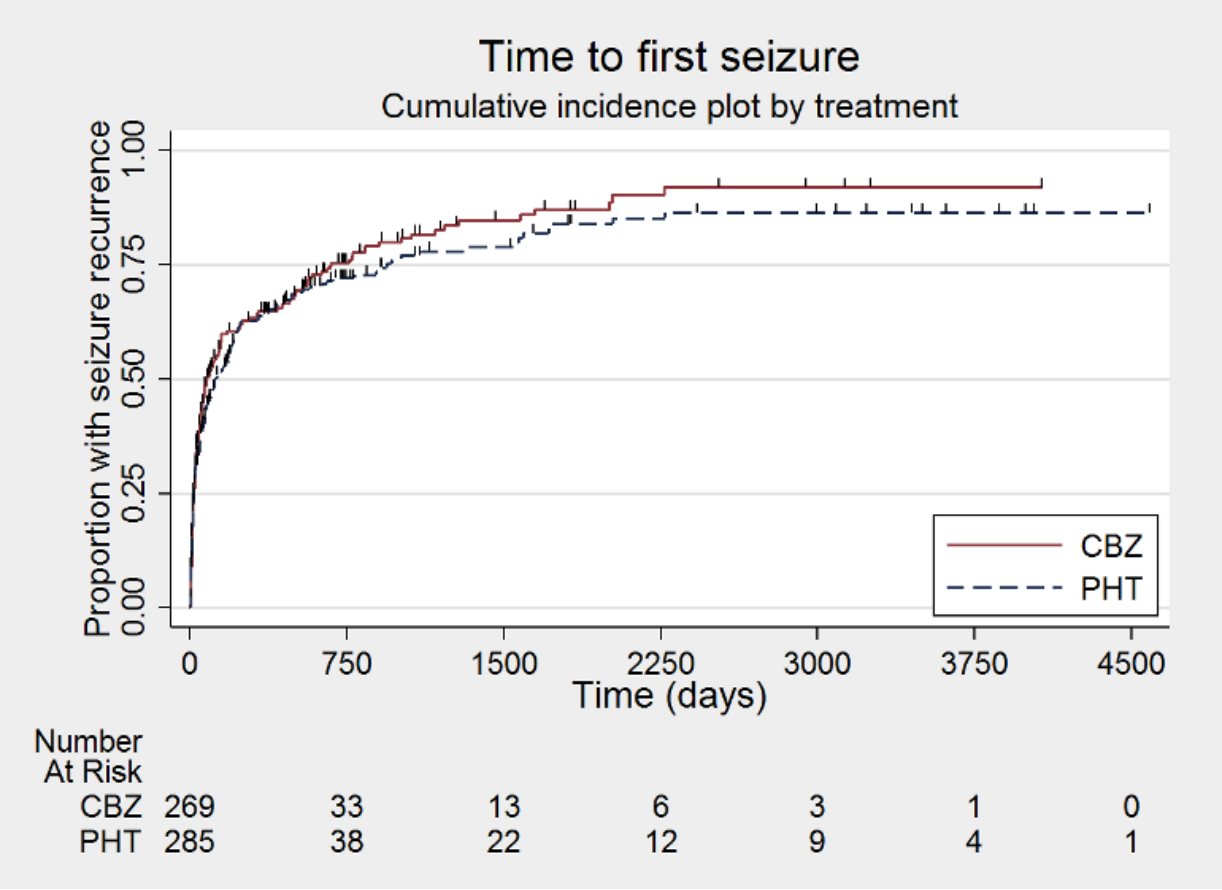
Figure 9



Caption

Time to treatment failure due to lack of efficacy, by epilepsy type (CBZ: carbamazepine; PHT: phenytoin)

