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

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[Intervention Review]

Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

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ABSTRACT

Background

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

Worldwide, sodium valproate and phenytoin are commonly used antiepileptic drugs for monotherapy treatment. It is generally believed that phenytoin is more effective for focal onset seizures, and that sodium valproate is more effective for generalised onset tonic-clonic seizures (with or without other generalised seizure types). This review is one in a series of Cochrane Reviews investigating pair-wise monotherapy comparisons. This is the latest updated version of the review first published in 2001, and updated in 2013 and 2016.

Objectives

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

Search methods

We searched the Cochrane Epilepsy Group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform ICTRP on 19 February 2018. We handsearched relevant journals, contacted pharmaceutical companies, original trial investigators and experts in the field.

Selection criteria

Randomised controlled trials (RCTs) comparing monotherapy with either sodium valproate 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 and our secondary outcomes were time to first seizure post-randomisation, time to six-month, and 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

We included 11 trials in this review and IPD were available for 669 individuals out of 1119 eligible individuals from five out of 11 trials, 60% of the potential data. Results apply to focal onset seizures (simple, complex and secondary generalised tonic-clonic seizures), and generalised tonic-clonic seizures, but not other generalised seizure types (absence or myoclonus seizure types). For remission outcomes, a HR of less than 1 indicates an advantage for phenytoin, and for first seizure and treatment failure outcomes a HR of less than 1 indicates an advantage for sodium valproate.

The main overall results were: time to treatment failure for any reason related to treatment (pooled HR adjusted for seizure type 0.88, 95% CI 0.61 to 1.27; 5 studies; 528 participants; moderate-quality evidence), time to treatment failure due to adverse events (pooled HR adjusted for seizure type 0.77, 95% CI 0.44 to 1.37; 4 studies; 418 participants; moderate-quality evidence), time to treatment failure due to lack of efficacy (pooled HR for all participants 1.16 (95% CI 0.71 to 1.89; 5 studies; 451 participants; moderate-quality evidence). These results suggest that treatment failure for any reason related to treatment and treatment failure due to adverse events may occur earlier on phenytoin compared to sodium valproate, while treatment failure due to lack of efficacy may occur earlier on sodium valproate than phenytoin; however none of these results were statistically significant.

Results for time to first seizure (pooled HR adjusted for seizure type 1.08, 95% CI 0.88 to 1.33; 5 studies; 639 participants; low-quality evidence) suggest that first seizure recurrence may occur slightly earlier on sodium valproate compared to phenytoin. There were no clear differences between drugs in terms of time to 12-month remission (pooled HR adjusted for seizure type 1.02, 95% CI 0.81 to 1.28; 4 studies; 514 participants; moderate-quality evidence) and time to six-month remission (pooled HR adjusted for seizure type 1.05, 95% CI 0.86 to 1.27; 5 studies; 639 participants; moderate-quality evidence).

Limited information was available regarding adverse events in the trials and we could not make comparisons between the rates of adverse events on sodium valproate and phenytoin. Some adverse events reported with both drugs were drowsiness, rash, dizziness, nausea and gastrointestinal problems. Weight gain was also reported with sodium valproate and gingival hypertrophy/hyperplasia was reported on phenytoin.

The methodological quality of the included trials was generally good, however four out of the five trials providing IPD for analysis were of an open-label design, therefore all results were at risk of detection bias. There was also evidence that misclassification of seizure type may have confounded the results of this review, particularly for the outcome 'time to first seizure' and heterogeneity was present in analysis of treatment failure outcomes which could not be explained by subgroup analysis by epilepsy type or by sensitivity analysis for misclassification of seizure type. Therefore, for treatment failure outcomes we judged the quality of the evidence to be moderate to low, for 'time to first seizure' we judged the quality of the evidence to be low, and for remission outcomes we judged the quality of the evidence to be moderate.

Authors' conclusions

We have not found evidence that a significant difference exists between valproate and phenytoin for any of the outcomes examined in this review. However detection bias, classification bias and heterogeneity may have impacted on the results of this review. We did not find any outright evidence to support or refute current treatment policies. We recommend 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

Sodium valproate versus phenytoin monotherapy (single drug treatment) for epilepsy

This is an updated version of the Cochrane Review previously published in Issue 4, 2016 of the *Cochrane Database of Systematic Reviews*.

Background

Epilepsy is a common neurological disorder in which abnormal electrical discharges from the brain cause recurrent seizures. We studied two types of epileptic seizures in this review: generalised onset seizures, in which electrical discharges begin in one part of the brain and move throughout the brain; and focal onset seizures, in which the seizure is generated in and affects one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain). Focal seizures may become generalised (secondary generalisation) and move from one part of the brain throughout the brain. For around 70% of people with epilepsy, a single antiepileptic medication can control generalised onset or focal onset seizures.

Objective

Sodium valproate and phenytoin are commonly used treatments for individuals with epilepsy. The aim of this review was to compare how effective these drugs are at controlling seizures and whether individuals choose to stop taking these treatments (treatment failure), to inform a choice between these drugs.

Methods

The last search for trials for this review was 19 February 2018. We assessed the evidence from 11 randomised controlled clinical trials comparing sodium valproate to phenytoin and we were able to combine data for 699 people from five of the 11 trials; for the remaining 450 people from six trials, data were not available to use in this review.

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) and controlling seizures (recurrence of seizures or achievement of a seizure-free period (remission) of 6 months or 12 months). The review also found no evidence to support or refute the policy of using sodium valproate for generalised onset tonic-clonic seizures and phenytoin for focal onset seizures.

However, up to 49% of people within the trials classified as having generalised seizures may have had their seizure type wrongly diagnosed and these people may have been experiencing focal seizures or an uncertain seizure type, and this misclassification may have influenced the results of this review. We were unable to address the issue of preferring sodium valproate for generalised onset seizure types other than tonic-clonic, such as absence or myoclonic seizures.

Quality of the evidence


We judged the quality 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 four of the five 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.

Conclusions

Sodium valproate and phenytoin are commonly used treatments for individuals with epilepsy, but we found no difference between these treatments for the outcomes of this review or between seizure types. More information is needed and we recommend that all future trials comparing these medications, or any other antiepileptic medications, should be designed using high-quality methods. Seizure types of people included in trials should also be classified very carefully to ensure that the results are also of high quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Sodium valproate compared with phenytoin monotherapy for epilepsy						
Patient or population: adults and children with newly-onset focal onset or generalised tonic-clonic seizures Settings: outpatients Intervention: sodium valproate Comparison: phenytoin						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenytoin	Sodium valproate				
Time to treatment failure (any reason related to treatment) <i>All participants</i> Range of follow-up: 0 to 4256 days	The median time to treatment failure was 2361 days in the phenytoin group	The median time to treatment failure was 2545 days (184 days longer) in the sodium valproate group	HR 0.88 (0.61 to 1.27) ^a	528 (5 studies)	⊕⊕⊕○ Moderate^b	HR < 1 indicates a clinical advantage for valproate There was also no statistically significant difference between drugs in treatment failure due to adverse events: HR 0.77 (95% CI 0.44 to 1.37, P = 0.38) or treatment failure due to lack of efficacy: HR 1.16 (95% CI 0.71 to 1.89, P = 0.55)
Time to treatment failure (any reason related to treatment) <i>Subgroup: focal onset seizures</i> Range of follow-up: 0 to 4256 days	The median time to treatment failure was 1838 days in the phenytoin group	The median time to treatment failure was 1772 days (66 days shorter) in the sodium valproate group	HR 0.83 (0.50 to 1.38)	187 (4 studies)	⊕⊕⊕○ Moderate^b	HR < 1 indicates a clinical advantage for valproate There was also no statistically significant difference between drugs in treatment failure due

						to adverse events: HR 0.81 (95% CI 0.34 to 1.90, P = 0.62) or treatment failure due to lack of efficacy: HR 1.01 (95% CI 0.55 to 1.85, P = 0.98)
Time to treatment failure (any reason related to treatment) <i>Subgroup: generalised onset seizures (tonic-clonic only)</i> Range of follow-up: 0 to 4394 days	The 25th percentile** of time to treatment failure was 1488 days in the phenytoin group	The 25th percentile** of time to treatment failure was 1778 days (290 days longer) in the sodium valproate group	HR 0.94 (0.55 to 1.61)	341 (5 studies)	 Low^{b,c}	HR < 1 indicates a clinical advantage for valproate There was also no statistically significant difference between drugs in treatment failure due to adverse events: HR 0.75 (95% CI 0.35 to 1.60, P = 0.46) or treatment failure due to lack of efficacy: HR 1.51 (95% CI 0.66 to 3.45, P = 0.33)

* Illustrative risks in the sodium valproate 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 HR) shows the comparison of 'time to treatment failure' between the treatment groups
 ** The 25th percentile of time to treatment failure (i.e. the time to 25% of participants failing or withdrawing from allocated treatment) is presented for the subgroup with generalised seizures as less than 50% of participants failed/withdrew from treatment, therefore the median time could not be calculated

Abbreviations: CI: confidence interval; HR: hazard ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

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

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aPooled HR for all participants adjusted for seizure type.

^bDowngraded once as risk of bias judged high for three unblinded studies (De Silva 1996; Heller 1995; Ramsay 1992); lack of blinding may have impacted on the withdrawal rates and treatment failure rates in the trials.

^cDowngraded once due to inconsistency: a large amount of heterogeneity is present within analysis ($I^2 = 59\%$) which could not be explained by sensitivity analysis for potential misclassification of epilepsy type.

BACKGROUND

This is an updated version of the original Cochrane review published in 2001 (Tudur Smith 2001), updated in 2013 and 2016 (Nolan 2013a; Nolan 2016a).

Description of the condition

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

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

Description of the intervention

The majority of people with epilepsy have their seizures controlled by a single drug (monotherapy) (Cockerell 1995). Worldwide, sodium valproate and phenytoin are commonly used antiepileptic drugs licensed for monotherapy. Phenytoin is used as a first-line drug in low- and middle-income countries as it is a low-cost drug and can be given as a single daily dose, but is no longer considered a first-line agent in the USA and much of Europe due to worries over adverse events (Wallace 1997; Wilder 1995). Phenytoin is associated with long-term cosmetic changes including gum hyperplasia, acne and coarsening of the facial features (Mattson 1985; Scheinfeld 2003), as well as low folic acid levels, predisposing participants to megaloblastic anaemia (Carl 1992), and is associated with congenital abnormalities (Gladstone 1992; Morrow

2006; Meador 2008; Nulman 1997), particularly foetal hydantoin syndrome (Scheinfeld 2003). Furthermore, due to the pharmacokinetic profile of phenytoin, the plasma concentrations are difficult to predict and dosing will usually need to be informed by measuring plasma concentration. Sodium valproate has also been shown to have teratogenic properties (Canger 1999; Morrow 2006; Tomson 2011), and is particularly associated with spina bifida and cardiac, craniofacial, skeletal and limb defects known as 'valproate syndrome' (Ornoy 2009). Systematic reviews have found sodium valproate to have the highest incidence of congenital malformations of standard antiepileptic drugs (Meador 2008; Weston 2017), and recent studies have shown an increased prevalence of neurodevelopmental disorders following prenatal sodium valproate exposure (Bromley 2013; Bromley 2014). Sodium valproate is also associated with weight gain in adults and children (Dinesen 1984; Easter 1997; Egger 1981; Novak 1999).

How the intervention might work

It is generally believed that sodium valproate monotherapy is more effective than phenytoin monotherapy in generalised onset seizures (generalised tonic-clonic seizures, absence, and myoclonus), while phenytoin monotherapy is more effective than sodium valproate monotherapy in focal onset seizures (simple focal, complex focal, and secondary generalised tonic-clonic seizures) (Chadwick 1994), although there is no conclusive evidence from individual randomised controlled trials (RCTs) to support this belief. Evidence in favour of sodium valproate for generalised seizures is predominantly anecdotal from observational studies, suggesting a dramatic benefit with sodium valproate in juvenile myoclonic epilepsy (Delgado-Escueta 1984; Penry 1989), and reports of efficacy of sodium valproate against absence seizures (Bourgeois 1987; Jeavons 1977). The results of two RCTs, recruiting children indicate that sodium valproate may be better tolerated in children than phenytoin (De Silva 1996; Thilothammal 1996); twice as many children experienced at least one side effect on phenytoin than sodium valproate in Thilothammal 1996, and phenytoin was more likely to be withdrawn due to unacceptable side effects than sodium valproate in De Silva 1996.

Some animal models have suggested that phenytoin has either no effect in absence seizures or may in fact worsen seizures (Liporace 1994). There is also anecdotal evidence that phenytoin may cause paradoxical intoxication (increased seizure frequency with increased anticonvulsant dose) and encephalopathy (Troupin 1975; Vallarta 1974).

Why it is important to do this review

Accepting that phenytoin should not be a drug of first choice for individuals experiencing absence, myoclonic and atonic seizures, we still have insufficient evidence from RCTs to guide a choice be-

tween sodium valproate and phenytoin for individuals with generalised onset tonic-clonic seizures or focal onset seizures. The aim of this review, therefore, is to summarise efficacy and tolerability data from existing trials comparing valproate and phenytoin when used as monotherapy treatments.

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 2013d; Williamson 2000).

Furthermore, although seizure data have been collected in most epilepsy monotherapy trials, 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 date of achieving maintenance dose. Trial investigators have also adopted differing approaches to the analysis, particularly with respect to the censoring of time-to-event data. For these reasons, we performed this review using individual participant data (IPD) which helps to overcome these problems. This review is one in a series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons (Marson 2000; Nevitt 2017b; Nolan 2013b; Nolan 2013c; Nolan 2016b; Nolan 2016c; Nevitt 2018). 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 of sodium valproate compared to phenytoin when used as monotherapy in people with focal onset seizures or generalised tonic-clonic seizures (with or without other generalised seizure types).

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) using either:
 - an adequate method of allocation concealment (e.g. sealed opaque envelopes); or

- a 'quasi' method of randomisation (e.g. allocation by date of birth).

- Studies may be double-blind, single-blind or unblinded.
- Studies must include a comparison of sodium valproate monotherapy with phenytoin monotherapy in individuals with epilepsy.

Types of participants

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

Types of interventions

Sodium valproate or phenytoin as monotherapy. For brevity, sodium valproate is referred to a 'valproate' herein.

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 inclusion in this review.