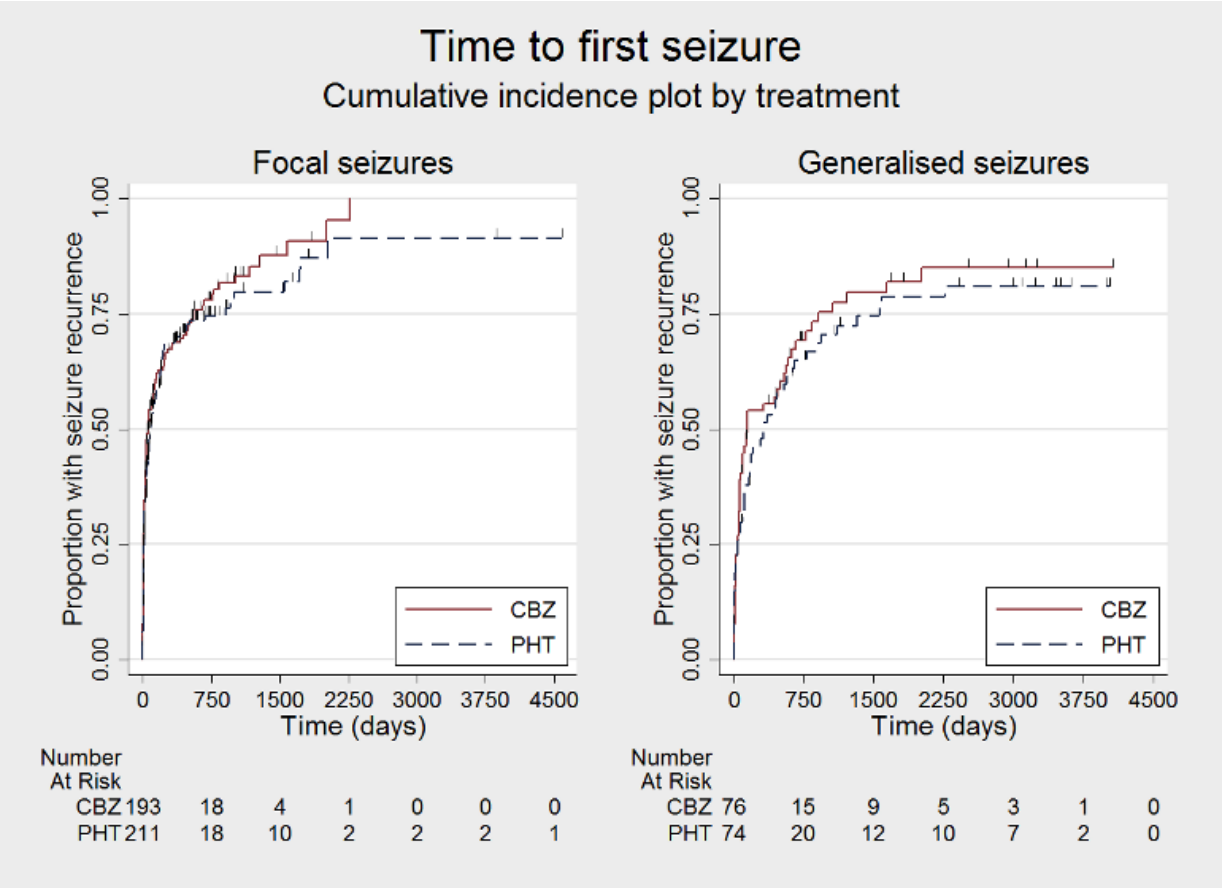
Figure 10



Caption

Time to first seizure (CBZ: carbamazepine; PHT: phenytoin)