Primary outcomes

- Time to treatment failure (retention time).

This is a combined outcome reflecting both efficacy and tolerability, as the following may have lead to failure of treatment: continued seizures, side effects, noncompliance 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). Time to treatment failure is considered according to three definitions.

- Time to treatment failure, for any treatment-related reason (continued seizures, side effects, noncompliance 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).
- Incidence of adverse events.

Search methods for identification of studies

Electronic searches

We searched the following databases. We did not impose any language restrictions.

- The Cochrane Epilepsy Group's Specialised Register (19 February 2018) using the search strategy outlined in [Appendix 1](#).
- The Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 2) in the Cochrane Library (searched 19 February 2018) using the search strategy outlined in [Appendix 2](#).
- MEDLINE (Ovid, 1946 to 19 February 2018) using the search strategy outlined in [Appendix 3](#).
- SCOPUS (last search 19 February 2013) using the search strategy outlined in [Appendix 4](#). We searched SCOPUS as an alternative to Embase, but this is no longer necessary, because randomised and quasi-RCTs in Embase are now included in CENTRAL, so we will not be updating the SCOPUS search.
- [ClinicalTrials.gov](#) (19 February 2018) using the search terms 'phenytoin AND valproate | Epilepsy'.
- [WHO International Clinical Trials Registry Platform ICTRP](#) (19 February 2018) using the search terms 'valproate and phenytoin and epilepsy'.

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 Sanofi (manufacturers of valproate in Europe), Abbott (manufacturers of valproate in the USA), Parke-Davis (manufacturers of phenytoin), and experts in the field for information about any ongoing studies.

Data collection and analysis

Selection of studies

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

Data extraction and management

We requested the following individual participant data (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 withdrawal or treatment failure and reasons for treatment withdrawal or treatment failure
 - dose
 - dates of dose changes

For each trial for which IPD were not obtained, we carried out an assessment to see whether any relevant aggregate level data had been reported. If possible, SJN extracted any aggregate level data from publications and extracted data were verified by JW.

For three trials, seizure data were provided in terms of the number of seizures recorded between clinic visits rather than specific dates of seizures ([Craig 1994](#); [Ramsay 1992](#); [Turnbull 1985](#)). To enable time-to-event outcomes to be calculated, we applied linear interpolation to approximate the dates on which seizures occurred. For example, if four seizures were recorded between two visits which occurred on 1 March and 1 May (an interval of 61 days), then date of first seizure would be approximately 13 March. This allowed an estimate of the time to achieve six-month and 12-month remission and the time to first seizure to be computed.

We calculated time to achieve 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 seizure(s) 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, these outcomes were censored at the previous visit. These outcomes were also censored 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 two trials for which outcome data were provided directly (De Silva 1996; Heller 1995).

Treatment failure data were not available for one trial (Craig 1994). For two trials, we extracted dates and reason for treatment failure from trial case report forms for the original review (De Silva 1996; Heller 1995). Two review authors (SJN and AGM) independently extracted data from all case report forms, resolving disagreements by discussion and reconsidering the case report forms. For the remaining trials (Ramsay 1992; Turnbull 1985), data on length of time spent in trial and reason for withdrawal from treatment or treatment failure were provided directly.

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

For the analysis of 'time to treatment failure due to adverse events,' only treatment failures which were documented to be due to adverse events (either as a sole reason or due to both a lack of efficacy and adverse events) were classed as an 'event' within time-to-event analyses and all other reasons for treatment failure were censored. Similarly, for the analysis of 'time to treatment failure due to lack of efficacy' only treatment failures which were documented to be due to lack of efficacy (i.e. continued seizures, either as a sole reason or due to both a lack of efficacy and adverse events) were classed as an 'event' within time-to-event analyses and all other reasons for treatment failure were censored.

Two trials presented times at which the allocated drug was withdrawn and the reason for treatment failure in the trial publication for each individual (Forsythe 1991; Shakir 1981). Hence, these two trials could be incorporated into the analysis of 'time to treatment failure'; one of the trials also presented information by seizure type (focal onset or generalised onset seizures) and there-

fore could also be included in the stratified analysis for 'time to treatment failure' (Shakir 1981).

Shakir 1981 presents 'time on trial drug' in months for each participant; therefore to calculate 'time to treatment failure', we assumed that if 'time spent on trial drug' was five months, the individual spent five full months (152 full days) on the trial drug before treatment failure. Forsythe 1991 presents 'withdrawal and time of occurrence by month' for each participant; therefore to calculate 'time to treatment failure', we assumed that if treatment failure occurred during the fifth month, that the treatment failure occurred halfway between the fifth and sixth month (i.e. participants spent 167 full days on treatment before treatment failure).

Assessment of risk of bias in included studies

Two review authors (SJN and JW) independently assessed the risk of bias for each trial using the Cochrane 'Risk of bias' tool, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We rated each of the following six domains as low, unclear or high risk of bias: method of generating random sequence, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias. Any discrepancies in risk of bias judgements of the two review authors were resolved by discussion. In the event of the presence of high risk of bias in included trials (due to inadequate allocation concealment or lack of blinding), we planned sensitivity analyses excluding these trials.

Measures of treatment effect

We measured all outcomes in this review as time-to-event outcomes with the hazard ratio (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-analyses were of a repeated measures (longitudinal) nature or of a cross-over design.

Dealing with missing data

For each trial that supplied IPD, we reproduced results 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. If trial authors could not resolve inconsistencies between the IPD and the published data, depending on the extent of the inconsistencies, we planned to

perform sensitivity analysis or excluded the data from the meta-analysis.

- We reviewed the chronological randomisation sequence and checked the balance of prognostic factors, taking account of factors stratified for in the randomisation procedure.

Assessment of heterogeneity

We assessed heterogeneity statistically using the Q test ($P < 0.10$ for significance) and the I^2 statistic (greater than 50% indicating considerable heterogeneity; Higgins 2003), and visually by inspecting forest plots.

Assessment of reporting biases

Two review authors (SJN and JW) undertook all full quality and risk of bias assessments. 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 (that is, we analysed participants in the group to which they were randomised, irrespective of which treatment they actually received). Therefore, for the time-to-event outcomes, 'time to six-month remission', 'time to 12-month remission', 'time to 24 month remission' and 'time to first seizure post-randomisation', we did not censor participants if treatment was withdrawn or if treatment failure occurred but follow-up within the trial continued (e.g. if a participant continued to be followed up on a different treatment).

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. We evaluated overall pooled estimates of HRs (with 95% CIs) using the generic inverse variance method. We expressed results as a HR and a 95% CI.

By convention, a HR greater than 1 indicates that an event is more likely to occur earlier on valproate than on phenytoin. Hence, for time to treatment failure or time to first seizure, a HR less than 1 indicates a clinical advantage for valproate (e.g. HR = 0.8 would suggest a 20% reduction in hazard of treatment failure from valproate compared to phenytoin), and for time to achieve six-month and 12-month remission, a HR less than 1 indicates a clinical advantage for phenytoin.

Subgroup analysis and investigation of heterogeneity

Due to the strong clinical belief that valproate is more effective in generalised onset seizures, while phenytoin is more effective in focal onset seizures, we have 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 χ^2 test of interaction between treatment and epilepsy type.

If we found significant statistical heterogeneity to be present, we performed meta-analysis with a random-effects model in addition to a fixed-effect model, presenting the result of both models and performing sensitivity analyses to investigate differences in study characteristics.

Sensitivity analysis

One trial recruited only individuals with generalised onset tonic-clonic seizures, some of whom were experiencing other generalised seizure types, such as absence or myoclonus (Ramsay 1992), and all generalised seizure types were recorded during follow-up for this trial. The remaining four trials recruited individuals with focal onset seizures (simple/complex focal or secondarily generalised tonic-clonic) and individuals with generalised onset tonic-clonic seizures. For the individuals with generalised onset tonic-clonic seizures recruited into these four trials, other generalised seizure types were not recorded during follow-up. As a result, the majority of the data from the five trials does not address the treatment of generalised seizure types, such as absence or myoclonus, but applies only to generalised onset tonic-clonic seizures. In our primary analysis, we use only the data for generalised onset tonic-clonic seizures during follow-up as this is the most consistent approach; we also report a sensitivity analysis which includes data on all generalised seizure types from Ramsay 1992 for the outcomes 'time to first seizure' and 'time to six-month remission' (Ramsay 1992 was less than one year duration so does not contribute to 'time to 12 month remission').

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 impacted upon 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; Nolan 2016c; Nevitt 2017b). Given the potential biases introduced into those reviews, we examined the distribution of age at onset for individuals with generalised seizures in the trials included in this review, to assess

the potential impact of misclassification of seizure type on the outcomes:

- 84 out of 86 individuals classified as having generalised onset seizures (98%) in [Craig 1994](#);
- 37 out of 71 individuals (52%) in [Heller 1995](#);
- 30 out of 136 (22%) in [Ramsay 1992](#);
- 2 out of 14 (14%) in [Shakir 1981](#); and
- 35 out of 77 (45%) in [Turnbull 1985](#).

Therefore, a total of up to 188 out of 384 individuals (49%) classified as having generalised onset seizures may have had their seizure type misclassified ([De Silva 1996](#) was a paediatric trial so no individuals over the age of 30 were recruited). Such a misclassification could bias our results against finding an interaction between treatment and seizure types (focal onset versus generalised onset). We undertook the following two analyses to investigate misclassification.

- We reclassified all individuals with generalised seizures and age at onset greater than 30 into an 'uncertain seizure type' group.
- We reclassified individuals with generalised seizures and age at onset greater than 30 as having focal onset seizures.

Summary of findings and quality of the evidence (GRADE)

For the 2013 update, in a post hoc change from protocol, we have added two 'Summary of findings' tables to the review (outcomes in the tables decided before the update started based on clinical relevance).

[Summary of findings for the main comparison](#) reports the primary outcome of 'time to treatment failure' in the subgroups of participants with focal onset seizures, generalised onset seizures and overall adjusted by epilepsy type.

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

We determined the quality of the evidence using the GRADE approach ([Schünemann 2013](#)), where we downgraded evidence in the presence of high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results and high probability of publication bias. We downgraded evidence by one level if the limitation was considered serious and two levels if considered very serious, as judged by the review authors.

RESULTS

Description of studies

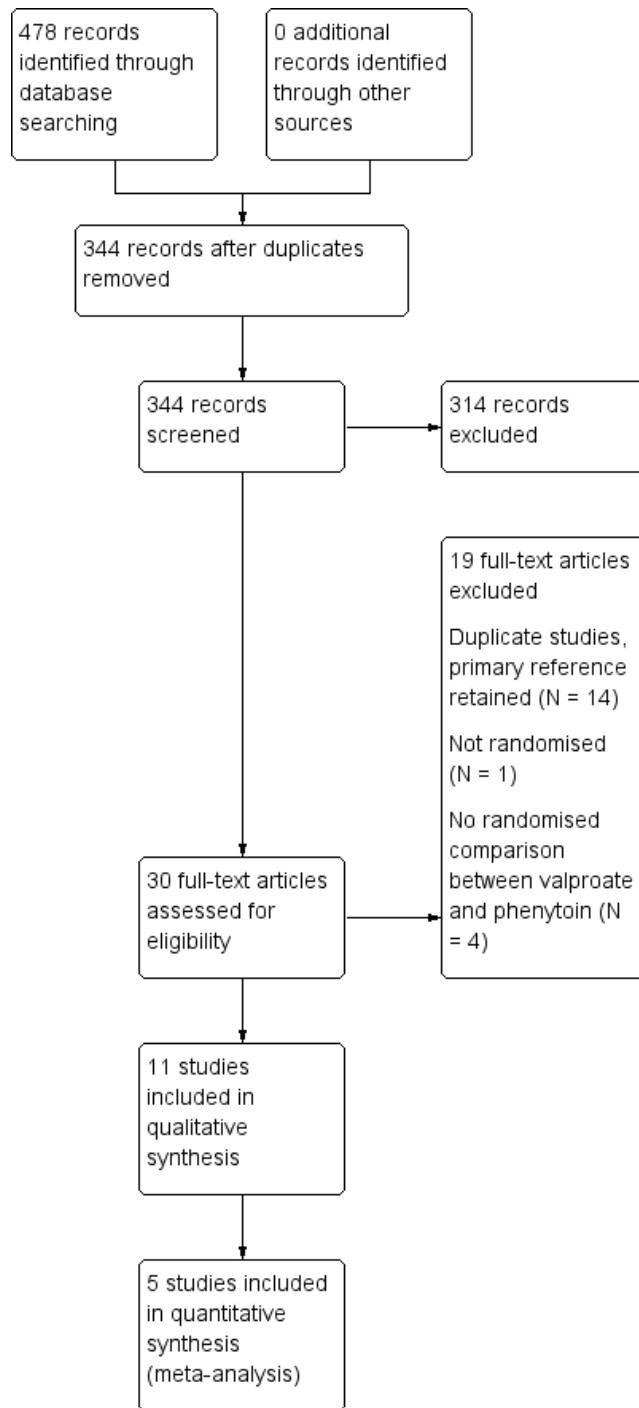
Results of the search

We identified 334 records from the databases and search strategies outlined in [Electronic searches](#). We found no further records by searching other resources. We removed 126 duplicate records and screened 208 records (title and abstract) for inclusion in the review. We excluded 178 records based on title and abstract and assessed 30 full-text articles for inclusion in the review. We excluded 19 studies from the review (see [Excluded studies](#) below) and included 11 trials in the review (see [Included studies](#) below). We updated the searches in May 2015, resulting in 35 hits. We removed seven duplicate records and screened 28 records (title and abstract); we excluded all 28 records.

For the 2018 update of this review we identified 129 records from the databases and search strategies outlined in [Electronic searches](#). We removed 21 duplicate records and screened 108 records (title and abstract) for inclusion in the review. All 108 records were clearly irrelevant and we excluded them.

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

Figure 1. Study flow diagram.



Included studies

We included 11 trials in the review (Callaghan 1985; Czapinski 1997a; Craig 1994; De Silva 1996; Forsythe 1991; Heller 1995; Ramsay 1992; Rastogi 1991; Shakir 1981; Thilothammal 1996; Turnbull 1985). One trial was available in abstract form only (Czapinski 1997a).

Four trials recruited individuals of all ages (Callaghan 1985; Ramsay 1992; Rastogi 1991; Shakir 1981), three trials recruited adults only (Czapinski 1997a; Heller 1995; Turnbull 1985), three trials recruited children only (De Silva 1996; Forsythe 1991; Thilothammal 1996), and one trial recruited elderly individuals only (Craig 1994).

One trial recruited individuals with focal onset seizures only (Czapinski 1997a), two trials recruited individuals with generalised onset seizures only (Ramsay 1992; Thilothammal 1996), seven trials recruited individuals with focal onset seizures and generalised onset seizures (Callaghan 1985; Craig 1994; De Silva 1996; Heller 1995; Rastogi 1991; Shakir 1981; Turnbull 1985), and one trial did not provide information on the seizure types of individuals recruited (Forsythe 1991).

Nine trials recruited individuals with new onset seizures only (Callaghan 1985; Craig 1994; Czapinski 1997a; De Silva 1996; Forsythe 1991; Heller 1995; Ramsay 1992; Thilothammal 1996; Turnbull 1985), 64% of individuals in one trial had new onset seizures, while the remaining individuals had uncontrolled seizures on current therapy (Shakir 1981), and one trial did not specify whether individuals were newly diagnosed (Rastogi 1991). Seven trials were conducted in Europe (Callaghan 1985; Craig 1994; Czapinski 1997a; De Silva 1996; Forsythe 1991; Heller 1995; Turnbull 1985), one trial in the USA (Ramsay 1992), two trials in India (Rastogi 1991; Thilothammal 1996), and one trial in two centres in Europe and New Zealand (Shakir 1981).

Individual participant data (IPD) were provided by trial authors for five trials which recruited a total of 669 participants, representing 60% of individuals from all 1119 eligible participants identified in eligible trials (Craig 1994; De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985). Data were converted from paper format to computer datasets in two trials (Ramsay 1992; Turnbull 1985), computerised data were provided directly in one trial (Craig 1994), and a combination of both (although mostly computerised) were supplied by the authors of two trials (De Silva 1996; Heller 1995).

Data were available for the following participant characteristics (percentage of participants with data available): seizure type (100%); gender (99.6%) age at randomisation (99.3%); number of seizures in the six months prior to randomisation (79%); and epilepsy duration (i.e. time since first seizure to randomisation, 73%). Electroencephalographic (EEG) data had been recorded for all five trials, but only computerised in two trials (Craig 1994; Turnbull 1985). Similar difficulties were encountered with computerised tomography/magnetic resonance imaging (CT/MRI) data available for only one trial (Turnbull 1985), and neurological examination findings, available for only two trials (De Silva 1996; Heller 1995). See the [Characteristics of included studies](#) tables, [Table 1](#) and [Table 2](#) for further details.

IPD were not provided for the remaining six of these trials (Callaghan 1985; Czapinski 1997a; Forsythe 1991; Rastogi 1991; Shakir 1981; Thilothammal 1996), in which a total of 450 individuals had been randomised to either phenytoin or valproate. Sufficient participant level data were presented in the trial publications of Forsythe 1991 and Shakir 1981 to include these studies within the analysis of 'time to treatment failure' (see [Data extraction and management](#) and [Effects of interventions](#)). We could not extract sufficient aggregate data from the trial publication in any other trial, or for any other outcomes to include in data synthesis. Full details of outcomes considered and a summary of results of each trial for which IPD were not available to us can be found in [Table 3](#).

Excluded studies

We excluded 14 duplicate trials (Berg 1993; Callaghan 1981; Callaghan 1983; Callaghan 1984; Craig 1993; Czapinski 1997b; Czapinski 1997c; Goggin 1984; Goggin 1986; Shakir 1980; Tallis 1994a; Tallis 1994b; Turnbull 1982; Wilder 1983), and we retained the most relevant primary reference for each trial in the review. One trial was not randomised (Zeng 2010), and four did not make a randomised comparison between valproate and phenytoin (Jannuzzi 2000; Kaminow 2003; Sabers 1995; Schmidt 2007; see [Characteristics of excluded studies](#) for detailed reasons for exclusion).

Risk of bias in included studies

For further details see [Characteristics of included studies](#), [Figure 2](#) and [Figure 3](#).

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

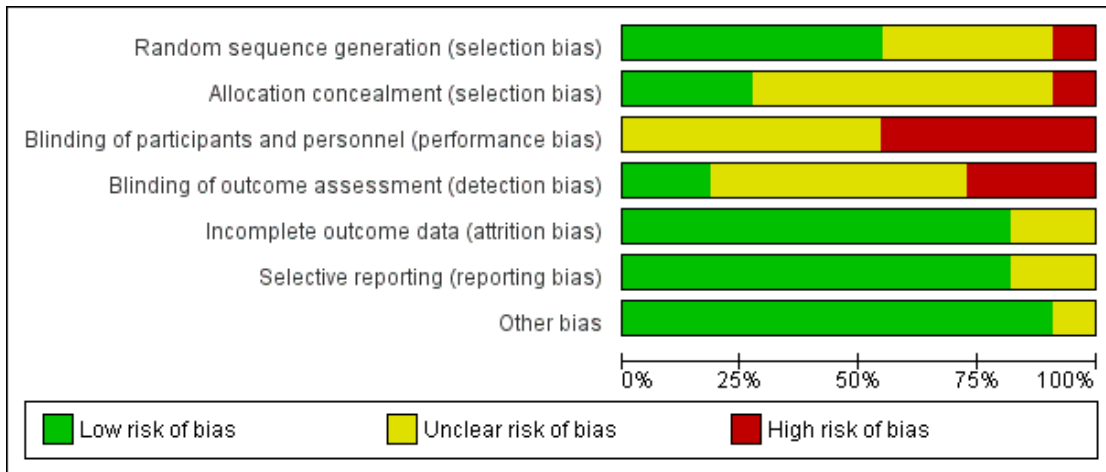


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Callaghan 1985	?	-	?	?	+	+	+
Craig 1994	+	+	-	+	+	+	+
Czapinski 1997a	?	?	?	?	?	?	?
De Silva 1996	+	+	-	-	+	+	+
Forsythe 1991	-	?	-	+	+	?	+
Heller 1995	+	+	-	-	+	+	+
Ramsay 1992	+	?	-	-	+	+	+
Rastogi 1991	?	?	?	?	?	+	+
Shakir 1981	+	?	?	?	+	+	+
Thilothammal 1996	+	?	?	?	+	+	+
Turnbull 1985	?	?	?	?	+	+	+

Allocation

(1) 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). One trial used a computer minimisation programme and a pharmacy-controlled allocation (Craig 1994); we judged these trials to be at low risk of bias for random sequence generation and allocation concealment. One trial reported that random number tables were used but did not report sufficient information about methods of allocation concealment (Ramsay 1992). One trial did not report sufficient information about methods of randomisation and allocation concealment (Turnbull 1985).

(2) Trials for which no IPD were available

Two trials reported adequate methods of randomisation: telephone randomisation in Shakir 1981, and a computer-generated list of randomised numbers in Thilothammal 1996; we judged these studies at low risk of bias for random sequence generation. Two trials reported no information on methods of randomisation (Czapinski 1997a; Rastogi 1991) (unclear risk of bias), one trial reported unclear information on randomisation (Callaghan 1985) (unclear risk of bias), and one trial reported an inadequate method of randomisation, i.e. quota allocation (Forsythe 1991) (high risk of bias). We judged five of the six trials to be at unclear risk of bias as they reported no information on allocation concealment (Czapinski 1997a; Forsythe 1991; Rastogi 1991; Shakir 1981; Thilothammal 1996), and one trial at high risk of bias as it reported an inadequate method of allocation concealment based on 'drug of first preference' (Callaghan 1985).

Blinding

(1) Trials for which IPD were provided

One trial was single-blinded (outcome assessor for cognitive testing) (Craig 1994) (low risk of bias), three trials were unblinded for "practical and ethical reasons" (De Silva 1996; Heller 1995; Ramsay 1992) (high risk of bias), and one trial provided no information on blinding (Turnbull 1985) (unclear risk of bias).

(2) Trials for which no IPD were available

One trial was described as double-blinded (Thilothammal 1996) but it was unclear who was blinded, one trial was single-blinded (outcome assessor for cognitive testing) (Forsythe 1991), and no information was provided on blinding in the other trials (Callaghan 1985; Czapinski 1997a; Rastogi 1991; Shakir 1981).

Incomplete outcome data

(1) 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 five trials reported attrition rates and provided IPD for all randomised individuals (Craig 1994; De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985); we judged all five trials at low risk of attrition bias.

(2) Trials for which no IPD were available

Four trials reported attrition rates and analysed all randomised participants using an intention-to-treat approach (Callaghan 1985; Forsythe 1991; Shakir 1981; Thilothammal 1996); low risk of attrition bias. Two trials did not provide sufficient information to assess attrition bias (Czapinski 1997a; Rastogi 1991); unclear risk of attrition bias.

Selective reporting

The authors of Craig 1994 provided a protocol; the outcomes specified in the protocol were consistent with the outcomes reported in the publication, and we therefore judged the risk of selective reporting bias to be low. Protocols were not available for any of the other 10 included trials so we made a judgement of the risk of bias based on the information included in the publications (see Characteristics of included studies for more information). We judged eight of the other 10 studies at low risk of reporting bias; Czapinski 1997a and Forsythe 1991 were judged at unclear risk of reporting bias.

(1) 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. Sufficient IPD were provided to calculate the four outcomes: 'time to treatment failure', 'time to achieve six-month remission', 'time to achieve 12-month remission' and 'time

to first seizure' for four of the five trials (De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985). Treatment failure information was not provided for one trial (Craig 1994), so we could not calculate 'time to treatment failure', but we had sufficient information to calculate the other three outcomes.

(2) Trials for which no IPD were available

Seizure outcomes and adverse events were well reported in four trials (Callaghan 1985; Rastogi 1991; Shakir 1981; Thilothammal 1996); low risk of reporting bias. One trial reported cognitive outcomes and adverse events, but no seizure outcomes (Forsythe 1991); however as no protocol was available for this trial we do not know whether seizure outcomes were planned a priori, and we judged this trial at unclear risk of reporting bias. One trial was in abstract form only and did not provide sufficient information to assess selective reporting bias (Czapinski 1997a); also judged at unclear risk of reporting bias.

Other potential sources of bias

We detected no other potential sources of bias in any of the 10 of the 11 trials included in the review, however limited information

was available for Czapinski 1997a which was only available as an abstract so we judged this trial to be at unclear risk of other bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Sodium valproate compared with phenytoin monotherapy for epilepsy (primary outcome); [Summary of findings 2](#) Sodium valproate compared with phenytoin monotherapy for epilepsy (secondary outcomes)

A summary of the outcomes reported in trials for which no IPD were available are reported in [Table 3](#).

See [Table 4](#) for details regarding the number of individuals (with IPD) contributing to each analysis, [Summary of findings for the main comparison](#) for a summary of the results for the primary outcome 'time to treatment failure' (stratified by epilepsy type), and [Summary of findings 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](#). All survival curve plots were produced in Stata software version 14 (Stata 2015), using data from all trials providing IPD combined.

Figure 4. Time to treatment failure - any reason related to the treatment (PHT: phenytoin; SV: sodium valproate)

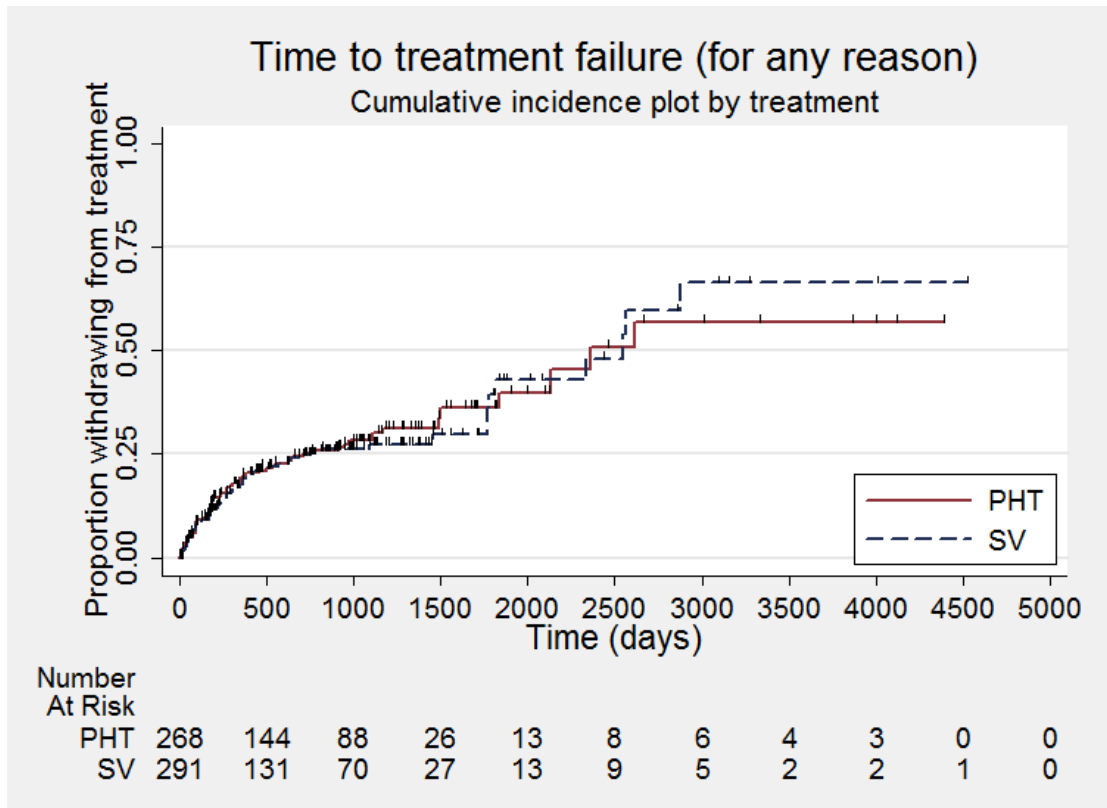


Figure 5. Time to treatment failure - any reason related to the treatment, by epilepsy type (PHT: phenytoin; SV: sodium valproate)