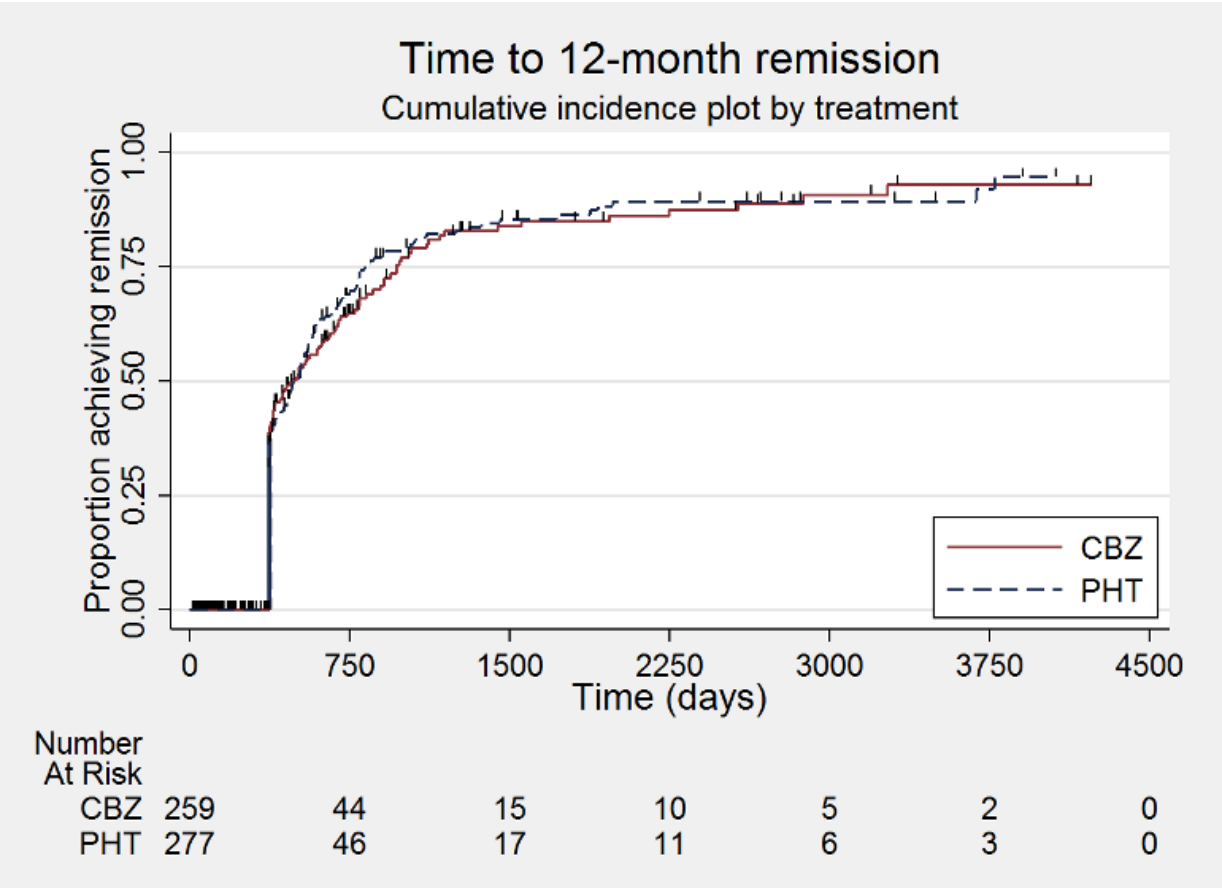
Figure 11



Caption

Time to first seizure, by epilepsy type (CBZ: carbamazepine; PHT: phenytoin)

Figure 12

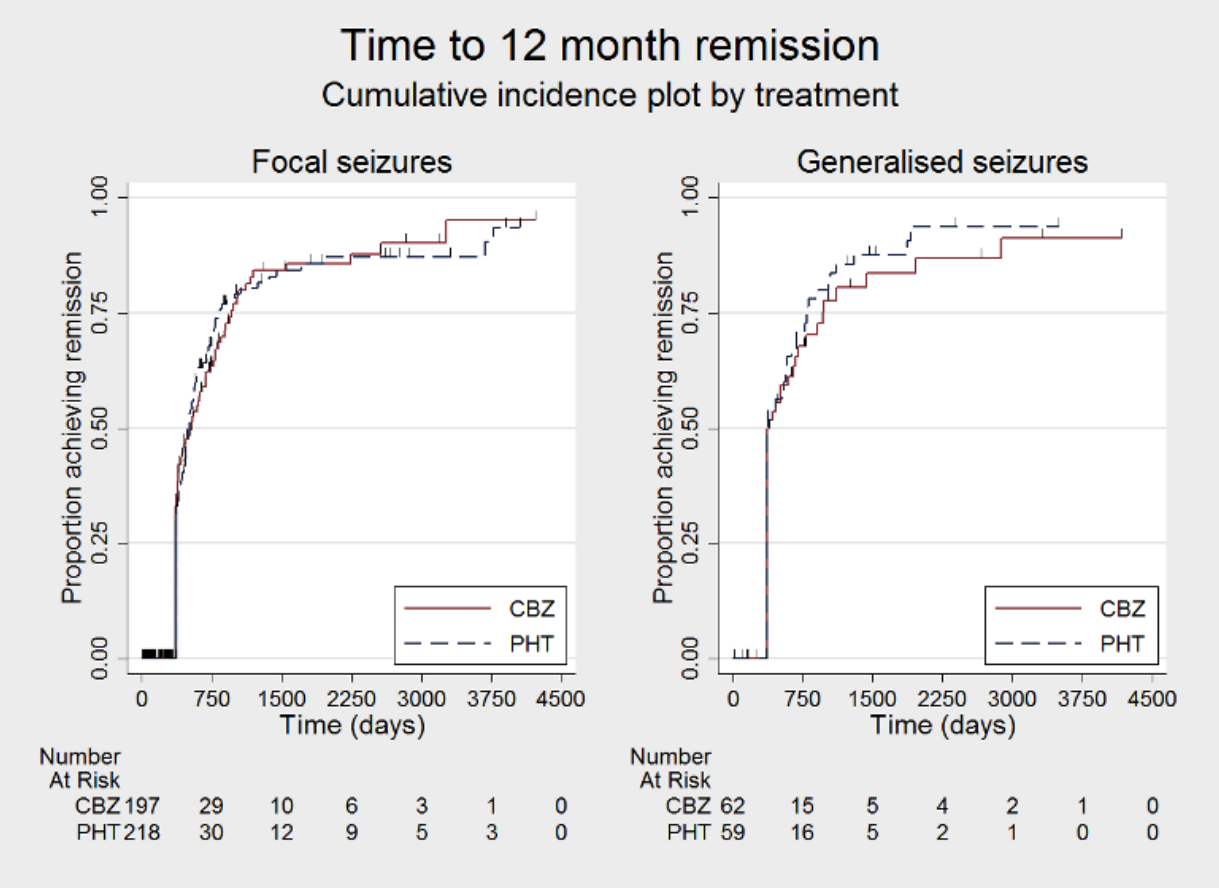


Caption

Caption

Time to 12 month remission (CBZ: carbamazepine; PHT: phenytoin)

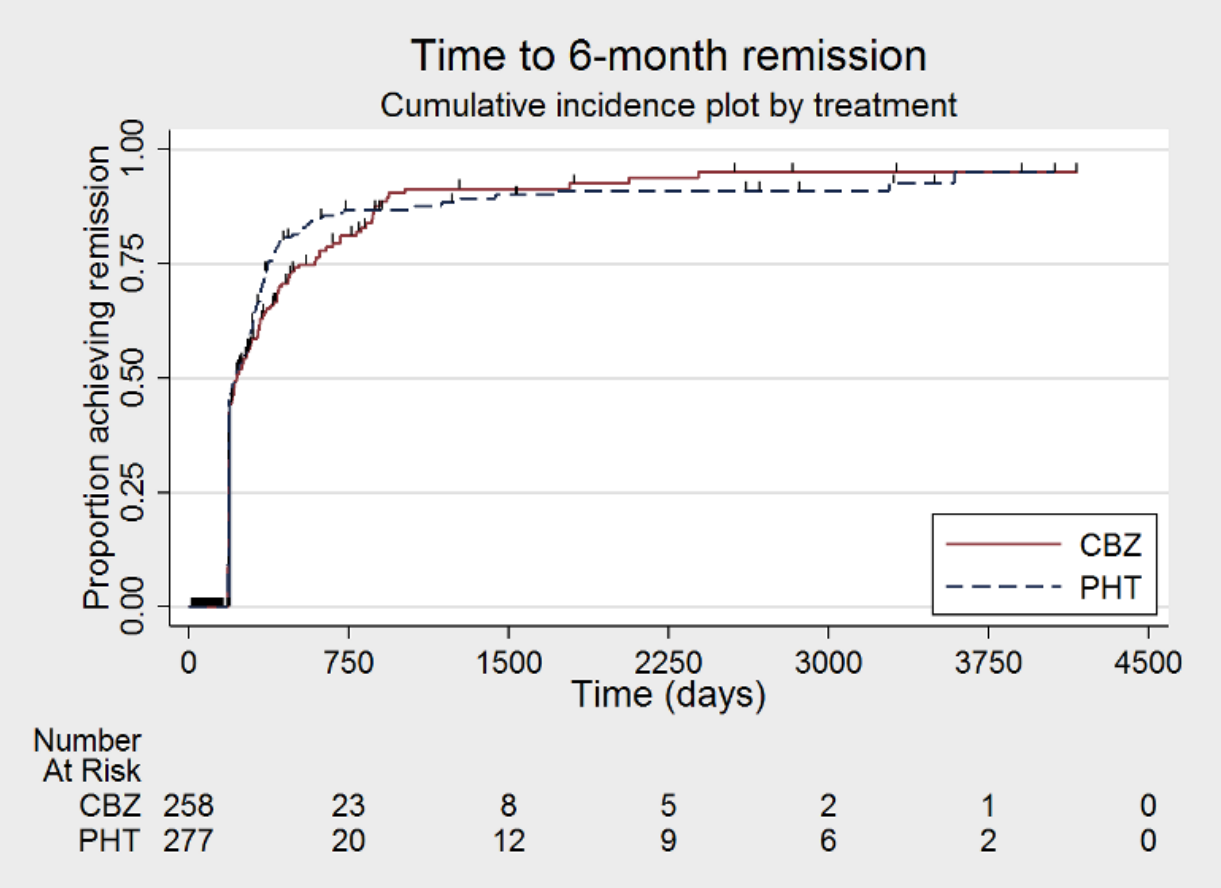
Figure 13



Caption

Time to 12 month remission, by epilepsy type (CBZ: carbamazepine; PHT: phenytoin)