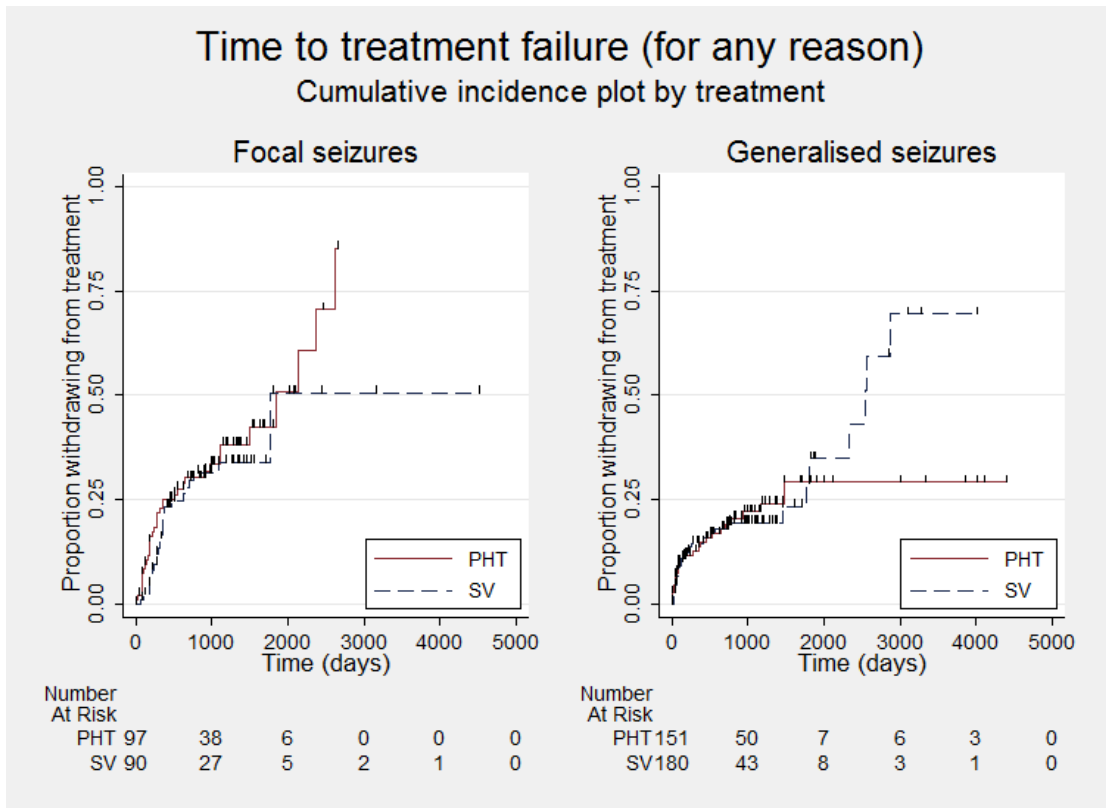


Figure 6. Time to treatment failure due to adverse events (PHT: phenytoin; SV: sodium valproate)

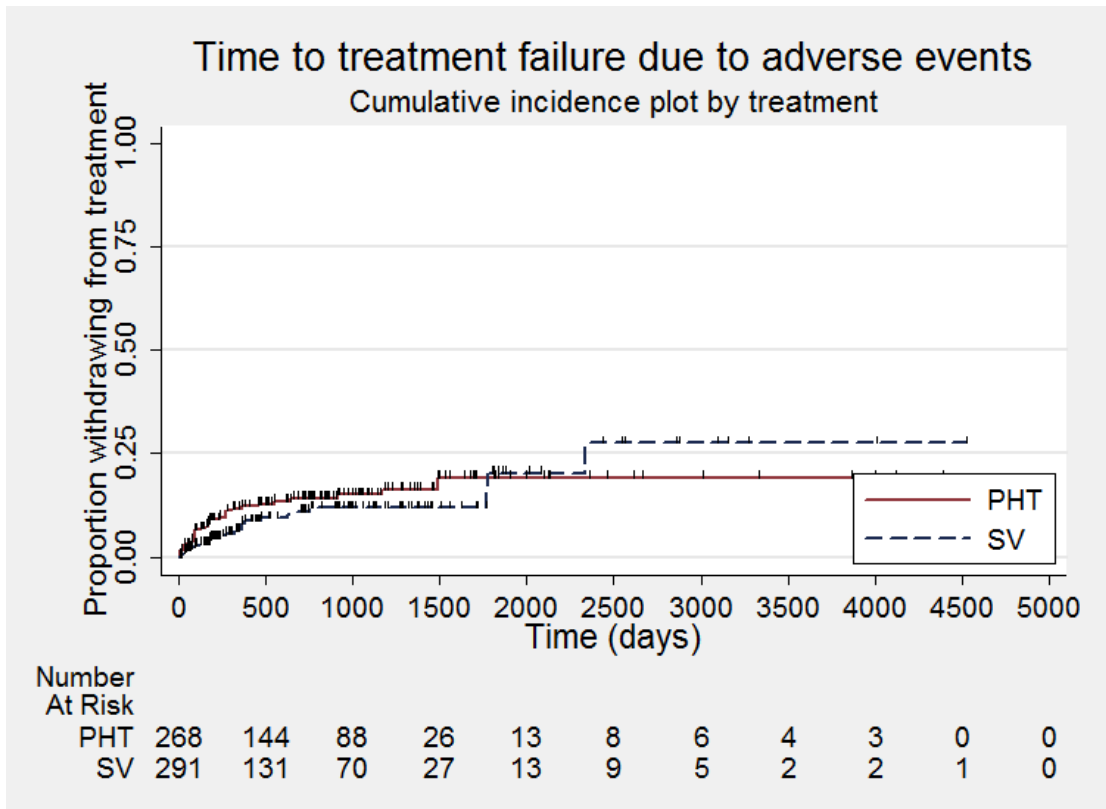


Figure 7. Time to treatment failure due to adverse events, by epilepsy type (PHT: phenytoin; SV: sodium valproate)

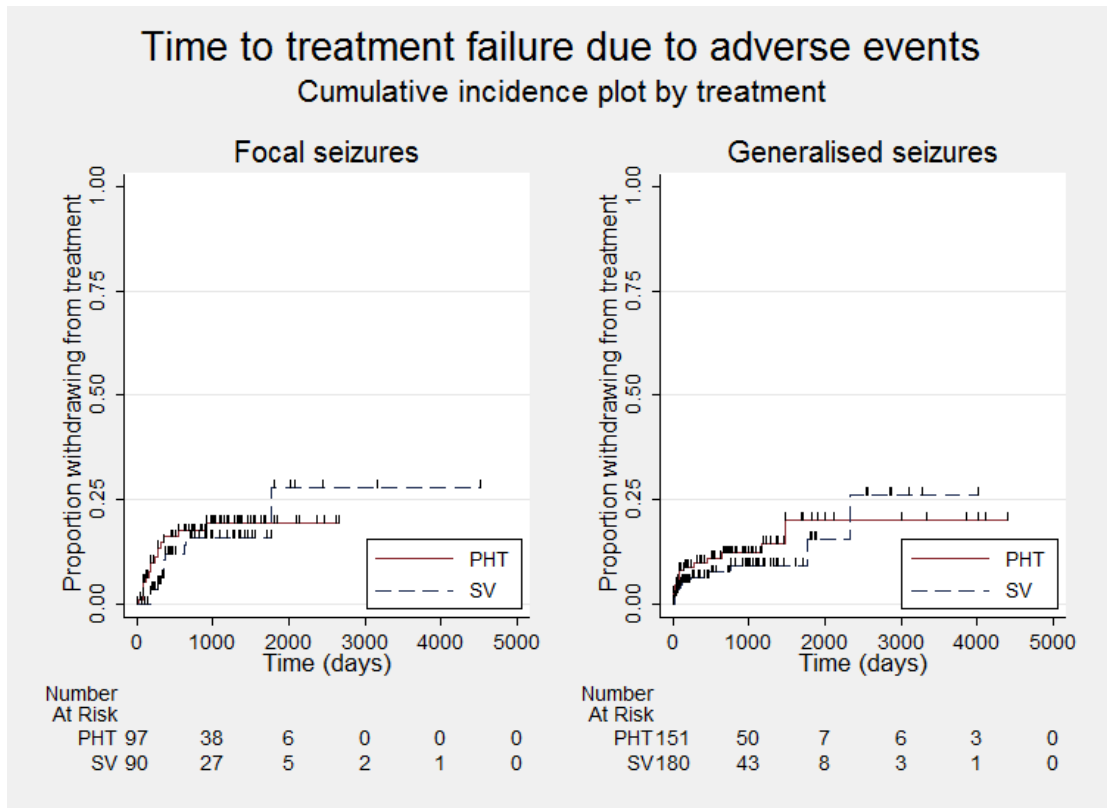


Figure 8. Time to treatment failure due to lack of efficacy (PHT: phenytoin; SV: sodium valproate)

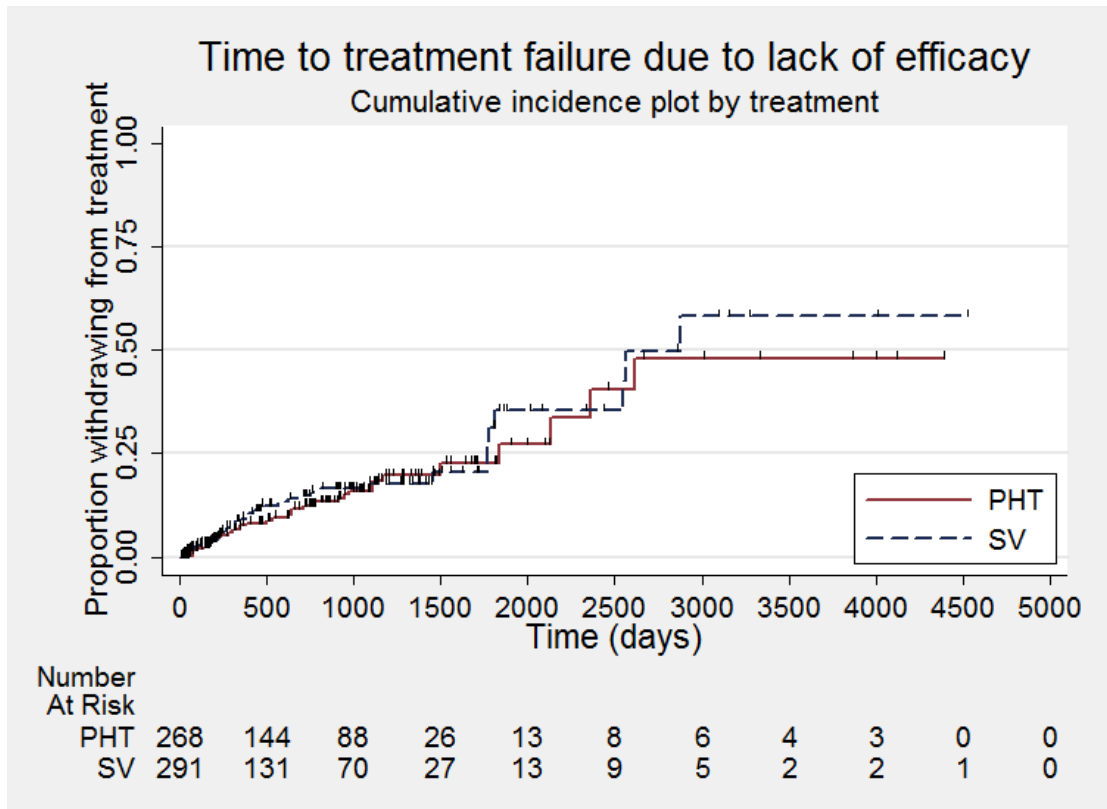


Figure 9. Time to treatment failure due to lack of efficacy, by epilepsy type (PHT: phenytoin; SV: sodium valproate)

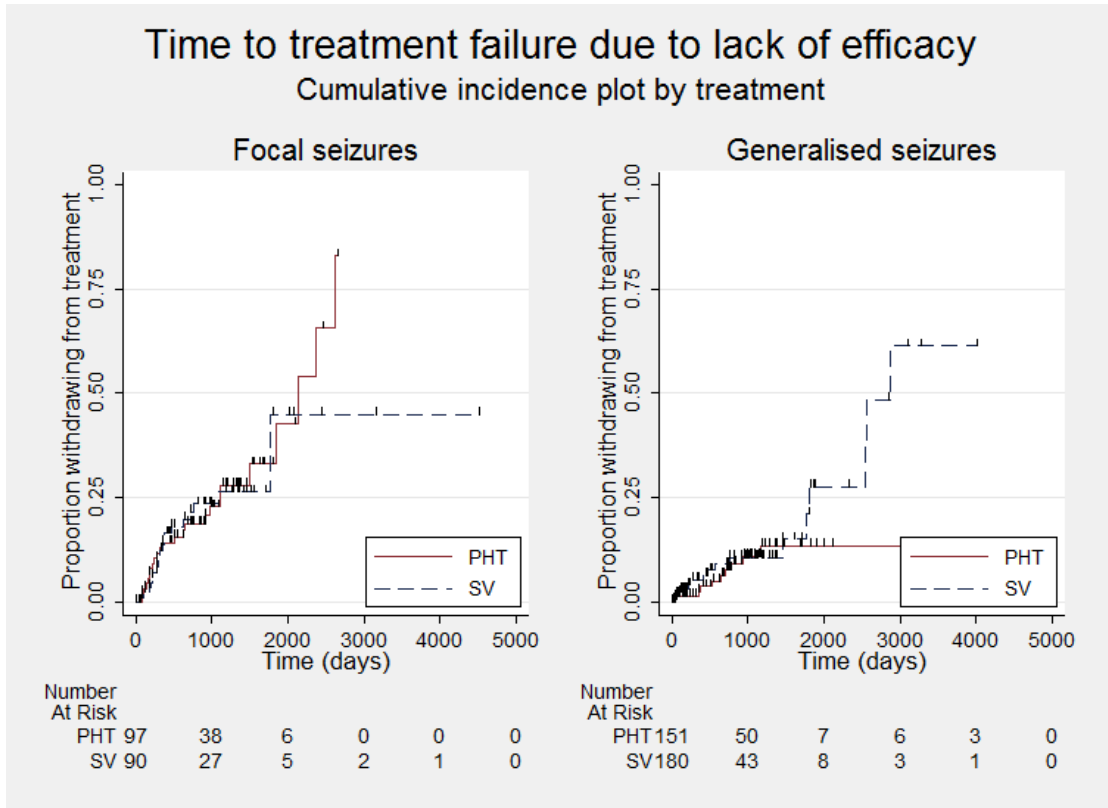


Figure 10. Time to first seizure (PHT: phenytoin; SV: sodium valproate)

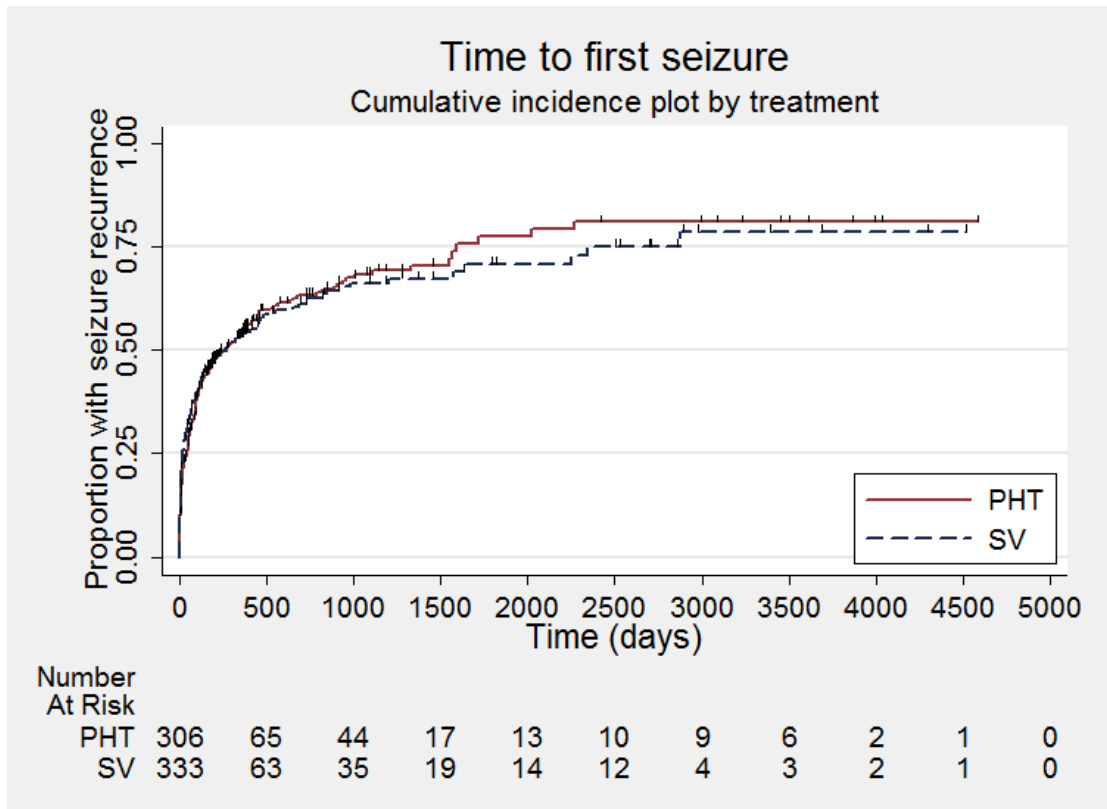


Figure 11. Time to first seizure - by epilepsy type. (PHT: phenytoin; SV: sodium valproate)

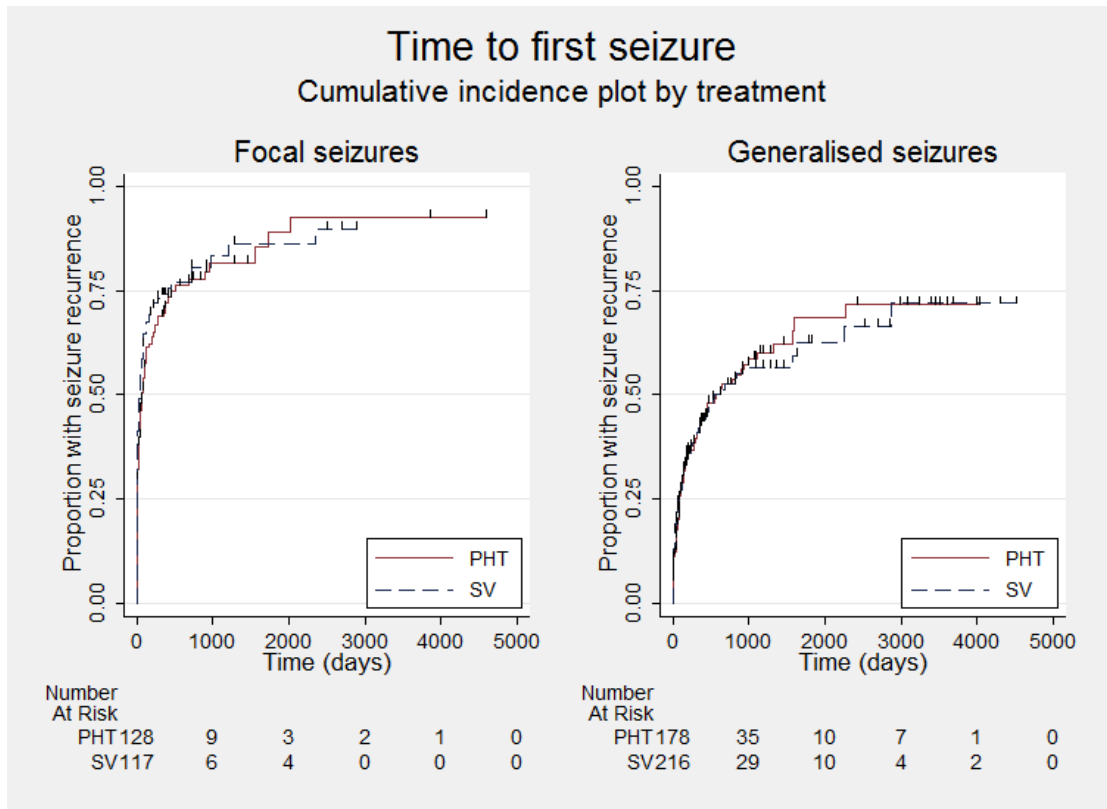


Figure 12. Time to achieve 12-month remission (PHT: phenytoin; SV: sodium valproate)

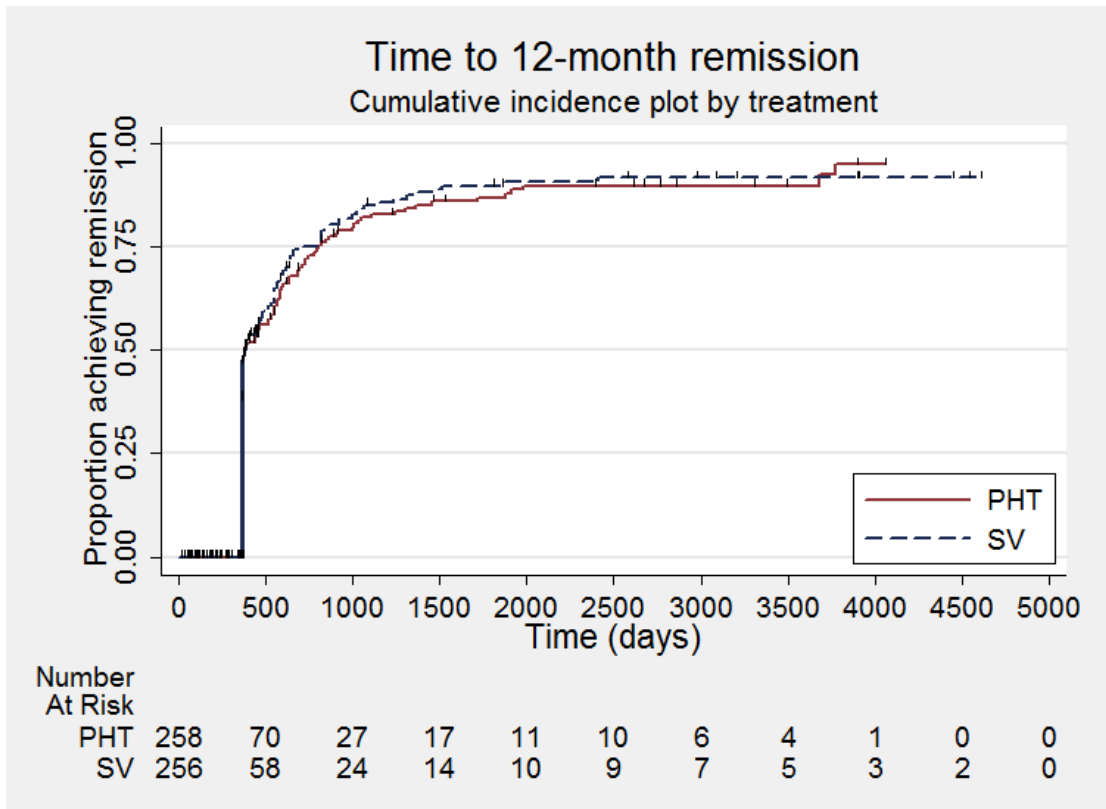


Figure 13. Time to achieve 12-month remission - by epilepsy type. (PHT: phenytoin; SV: sodium valproate)

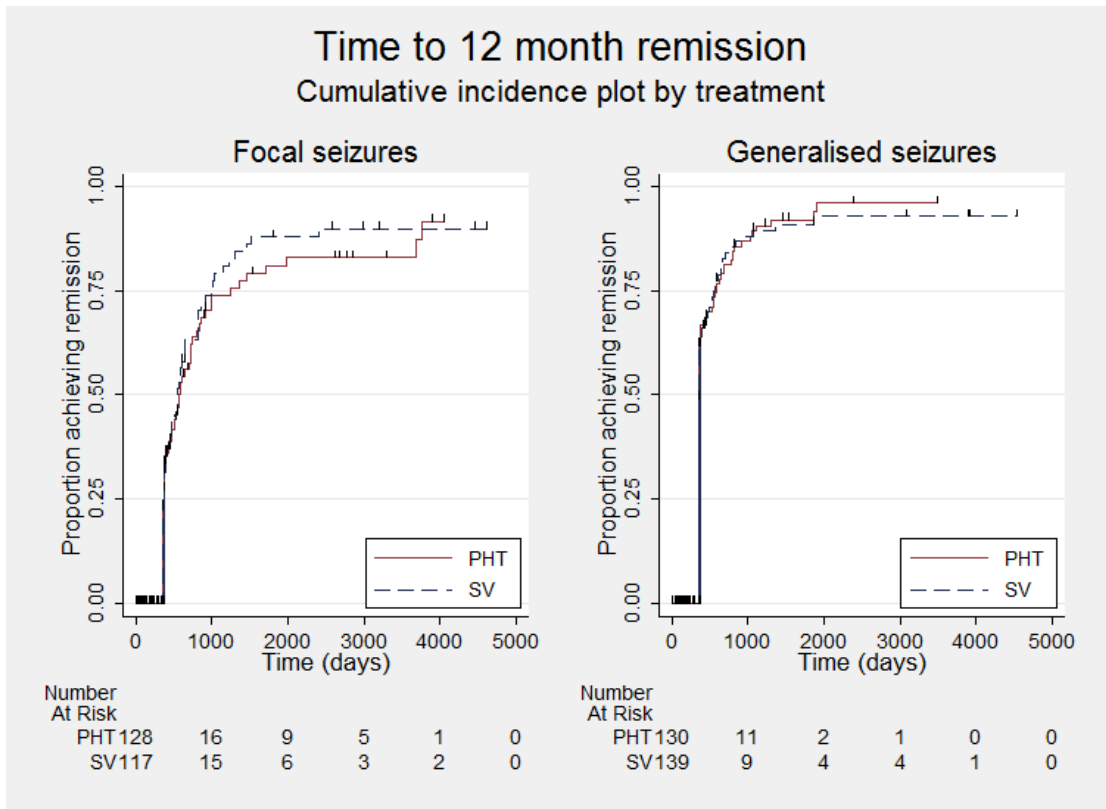


Figure 14. Time to achieve six-month remission (PHT: phenytoin; SV: sodium valproate)