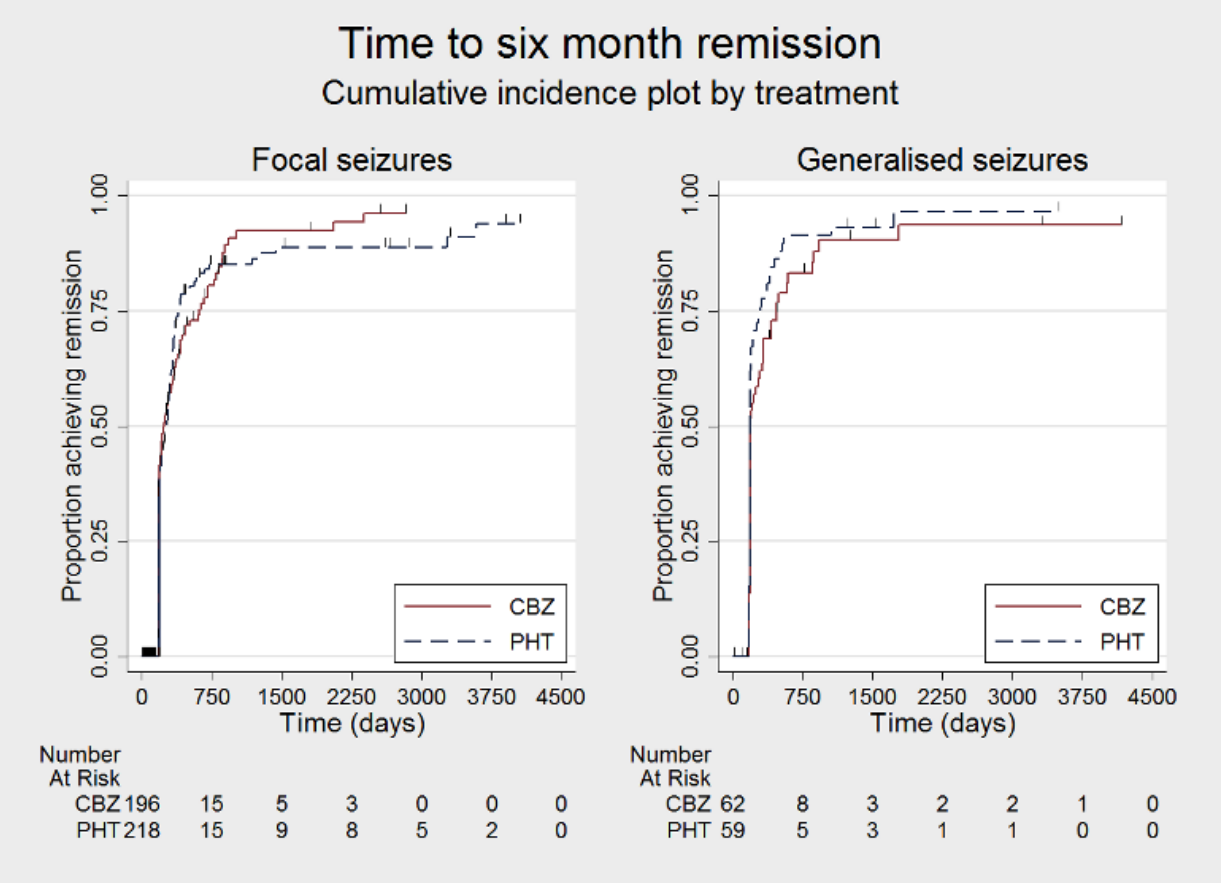
Figure 14



Caption

Time to 6 month remission (CBZ: carbamazepine; PHT: phenytoin)