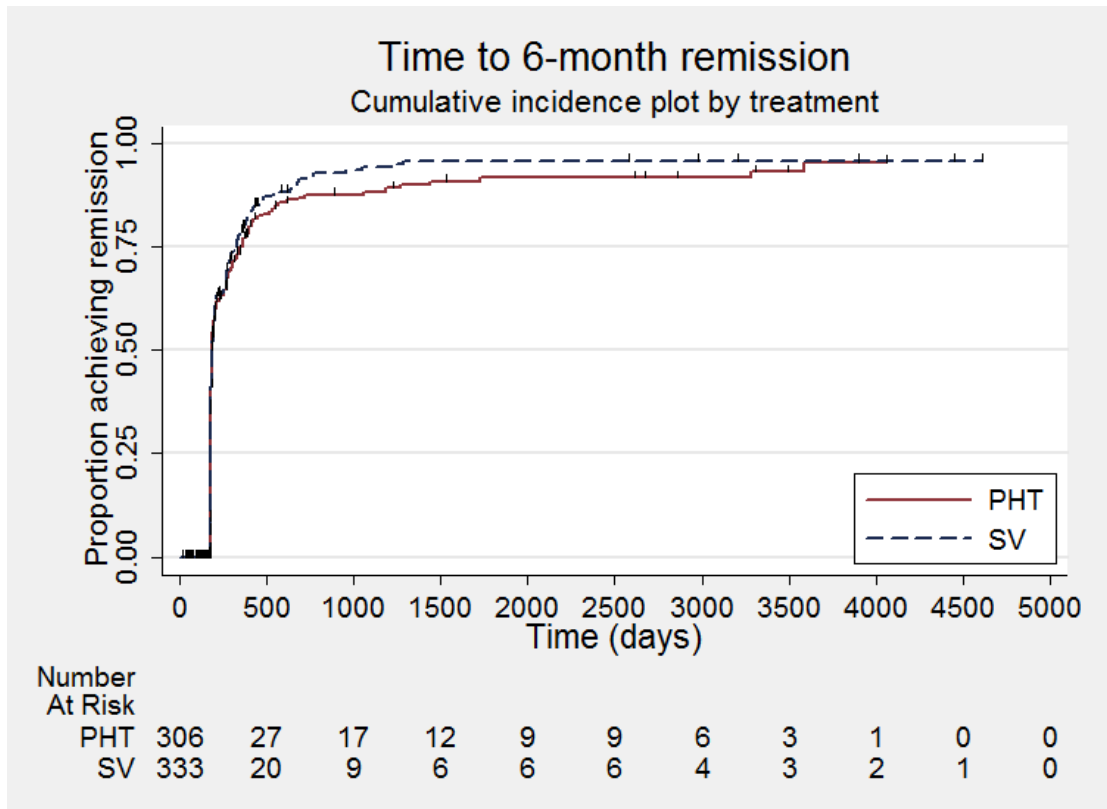
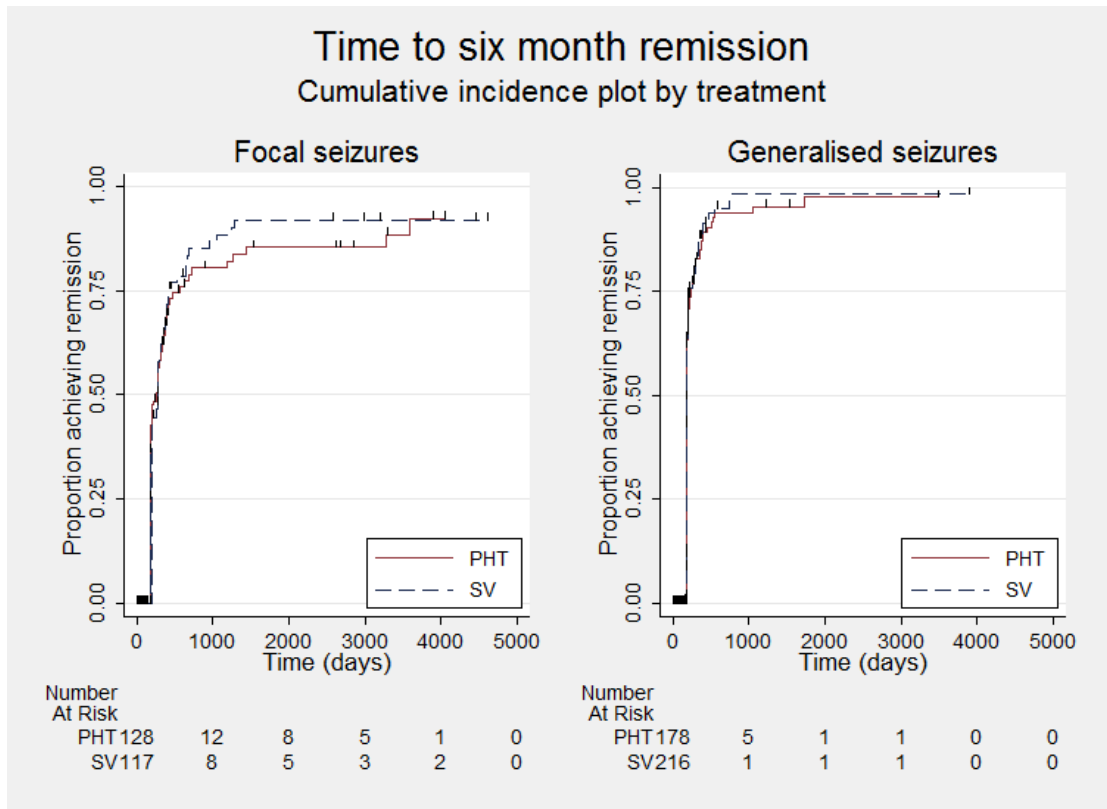


Figure 15. Time to achieve six-month remission (PHT: phenytoin; SV: sodium valproate)



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

Primary outcome

Time to treatment failure (retention time)

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

Time to treatment failure and reason for treatment withdrawal or treatment failure were available for 495 individuals from four trials

(De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985); 74% of individuals from five trials providing IPD (44% of all 1119 eligible individuals). Treatment failure data were not available for the fifth trial (Craig 1994). Sufficient IPD were available in the trial publications for a further 74 individuals from two trials (Forsythe 1991; Shakir 1981). Therefore, a total of 569 individuals (51% of 1119 eligible individuals) from six trials could contribute to the analysis of this outcome.

Reasons for premature discontinuation of treatment (treatment failure) were provided for 571 participants in the six trials (reasons for treatment failure but no date of treatment failure provided for two participants). See Table 5 for reasons for premature termination of the study by treatment and how we classified these reasons in analysis.

Out of 571 participants for whom we had reasons for treatment failure or withdrawal, 243 participants prematurely withdrew from treatment (43%): 122 out of 300 (41%) participants randomised to valproate and 121 out of 271 (45%) participants randomised to phenytoin.

We deemed 138 participants (57% of total treatment failures) to

have withdrawn for reasons related to the allocated drug: 69 (57% of treatment failures) on valproate and 69 (57% of treatment failures) on phenytoin and we classified these reasons as 'events' in the analysis. The most common treatment-related reasons for treatment failure were lack of efficacy: 54 withdrawals (22% of total treatment failures), 28 (23% of total treatment failures) on valproate and 26 (21% of total treatment failures) on phenytoin; and adverse events: 42 withdrawals (17% of total treatment failures), 16 (13% of total treatment failures) on valproate and 26 (21% of total treatment failures) on phenytoin.

We classed the other 105 reasons (53 on valproate and 52 on phenytoin), which were mostly withdrawal from treatment due to seizure remission (64% of other withdrawals), to be not related to the treatment and censored these participants in the analysis, in addition to the 328 participants (178 on valproate and 150 on carbamazepine) 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 569 participants providing IPD from 6 trials) was 0.94 (95% confidence interval (CI) 0.67 to 1.32, $P = 0.17$; moderate-quality evidence) indicating no clear advantage for either drug (Analysis 1.1). No important heterogeneity was present between trials ($I^2 = 15\%$).

Considering time to treatment failure due to adverse events (all other reasons for treatment failure or treatment withdrawal censored in analysis), 495 participants provided IPD from four trials; no participants withdrew from one or both of the drugs due to lack of efficacy in two of the trials (Forsythe 1991; Shakir 1981, see Table 5). The overall pooled HR was 0.68 (95% CI 0.40 to 1.17, $P = 0.16$; moderate-quality evidence) which suggests a slight advantage towards valproate (i.e. a suggestion that treatment failures due to adverse events may occur later on valproate than on phenytoin), but this is not statistically significant (Analysis 1.2). A substantial amount of heterogeneity was present between trials ($I^2 = 67\%$) and when analysis is repeated with random-effects, the CIs of the pooled HR are substantially wider 0.75 (95% CI 0.28 to 1.98). This heterogeneity is investigated further in subgroup analysis by epilepsy type below.

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 569 participants providing IPD from 6 trials) was 1.23 (95% CI 0.77 to 1.97, $P = 0.38$; moderate-quality evidence) which suggests a slight advantage towards phenytoin (i.e. a suggestion that treatment failures due to lack of efficacy may occur later on phenytoin than on valproate), but this is not statistically significant (Analysis 1.3). No heterogeneity was present between trials ($I^2 = 0\%$).

Subgroup analyses: epilepsy type (focal versus generalised onset)

Treatment failure data for 41 participants extracted from Forsythe

1991 did not distinguish between epilepsy type (focal onset or generalised onset) and therefore could not be included in the meta-analysis stratified by epilepsy type.

Considering time to treatment failure for any reason related to the treatment, the overall pooled HR (adjusted by epilepsy type for 528 participants from 5 trials) was 0.88 (95% CI 0.61 to 1.27, $P = 0.51$, $I^2 = 29\%$; moderate-quality evidence; Analysis 1.4). This result is similar to the unadjusted pooled HR (Analysis 1.1), and conclusions remain unchanged following the exclusion of 41 individuals in the stratified analysis (Forsythe 1991).

For individuals with generalised onset seizures (341 participants from 5 trials), the pooled HR was 0.94 (95% CI 0.55 to 1.61, $P = 0.82$, $I^2 = 59\%$; low-quality evidence), indicating no clear advantage for either drug. For individuals with focal onset seizures (187 participants from 4 trials), the pooled HR was 0.83 (95% CI 0.50 to 1.38, $P = 0.48$, $I^2 = 0\%$; moderate-quality evidence), suggesting a slight advantage for valproate which is not statistically significant. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect ($\text{Chi}^2 = 0.10$, $\text{df} = 1$, $P = 0.75$, $I^2 = 0\%$; Analysis 1.4).

A large amount of heterogeneity was present between trials within the generalised onset seizure subgroup ($I^2 = 59\%$) and when analysis is repeated with random-effects, the CIs of the pooled HR become much wider: 0.93 (95% CI 0.37 to 2.31). On visual inspection of the forest plot (see Analysis 1.4), one trial appears to be the source of this variability (Heller 1995), as this trial shows a large statistically significant treatment effect in favour of phenytoin, while the other four trials show general non-significant results, mostly in favour of valproate (De Silva 1996; Ramsay 1992; Shakir 1981; Turnbull 1985). Additionally, this heterogeneity may be due to misclassification of epilepsy type (specifically where generalised onset seizures have been incorrectly classified); this is investigated further in sensitivity analysis below.

Considering time to treatment failure due to adverse events, no individuals withdrew from either drug due to adverse events in Shakir 1981 so this trial is not included in this analysis and no individuals with generalised onset seizures withdrew from valproate due to adverse events in Turnbull 1985 so this epilepsy type subgroup was not included in this analysis. The overall pooled HR (adjusted by epilepsy type for 418 participants from 4 trials) was 0.77 (95% CI 0.44 to 1.37, $P = 0.38$, $I^2 = 37\%$; moderate-quality 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 Shakir 1981 and Turnbull 1985.

For individuals with generalised onset seizures (250 participants from 3 trials), the pooled HR was 0.75 (95% CI 0.35 to 1.60, $P = 0.46$, $I^2 = 71\%$; low-quality evidence), suggesting a slight advantage for valproate which is not statistically significant. For individuals with focal onset seizures (168 participants from 3 trials), the pooled HR was 0.81 (95% CI 0.34 to 1.90, $P = 0.62$, $I^2 = 0\%$; moderate-quality evidence), again suggesting a slight advantage for valproate which is not statistically significant. There was

no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect ($\text{Chi}^2 = 0.02$, $\text{df} = 1$, $P = 0.90$, $I^2 = 0\%$; [Analysis 1.5](#)).

Again, a large amount of heterogeneity was present between trials within the generalised onset seizure subgroup ($I^2 = 71\%$), and when analysis is repeated with random-effects, the CIs of the pooled HR are substantially wider 1.15 (95% CI 0.21 to 6.23). This variability may also originate from fairly small numbers of individuals with generalised seizures failing treatment due to adverse events (see [Table 5](#)), or similarly to the analysis of 'time to treatment failure' for any reason related to treatment, this may be due to potential misclassification of epilepsy type; this is investigated further in sensitivity analysis below.

Considering time to treatment failure due to lack of efficacy, no individuals with generalised onset seizures withdrew from either drug due to lack of efficacy in [Turnbull 1985](#) so this epilepsy type subgroup was not included in this analysis. The overall pooled HR (adjusted by epilepsy type for 451 participants from 5 trials) was 1.16 (95% CI 0.71 to 1.89, $P = 0.55$, $I^2 = 0\%$; moderate-quality 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 [Turnbull 1985](#).

For individuals with generalised onset seizures (264 participants from 4 trials), the pooled HR was 1.51 (95% CI 0.66 to 3.45, $P = 0.33$, $I^2 = 23\%$; low-quality evidence), suggesting a slight advantage for phenytoin which is not statistically significant. For individuals with focal onset seizures (187 participants from 4 trials), the pooled HR was 1.01 (95% CI 0.55 to 1.85, $P = 0.98$, $I^2 = 0\%$; moderate-quality evidence), indicating no clear advantage for either drug. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect ($\text{Chi}^2 = 0.60$, $\text{df} = 1$, $P = 0.44$, $I^2 = 0\%$; [Analysis 1.6](#)). No important heterogeneity was present in overall analysis or within epilepsy type subgroups ($I^2 < 25\%$ for all analyses).

Sensitivity analysis

Sensitivity analyses were conducted to investigate misclassification of seizure type, reclassifying up to 100 individuals from four trials ([Heller 1995](#); [Ramsay 1992](#); [Shakir 1981](#); [Turnbull 1985](#)) 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 6](#).

For all three treatment failure outcomes: time to treatment failure for any reason related to treatment; due to adverse events; and due to lack of efficacy, sensitivity analyses in which individuals classified as experiencing generalised onset seizures and age at onset > 30 years reclassified as experiencing focal onset seizures, show numerically similar results and conclusions remain unchanged. There was no evidence of an association between epilepsy type and treatment effect following reclassification for any of the treatment failure outcomes

Sensitivity analysis in which individuals classified as experiencing generalised onset seizures and age at onset > 30 years were reclassified as experiencing uncertain seizure type was performed only for time to treatment failure for any reason related to treatment.

In the sensitivity analysis of 'time to treatment failure for any reason related to treatment' in which individuals classified as experiencing generalised onset seizures and age at onset > 30 years were reclassified as uncertain seizure type, a large, but non-significant advantage for phenytoin was shown in the uncertain seizure type group: (pooled HR 6.83, 0.82 to 57.16), which was substantially different in the direction of effect from estimates for the 'focal onset seizures' subgroup (pooled HR 0.83, 95% CI 0.50 to 1.38), and 'generalised onset seizures' groups (pooled HR 0.77, 95% CI 0.42 to 1.41), both indicating a non-significant advantage for valproate. There was, however, still no evidence of an association between epilepsy type and treatment effect in this analysis ($\text{Chi}^2 = 3.80$, $\text{df} = 2$; ($P = 0.15$), $I^2 = 47.3\%$) and the result within the uncertain seizure type group should be interpreted with caution due to relatively small numbers of individuals with uncertain seizure types failing treatment in each trial.

The sensitivity analysis could not be performed for 'time to treatment failure due to adverse events' or 'due to lack of efficacy' due to very small numbers of participants failing treatment for these reasons in the uncertain epilepsy type groups in each trial.

Heterogeneity present within analyses for individuals with generalised onset seizures (see [Analysis 1.4](#) and [Analysis 1.5](#)), does not seem to be explained by the potential misclassification of seizure type; therefore results for individuals with generalised onset seizures should be interpreted with caution due to this unexplained inconsistency in results.