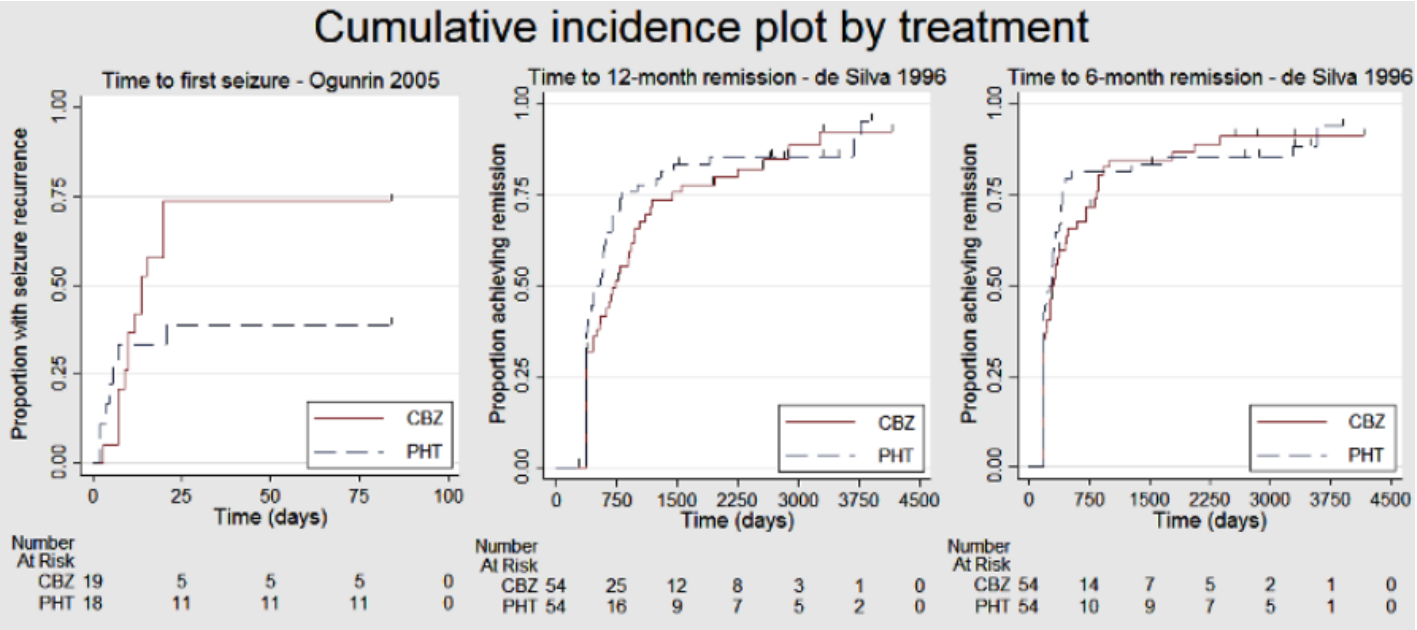
Figure 15



Caption

Time to 6 month remission, by epilepsy type (CBZ: carbamazepine; PHT: phenytoin)

Figure 16



Caption

Cumulative incidence plots, proportional hazards assumption checks

Sources of support

Internal sources

- No sources of support provided

External sources

- Medical Research Council, UK
- National Institute for Health Research (NIHR), UK

Feedback

Appendices

1 Cochrane Register of Studies (CRS Web) Search Strategy

1. MeSH DESCRIPTOR Carbamazepine Explode All AND CENTRAL:TARGET

2. (Carbamazepine OR Carbamezepine OR CBZ OR SPD417 OR Apo-Carbamazepine OR Atretol OR Biston OR Calepsin OR Carbagen OR Carbamazepen OR Carbatrol OR Carbazepine OR Carbelan OR Epitol OR Equetro OR Finlepsin OR Karbamazepin OR Lexin OR Neurotop OR Novo-Carbamaz OR Nu-Carbamazepine OR Sirtal OR Stazepin OR Stazepine OR Taro-Carbamazepine OR Tegretal OR Tegretol OR Telesmin OR Teril OR Timonil):AB, KW,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2 AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Phenytoin Explode All AND CENTRAL:TARGET