Secondary outcomes

Time to first seizure post-randomisation

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

Data for 639 individuals (96% of those providing IPD) from five trials were available for the analysis of this outcome. Seizure recurrence occurred in 371 out of 639 participants (58%), 189 out of 333 (57%) on valproate and 181 out of 306 (59%) on phenytoin. The overall pooled HR (for 639 participants) was 1.04 (95% CI 0.85 to 1.28, $P = 0.70$; low-quality evidence) indicating no clear advantage for either drug. There was no important statistical heterogeneity between trials ($I^2 = 5\%$; [Analysis 1.7](#)).

Subgroup analyses: epilepsy type (focal versus generalised onset)

For individuals with generalised seizures (395 participants from 5 trials), the pooled HR was 0.97 (95% CI 0.72 to 1.30, $P =$

0.82; low-quality evidence), indicating no clear advantage for either drug. For individuals with focal onset seizures (244 participants from 4 trials), the pooled HR was 1.20 (95% CI 0.90 to 1.60, $P = 0.22$; low-quality evidence), suggesting an advantage for phenytoin (i.e. that first seizure recurrence may occur later on phenytoin compared to valproate), but this advantage is not statistically significant. Overall, the pooled HR (adjusted for seizure type for 639 participants) was 1.08 (95% CI 0.88 to 1.33, $P = 0.47$; low-quality evidence), 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 ($\text{Chi}^2 = 1.06$, $\text{df} = 1$ ($P = 0.30$), $I^2 = 5.6\%$) and no heterogeneity was present in any analysis ($I^2 = 0\%$; [Analysis 1.8](#)).

Sensitivity analysis

A sensitivity analysis including generalised seizures of all types during follow-up (only recorded in [Ramsay 1992](#)), produced the following results: for individuals with generalised seizures, the pooled HR was 0.95 (95% CI 0.71 to 1.27, $P = 0.74$), indicating no clear advantage for either drug. For individuals with focal onset seizures, the pooled HR was unchanged: 1.20 (95% CI 0.90 to 1.60, $P = 0.22$), suggesting an advantage for phenytoin which is not statistically significant. Overall, the pooled HR (adjusted for seizure type) was 1.08 (95% CI 0.86 to 1.32, $P = 0.49$), suggesting an advantage for phenytoin which is not statistically significant. Numerical results are very similar to those presented in [Analysis 1.7](#) and [Analysis 1.8](#) and overall conclusions are unchanged, therefore, results for time to first seizure (post-randomisation) seem robust to the exclusion of other generalised seizure types (other than generalised tonic-clonic seizures) in [Ramsay 1992](#).

Sensitivity analyses were conducted to investigate misclassification of seizure type, reclassifying 171 individuals from four trials ([Craig 1994](#); [Heller 1995](#); [Ramsay 1992](#); [Turnbull 1985](#)) 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 6](#).

Within both of the sensitivity analyses, following reclassification, an association between epilepsy type and treatment effect is suggested. For generalised seizures, and age of onset > 30 years reclassified as 'focal onset seizures', the result of the test for subgroup differences is statistically significant: $\text{Chi}^2 = 5.46$, $\text{df} = 1$ ($P = 0.02$), $I^2 = 81.7\%$ ([Analysis 1.9](#)). Within the focal onset seizure group, a non-significant advantage to phenytoin is suggested: 1.23 (95% CI 0.96 to 1.57, $P = 0.09$), while in the generalised onset seizure group, a non-significant advantage to valproate is suggested: pooled HR 0.72 (95% CI 0.50 to 1.05, $P = 0.09$); although neither result is statistically significant, the observed directions of effect within this sensitivity analysis was anticipated a priori (see [How the intervention might work](#) and [Subgroup analysis and investigation of heterogeneity](#)).

For generalised seizures, and age of onset > 30 years reclassified as 'uncertain seizure type', the result of the test for subgroup differences is not statistically significant, but subgroup analysis does suggest some potential differences between the epilepsy type subgroups: $\text{Chi}^2 = 5.79$, $\text{df} = 2$ ($P = 0.06$), $I^2 = 65.5\%$ ([Analysis 1.10](#)). The direction of effect for the 'uncertain seizure type' subgroup (pooled HR 1.35, 95% CI 0.85 to 2.14; $P = 0.22$) is similar to that of the 'focal onset' subgroup (pooled HR 1.20, 95% CI 0.90 to 1.60; $P = 0.22$), both indicating a non-significant advantage for phenytoin and also suggesting that these individuals with 'uncertain' seizure types (who were originally classified as experiencing generalised onset seizures) are actually experiencing focal onset seizures. Furthermore, valproate now appears more effective in generalised onset seizures (pooled HR 0.72, 95% CI 0.50 to 1.05; $P = 0.09$) when compared to the original analysis ([Analysis 1.8](#); [Analysis 1.10](#)). Again, although neither result is statistically significant, the observed directions of effect within this sensitivity analysis were anticipated a priori (see [How the intervention might work](#) and [Subgroup analysis and investigation of heterogeneity](#)). Therefore, due to the potential impact of any misclassification of epilepsy type on the numerical results and conclusions for the outcome, 'time to first seizure', results of [Analysis 1.7](#), [Analysis 1.8](#), [Analysis 1.9](#) and [Analysis 1.10](#) should be interpreted with caution.

Time to achieve 12-month remission (seizure-free period)

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

Data for 514 individuals (77% of those providing IPD) from four trials were available for the analysis of this outcome ([Craig 1994](#); [De Silva 1996](#); [Heller 1995](#); [Turnbull 1985](#); see [Table 4](#)). Individuals were only followed up for six months in the fifth trial ([Ramsay 1992](#)), which could not contribute data to this outcome. Twelve-month remission was achieved by 302 out of 514 participants (59%); 147 out of 256 (57%) on valproate and 155 out of 258 (60%) on phenytoin. The overall pooled HR (for 514 participants) was 1.03 (95% CI 0.82 to 1.29, $P = 0.80$; moderate-quality evidence), indicating no clear advantage to either drug. There is no evidence of statistical heterogeneity between trials ($I^2 = 0\%$; [Analysis 1.11](#)).

Subgroup analyses: epilepsy type (focal versus generalised onset)

For individuals with generalised seizures (270 participants from 4 trials), the pooled HR was 0.96 (95% CI 0.71 to 1.29, $P = 0.79$; moderate-quality evidence), indicating no clear advantage for either drug. For individuals with focal onset seizures (244 participants from 4 trials), the pooled HR was 1.11 (95% CI 0.78 to 1.60, $P = 0.56$; moderate-quality evidence), indicating a slight advantage for valproate (i.e. that 12-month remission may occur slightly earlier on valproate than phenytoin), but this advantage

is not statistically significant. Overall, the pooled HR (adjusted for epilepsy type for 514 participants) was 1.02 (95% CI 0.81 to 1.28, $P = 0.87$; moderate-quality evidence), suggesting no clear clinical advantage for either drug. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment ($\text{Chi}^2 = 0.39$, $df = 1$, $P = 0.53$, $I^2 = 0\%$) and no heterogeneity was present in any analysis ($I^2 = 0\%$; [Analysis 1.12](#)).

Sensitivity analysis

Sensitivity analyses were conducted to investigate misclassification of seizure type, reclassifying 145 individuals from three ([Craig 1994](#); [Heller 1995](#); [Turnbull 1985](#)) 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 6](#).

Results are numerically similar for individuals with focal onset seizures, individuals with generalised onset seizures and overall for all participants; conclusions are unchanged and there is no evidence of an association between epilepsy type and treatment effect following reclassification.

Time to achieve six-month remission (seizure-free period)

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

Data for 639 individuals (96% of those providing IPD) from five trials were available for the analysis of this outcome (see [Table 4](#)). Six-month remission was achieved by 434 out of 639 participants (68%); 228 out of 333 (68%) on valproate and 206 out of 306 (67%) on phenytoin. The overall pooled HR (for 639 participants) was 1.08 (95% CI 0.89 to 1.30, $P = 0.44$; moderate-quality evidence), suggesting a slight advantage to valproate (i.e. that six-month remission may occur slightly earlier on valproate than phenytoin), but this advantage is not statistically significant. There is no evidence of statistical heterogeneity between trials ($I^2 = 0\%$; see [Analysis 1.13](#)).

Subgroup analyses: epilepsy type (focal versus generalised onset)

For individuals with generalised seizures (395 participants from 5 trials), the pooled HR was 1.08 (95% CI 0.84 to 1.38, $P = 0.54$; moderate-quality evidence), suggesting an advantage for valproate which is not statistically significant. For individuals with focal onset seizures (244 participants from 4 trials), the pooled HR was 1.00 (95% CI 0.73 to 1.35, $P = 0.98$; moderate-quality evidence), indicating no clear advantage for either drug. Overall, the pooled HR (adjusted for epilepsy type for 639 participants) was 1.05 (95% CI 0.86 to 1.27, $P = 0.64$; moderate-quality evidence), suggesting no clear advantage for either drug. There was no evidence of an interaction between epilepsy type (focal onset versus generalised

onset) and treatment ($\text{Chi}^2 = 0.16$, $df = 1$, $P = 0.69$, $I^2 = 0\%$) and no heterogeneity was present in any analysis ($I^2 = 0\%$; [Analysis 1.14](#)).

Sensitivity analyses

A sensitivity analysis including generalised seizures of all types during follow-up (only recorded in [Ramsay 1992](#)) produced the following results: for individuals with generalised seizures (395 participants from 5 trials), the pooled HR was 1.19 (95% CI 0.88 to 1.61, $P = 0.26$), suggesting an advantage for valproate, which is not statistically significant. For individuals with focal onset seizures (244 participants from 4 trials), the pooled HR was unchanged: 1.00 (95% CI 0.73 to 1.35, $P = 0.98$), indicating no clear advantage for either drug. Overall, the pooled HR (adjusted for epilepsy type) was 1.09 (95% CI 0.88 to 1.37, $P = 0.40$), suggesting an advantage for valproate, which is not statistically significant.

By including information on other generalised seizure types in the trial by [Ramsay 1992](#), a very slightly greater advantage for valproate emerges. However, as numerical results are similar to those presented in [Analysis 1.13](#) and [Analysis 1.14](#) and overall conclusions are unchanged, results for time to six-month remission seem robust to the exclusion of other generalised seizure types (other than generalised tonic-clonic seizures) in [Ramsay 1992](#).

Sensitivity analyses were conducted to investigate misclassification of seizure type, reclassifying 171 individuals from four trials ([Craig 1994](#); [Heller 1995](#); [Ramsay 1992](#); [Turnbull 1985](#)) 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 6](#).

Results are numerically similar for individuals with focal onset seizures, individuals with generalised onset seizures and overall for all participants; conclusions are unchanged and there is no evidence of an association between epilepsy type and treatment effect following reclassification.

Incidence of adverse events

See [Table 7](#) for details of all adverse event data provided in the studies included in this review. It is difficult to summarise the 'most common' adverse events overall across the 11 studies due to the differences in methods and differences in the levels of detail in the reporting of adverse event data across the studies. In summary, the adverse events reported by two or more studies in this review are the following.

For valproate:

- drowsiness/somnolence/sedation (reported by [Callaghan 1985](#); [Craig 1994](#); [De Silva 1996](#); [Ramsay 1992](#); [Rastogi 1991](#));
- weight gain (reported by [Callaghan 1985](#); [Craig 1994](#); [Rastogi 1991](#); [Shakir 1981](#));
- tremor (reported by [Craig 1994](#); [De Silva 1996](#); [Ramsay 1992](#); [Turnbull 1985](#));

- alopecia/hair loss (reported by [Craig 1994](#); [Shakir 1981](#); [Turnbull 1985](#));
- dizziness/unsteadiness (reported by [Craig 1994](#); [Heller 1995](#); [Ramsay 1992](#));
- skin allergy/rash (reported by [Ramsay 1992](#); [Thilothammal 1996](#)); and
- gastrointestinal problems (reported by [Rastogi 1991](#); [Shakir 1981](#)).

For phenytoin:

- gingival (gum) hypertrophy/hyperplasia (reported by [Callaghan 1985](#); [Rastogi 1991](#); [Thilothammal 1996](#));
- rash (reported by [Callaghan 1985](#); [Craig 1994](#); [De Silva](#)

[1996](#); [Ramsay 1992](#));

- ataxia (reported by [Callaghan 1985](#); [Rastogi 1991](#); [Shakir 1981](#); [Thilothammal 1996](#); [Turnbull 1985](#));
- nausea (reported by [Ramsay 1992](#); [Thilothammal 1996](#));
- dizziness/unsteadiness (reported by [Craig 1994](#); [Ramsay 1992](#));
- nystagmus (reported by [Craig 1994](#); [Rastogi 1991](#); [Thilothammal 1996](#); [Turnbull 1985](#));
- drowsiness/somnolence/sedation (reported by [Craig 1994](#); [De Silva 1996](#); [Ramsay 1992](#); [Rastogi 1991](#); [Thilothammal 1996](#)); and
- tremor (reported by [Ramsay 1992](#); [Turnbull 1985](#)).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Valproate compared with phenytoin monotherapy for epilepsy						
Patient or population: adults and children with newly-onset focal onset or generalised tonic-clonic seizures Settings: outpatients Intervention: sodium valproate Comparison: phenytoin						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenytoin	Sodium valproate				
Time to first seizure (post-randomisation) <i>All participants</i> Range of follow-up: 0 to 4859 days	The median time to first seizure post-randomisation was 275 days in the phenytoin group	The median time to first seizure post-randomisation was 267 days (7 days shorter) in the sodium valproate group	HR 1.08 (0.88 to 1.33) ^a	639 (5 studies)	⊕⊕○○ Low^{b,c}	HR < 1 indicates a clinical advantage for valproate
Time to first seizure (post-randomisation) <i>Subgroup: focal onset seizures</i> Range of follow-up: 0 to 4859 days	The median time to first seizure post-randomisation was 75 days in the phenytoin group	The median time to first seizure post-randomisation was 41 days (34 days shorter) in the sodium valproate group	HR 1.20 (0.90 to 1.60)	244 (4 studies)	⊕⊕○○ Low^{b,c}	HR < 1 indicates a clinical advantage for valproate
Time to first seizure (post-randomisation) <i>Subgroup: generalised onset seizures (tonic-clonic only)</i> Range of follow-up: 1 to 4520 days	The median time to first seizure post-randomisation was 572 days in the phenytoin group	The median time to first seizure post-randomisation was 549 days (23 days shorter) in the sodium valproate group	HR 0.97 (0.72 to 1.30)	395 (5 studies)	⊕⊕○○ Low^{b,c}	HR < 1 indicates a clinical advantage for valproate