5. (Phenytoin OR Dihydantoin OR Diphenylhydantoin OR Diphenylhydantoine OR Diphenylhydatanoin OR Fenitoina OR Phenytoine OR Phenytoinum OR Aleviatin OR Antisacer OR Auranile OR Causoin OR Citrullamon OR Citrulliamon OR Comital OR Comitoina OR Convul OR Danten OR Dantinal OR Dantoinal OR Dantoine OR Denyl OR Di-Hydan OR Di-Lan OR Di-Phetine OR Didan OR Difenilhidantoina OR Difenin OR Difetoin OR Difhydan OR Dihycon OR Dilabid OR Dilantin OR Dilantine OR Dillantin OR Dintoin OR Dintoina OR Diphantoin OR Diphedal OR Diphedan OR Diphenat OR Diphenin OR Diphenine OR Dipheninum OR Diphentoin OR Diphentyn OR Diphenylan OR Ditoinate OR Ekko OR Elepsindon OR Enkelfel OR Epamin OR Epanutin OR Epasmir OR Epdantoin OR Epdantoine OR Epelin OR Epifenyl OR Epihydan OR Epilan OR Epilantin OR Epinat OR Epised OR Eptal OR Eptoin OR Fenantoin OR Fenidantoin OR Fentoin OR Fenylepsin OR Fenytoin OR Fenytoine OR Gerot-epilan-D OR Hidan OR Hidantal OR Hidantilo OR Hidantina OR Hidantomin OR Hindatal OR Hydantal OR Hydantin OR Hydantoin OR Hydantoinal OR Hydantol OR Ictalis OR Idantoil OR Idantoin OR Iphenylhydantoin OR Kessodanten OR Labopal OR Lehydan OR Lepitoin OR Lepsin OR Mesantoin OR Minetoin OR Neos-Hidantoina OR Neosidantoina OR Novantoina OR Novophenytoin OR Om-hidantoina OR Om-Hydantoine OR Oxylan OR Phanantin OR Phanatine OR Phenatine OR Phenatoine OR Phenhydan OR Phenhydanin OR Phenitoin OR Phentoin OR Phentytoin OR Phenytek OR Phenytex OR Ritmenal OR Saceril OR Sanepil OR Silantin OR Sinergina OR Sodanthon OR Sodantoin OR Sodanton OR Solantin OR Solantoin OR Solantyl OR Sylantoic OR Tacosal OR Thilophenyl OR TOIN OR Zentronal OR Zentropil OR PHT):AB,KW,MC,MH,TI AND CENTRAL:TARGET

6. #4 OR #5 AND CENTRAL:TARGET

7. ((adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*)):TI AND CENTRAL:TARGET

8. (#3 AND #6) NOT #7 AND CENTRAL:TARGET

9. >01/11/2016:CRSCREATED AND CENTRAL:TARGET

10. #8 AND #9 AND CENTRAL:TARGET

11. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

12. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

13. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

14. #11 OR #12 OR #13 AND CENTRAL:TARGET

15. #10 AND #14

2 MEDLINE (Ovid) search strategy

The following search is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (Lefebvre 2011).

1. exp Carbamazepine/

2. (Carbamazepin$ or Carbamezepine or CBZ or SPD417 or Apo-Carbamazepine or Atretol or Biston or Calepsin or Carbagen or Carbamazepen or Carbatrol or Carbazepine or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotop or Novo-Carbamaz or Nu-Carbamazepine or Sirtal or Stazepin or Stazepine or Taro-Carbamazepine or Tegretal or Tegretol or Telesmin or Teril or Timonil).tw.

3. 1 or 2

4. exp Phenytoin/

5. (Phenytoin$ or Dihydantoin or Diphenylhydantoin or Diphenylhydantoine or Diphenylhydatanoin or Fenitoina or Phenytoine or Phenytoinum or Aleviatin or Antisacer or Auranile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoinal or Dantoine or Denyl or Di-Hydan or Di-Lan or Di-Phetine or Didan or Difenilhidantoina or Difenin or Difetoin or Difhydan or Dihycon or Dilabid or Dilantin or Dilantine or Dillantin or Dintoin or Dintoina or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin or Diphenine or Dipheninum or Diphentoin or Diphentyn or Diphenylan or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin or Epdantoine or Epelin or Epifenyl or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fentoin or Fenylepsin or Fenytoin or Fenytoine or Gerot-epilan-D or Hidan or Hidantal or Hidantilo or Hidantina or Hidantomin or Hindatal or Hydantal or Hydantin or Hydantoin or Hydantoinal or Hydantol or Ictalis or Idantoil or Idantoin or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or Neos-Hidantoina or Neosidantoina or Novantoina or Novophenytoin or Om-hidantoina or Om-Hydantoine or Oxylan or Phanantin or Phanatine or Phenatine or Phenatoine or Phenhydan or Phenhydanin or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytex or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodantoin or Sodanton or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentronal or Zentropil or PHT).tw.

6. 4 or 5

7. exp Epilepsy/

8. exp Seizures/

9. (epilep$ or seizure$ or convuls$).tw.

10. 7 or 8 or 9

11. exp Pre-Eclampsia/ or exp Eclampsia/

12. 10 not 11

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

14. clinical trials as topic.sh.

15. trial.ti.

16. 13 or 14 or 15

17. exp animals/ not humans.sh.

18. 16 not 17

19. 3 and 6 and 12 and 18

20. ((adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$) not (monotherap$ or alone

or singl$)).ti.

21. 19 not 20

22. limit 21 to ed=20161101-20180813

23. 21 not (1$ or 2$).ed.

24. 23 and (2016$ or 2017$ or 2018$).dt.

25. 22 or 24

26. remove duplicates from 25

3 ClinicalTrials.gov search strategy

Interventional Studies | Epilepsy | carbamazepine AND phenytoin | First posted on or after 11/01/2016

4 ICTRP search strategy

Condition: epilepsy

Intervention: carbamazepine and phenytoin

Date of registration between 01/11/2016 and 13/08/2018

Recruitment status: all

Phases: 2, 3, 4

5 SCOPUS Search Strategy

(((TITLE(carbamazepine OR carbamezepine OR cbz OR spd417 OR apo-carbamazepine OR atretol OR biston OR calepsin OR carbagen OR carbamazepen OR carbatrol OR carbazepine OR carbelan OR epitol OR equetro OR finlepsin OR karbamazepin OR lexin OR neurotop OR novo-carbamaz OR nu-carbamazepine OR sirtal OR stazepin OR stazepine OR taro-carbamazepine OR tegretal OR tegretol OR telesmin OR teril OR timonil)) OR (ABS(carbamazepine OR carbamezepine OR cbz OR spd417 OR apo-carbamazepine OR atretol OR biston OR calepsin OR carbagen OR carbamazepen OR carbatrol OR carbazepine OR carbelan OR epitol OR equetro OR finlepsin OR karbamazepin OR lexin OR neurotop OR novo-carbamaz OR nu-carbamazepine OR sirtal OR stazepin OR stazepine OR taro-carbamazepine OR tegretal OR tegretol OR telesmin OR teril OR timonil))) AND ((TITLE(phenytoin OR dihydantoin OR diphenylhydantoin OR diphenylhydantoine OR diphenylhydatanoin OR fenitoina OR phenytoine OR phenytoinum OR aleviatin OR antisacer OR auranile OR causoin OR citrullamon OR citrulliamon OR comital OR comitoina OR convul OR danten OR dantinal OR dantoinal OR dantoine OR denyl OR di-hydan OR di-lan OR di-phetine OR didan OR difenilhidantoina OR difenin OR difetoin OR difhydan OR dihycon OR dilabid OR dilantin OR dilantine OR dillantin OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifenyl OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantin OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR lepitoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phentytoin OR phenytek OR phenytex OR ritmenal OR saceril OR sanepil OR silantin OR sinergina OR sodanthon OR sodantoin OR sodanton OR solantin OR solantoin OR solantyl OR sylantoic OR tacosal OR thilophenyl OR toin OR zentronal OR zentropil OR pht)) OR (ABS(phenytoin OR dihydantoin OR diphenylhydantoin OR diphenylhydantoine OR diphenylhydatanoin OR fenitoina OR phenytoine OR phenytoinum OR aleviatin OR antisacer OR auranile OR causoin OR citrullamon OR citrulliamon OR comital OR comitoina OR convul OR danten OR dantinal OR dantoinal OR dantoine OR denyl OR di-hydan OR di-lan OR di-phetine OR didan OR difenilhidantoina OR difenin OR difetoin OR difhydan OR dihycon OR dilabid OR dilantin OR dilantine OR dillantin OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifenyl OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantin OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR lepitoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phentytoin OR phenytek OR phenytex OR ritmenal OR saceril OR sanepil OR silantin OR sinergina OR sodanthon OR sodantoin OR sodanton OR solantin OR solantoin OR solantyl OR sylantoic OR tacosal OR thilophenyl OR toin OR zentronal OR zentropil OR pht))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR

"ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)))) AND NOT (TITLE((adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*) AND NOT (monotherap* OR alone OR singl*)))