<p>Time to achieve 12-month remission (seizure-free period) <i>All participants</i> Range of follow-up: 5 to 4614 days</p>	<p>The median time to achieve 12-month remission was 380 days in the phenytoin group</p>	<p>The median time to achieve 12-month remission was 386 days (6 days longer) in the sodium valproate group</p>	<p>HR 1.02 (0.81 to 1.28)</p>	<p>514 (4 studies)</p>	<p>⊕⊕⊕○ Moderate^b</p>	<p>HR < 1 indicates a clinical advantage for phenytoin</p>
<p>Time to achieve 12-month remission (seizure-free period) <i>Subgroup: focal onset seizures</i> Range of follow-up: 5 to 4614 days</p>	<p>The median time to achieve 12-month remission was 575 days in the phenytoin group</p>	<p>The median time to achieve 12-month remission was 549 days (26 days shorter) in the sodium valproate group</p>	<p>HR 1.11 (0.78 to 1.60)</p>	<p>244 (4 studies)</p>	<p>⊕⊕⊕○ Moderate^b</p>	<p>HR < 1 indicates a clinical advantage for phenytoin</p>
<p>Time to achieve 12-month remission (seizure-free period) <i>Subgroup: generalised onset seizures (tonic-clonic only)</i> Range of follow-up: 7 to 4544 days</p>	<p>The median time to achieve 12-month remission was 365 days in the phenytoin group</p>	<p>The median time to achieve 12-month remission was 366 days (1 day longer) in the sodium valproate group</p>	<p>HR 0.96 (0.71 to 1.29)</p>	<p>270 (4 studies)</p>	<p>⊕⊕⊕○ Moderate^b</p>	<p>HR < 1 indicates a clinical advantage for phenytoin</p>

* Illustrative risks in the phenytoin and sodium valproate 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 HR) shows the comparison of 'time to first seizure' or 'time to 12-month remission' between the treatment groups

Abbreviations: CI: confidence interval; HR: hazard ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

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

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aPooled HR for all participants adjusted for seizure type.

^bDowngraded once as risk of bias judged high for four unblinded studies ([Craig 1994](#); [De Silva 1996](#); [Heller 1995](#); [Ramsay 1992](#)).

^cDowngraded once due to applicability: as up to 49% in the 5 trials classified as experiencing generalised onset seizures may have had their seizure type wrongly classified; sensitivity analyses show misclassification has an impact on results and conclusions.

DISCUSSION

Summary of main results

The results of this review do not demonstrate a statistically significant effect in favour of either valproate or phenytoin for the primary global outcome 'time to treatment failure for any reason related to the treatment (retention time)'. This outcome is influenced by both the relative efficacy of the two drugs, and differences in tolerability and safety.

As a difference in efficacy in one direction may be confounded by a difference in tolerability in the other, it may not be surprising that any estimated differences are small, yet when considering specific reasons for treatment failure (adverse events or lack of efficacy), still no statistically significant differences were found between the two drugs. The confidence intervals for the treatment failure outcomes are relatively wide; too wide to confirm equivalence and clinically important differences have not been excluded, particularly when results for generalised and focal onset seizure subgroups are examined. Furthermore, as at least three of the trials contributing individual participant data (IPD) to this outcome were open-label, clinical preconceptions about the two treatments, such as that valproate is more effective in generalised seizures, while phenytoin is more effective in focal onset seizures, and lack of masking, may have influenced the treatment failure rates of the two treatments. Similarly for the secondary outcomes 'time to achieve 12-month remission (seizure-free period)', 'time to achieve six-month remission (seizure-free period)', and 'time to first seizure', although no statistically significant differences were found between valproate and phenytoin, the confidence intervals are too wide to confirm equivalence.

Overall completeness and applicability of evidence

We have gratefully received IPD for 669 individuals (60% of individuals from all eligible trials) from the authors of five trials, which included a comparison of phenytoin with valproate for the treatment of epilepsy (Craig 1994; De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985). However, 376 individuals (34%) from four relevant trials could not be included in any analysis, as IPD were not available and outcomes of interest were not reported in the published reports (Callaghan 1985; Czapinski 1997a; Rastogi 1991; Thilothammal 1996). Sufficient data for 74 individuals (6%) were published in two trials to contribute to analysis for the primary outcome 'time to treatment failure' (Forsythe 1991; Shakir 1981), but insufficient data were available to include these individuals in the analyses of other outcomes. Having to exclude data for one-third of eligible participants due to lack of IPD and insufficient reporting in study publications is likely to impact on the applicability of the evidence, however it is difficult to quantify exactly how large this impact could be.

We did not find evidence of an interaction between treatment and seizure type in any analysis using the epileptic seizure types that participants were classified with in the original analysis. This result is surprising, given the strong clinical impression that valproate is more effective in generalised onset seizures while phenytoin is more effective in focal onset seizures.

It may well be that an interaction does not exist. Alternatively, it may be that an interaction does exist but that our meta-analysis may not have the statistical power needed to detect an interaction; it must be understood that the confidence intervals around the estimates are wide, and that these results do not exclude the possibility of important differences existing. Additionally, subgroup analyses by epilepsy type show some inconsistent results, such as for our primary outcome 'time to treatment failure for any reason related to the treatment', treatment effect estimates indicate a potentially important advantage for valproate for focal onset seizures, with no clear advantage for either drug for generalised tonic-clonic seizures, which goes against current practice and belief. Furthermore, a substantial amount of statistical heterogeneity was present in some analyses of 'time to treatment failure,' particularly within analyses of individuals with generalised onset seizures, which could not be explained by sensitivity analyses.

The impression that valproate is better for generalised seizures may derive from its effects on generalised seizures other than tonic-clonic, but important differences could exist for absence and myoclonus seizure types. However, were this the case, we might have expected to see a treatment-seizure type interaction for the outcome 'time to treatment failure', if treatment had failed or a further drug added to combat other seizure types. We were unable to investigate these seizure types in detail in this review as most of the trials providing IPD did not record post-randomisation generalised seizure types other than tonic-clonic occurring post-randomisation.

The results of the original trials, and hence this meta-analysis, may have been confounded by classification bias, i.e. individuals with generalised seizures may have been misclassified as having focal onset seizures and vice versa. There is good evidence from our three reviews in our series of pair-wise reviews for monotherapy in epilepsy comparing carbamazepine to phenobarbitone, phenytoin and valproate that misclassification is indeed an important issue in epilepsy trials (Marson 2000; Nolan 2016c; Nevitt 2017b). Within our review, the most striking indication that misclassification may be a problem is the classification of subjects in Craig 1994. In this trial, 95 out of 166 (56%) of the recruited individuals were classified as having a generalised epilepsy, which seems unlikely given that the individuals were newly diagnosed and over the age of 60 (Malafosse 1994). It is also interesting to note that Ramsay 1992 is the only trial in this review that attempted to recruit only individuals with generalised tonic-clonic seizures, However, this trial recruited too few individuals to have the power to detect a difference between valproate and phenytoin. In this trial, for a subgroup of individuals with definite electroencephalo-

graphic (EEG) changes to support a diagnosis of an idiopathic generalised epilepsy, there appeared to be a greater (but not significant) advantage for valproate, compared to the trial population overall. This could again be interpreted as supporting the potential for misclassification, which in turn could confound an interaction between treatment and seizure type. We were unable to test for the effects of EEG changes on the interaction between treatment and seizure type due to EEG data not being collected for all trials, and even where it was available, it was not done in a uniform way. It is likely that these trials were initiated before the publication of the International League Against Epilepsy Classification of Epileptic Syndromes in 1989 (Commission 1989), but they did use the International League Against Epilepsy Classification of Epileptic Seizures that was published in 1981 (Commission 1981), which does allow individuals to be classified as those with focal onset or generalised seizures. The age of onset distribution of individuals classified as having generalised seizures indicates misclassification is likely to have occurred in up to 188 out of 384 (49%) individuals classified as having generalised onset seizures. Our results, based on reclassifying the 188 individuals, indicate that classification bias is a potentially important confounder of the results of this review, particularly the outcome 'time to first seizure'.

Finally, it should be mentioned that the preparation of valproate used in the included trials may have influenced the results. The trials conducted in the UK all used valproate (Epilim) (Craig 1994; De Silva 1996; Heller 1995; Turnbull 1985). Ramsay 1992, conducted in the USA, used valproic acid (Depakene) which is thought to cause more gastrointestinal side effects than preparations containing either a mixture of valproate and valproic acid, or valproate alone. There is no evidence from RCTs to support this, but there are some data from observational studies (Brasfield 1999; Cranor 1997; Wilder 1983a). Given that this meta-analysis, and a similar meta-analysis comparing valproate and carbamazepine have failed to find convincing evidence of differences in effect between different drugs (Marson 2000), it seems unlikely that differing preparations of the same drug are likely to have a major effect.

Quality of the evidence

The five trials for which IPD were made available were of generally good quality, with all five trials describing adequate methods of randomisation, and Craig 1994, De Silva 1996 and Heller 1995 also describing adequate methods of allocation concealment. However, none of the five trials described a method of blinding of participants and personnel, and only one trial stated that cognitive outcome assessors were blinded to treatment allocation, raising the possibility of performance and detection bias (Craig 1994). Three trials were designed as open-label for "practical and ethical reasons" (De Silva 1996; Heller 1995; Ramsay 1992); for example, Ramsay 1992 stated that the side effects of the respective drugs would "quickly unblind" the trial anyway. A further differ-

ence between the five trials was the population recruited; two trials recruited adults of all ages (Heller 1995; Turnbull 1985), one recruited children only (De Silva 1996), one recruited adults and children (Ramsay 1992), and one recruited adults over the age of 60 only (Craig 1994).

As explained within Overall completeness and applicability of evidence, misclassification of seizure type (classification bias) is likely to have impacted upon the results of the outcome 'time to first seizure' and for treatment failure outcomes, unexplained heterogeneity was present in analysis, following subgroup analysis and sensitivity analysis (including reclassification of seizure type). For the reasons outlined in this section, we judged the quality of the evidence to be moderate to low for 'time to treatment failure' due to risk of detection bias and unexplained heterogeneity (Summary of findings for the main comparison), and low/moderate for the outcomes of 'time to first seizure' and 'time to 12-month remission' respectively, due to risk of detection bias and classification bias (see Summary of findings 2).

Potential biases in the review process

We were able to include IPD up to 743 out of 1119 eligible participants (66%) from seven out of 11 trials in this review in the analysis of at least one outcome. Such an approach has many advantages, such as allowing the standardisation of definitions of outcomes across trials, and attrition and reporting biases are reduced as we can perform additional analyses and calculate additional outcomes from unpublished data. For the outcomes we used in this review that are of a time-to-event nature, an IPD approach is considered to be the 'gold standard' approach to analysis (Parmar 1998).

For reasons outside of our control, we were unable to obtain or extract any IPD for 376 participants (34%) from four trials for inclusion in any outcomes of this review; it is difficult to quantify whether the exclusion of at least 34% of eligible participants from analyses is likely to have impacted on the conclusions of this review. Finally, we made some assumptions in the statistical methodology used in this review. Firstly, when we received only follow-up dates and seizure frequencies, we used linear interpolation to estimate. We are aware that an individual's seizure patterns may be non-linear; therefore for this reason, in addition to the reasons outlined in Overall completeness and applicability of evidence, we recommend caution when interpreting the numerical results of the seizure-related outcomes.

Agreements and disagreements with other studies or reviews

No single trial has found convincing differences between valproate and phenytoin with respect to seizure control or seizure type (Callaghan 1985; Craig 1994; Czapinski 1997a; De Silva 1996; Forsythe 1991; Heller 1995; Ramsay 1992; Rastogi 1991; Shakir

1981; Thilothammal 1996; Turnbull 1985). However, confidence intervals around estimates have been wide and equivalence cannot be inferred. Furthermore, this systematic review and meta-analysis has not found any statistically significant differences between valproate and phenytoin for any of the outcomes measures. To our knowledge, this is the only systematic review and meta-analysis which compares valproate 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 phenytoin, valproate and other standard and new antiepileptic drugs licensed for monotherapy, and it also found no differences between valproate and phenytoin for the outcomes specified in this review.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review do not provide any conclusive evidence for or against the current practice of using valproate as a first-line treatment for individuals with generalised onset tonic-clonic seizures, and phenytoin as monotherapy for individuals with focal onset seizures. Guidelines currently recommend lamotrigine and carbamazepine as a first-line treatment for focal onset seizures (NICE 2012); the results of this review do not inform current treatment policy.

Implications for research

Finding overall differences between these standard antiepileptic drugs has proved elusive. If overall differences do exist across heterogeneous populations of individuals, such as those studied here, those differences are likely to be small, and in order to be clinically useful, future comparative antiepileptic drug trials will need to be powered accordingly. It has been argued that future comparative antiepileptic drug trials 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 future antiepileptic drug monotherapy trials that recruit individuals with specific epilepsy syndromes, to be designed and 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 with a system to recognise uncertainty surrounding epilepsy syndromes in individuals within trials.

Clinical uncertainty about seizure and syndrome classification is often present at the time of diagnosis and initial treatment of epilepsy, and significant numbers of individuals with newly diagnosed epilepsy cannot be classified (Bodensteiner 1988; Ottman 1993). Seizures may have been few and unwitnessed, and investigations are commonly unhelpful, but there is nevertheless no doubt that seizures have occurred and should be treated. This most commonly applies to tonic-clonic seizures that may be generalised at onset, or which may be secondarily generalised. In any trial, such unclassified individuals need to be clearly identified, because if they are not they may confound interpretation of results for well classified individuals. We need to know how to manage those whose classification we find more difficult.

The choice of outcomes at the design stage of a trial and the presentation of the results of outcomes, particularly of a time-to-event nature, require very careful consideration. While the majority of trials of a monotherapy design record an outcome measuring efficacy (seizure control) and an outcome measuring tolerability (adverse events), there is little uniformity between the definition of the outcomes and the reporting of the summary statistics related to the outcomes (Nolan 2013a), making an aggregate data approach to meta-analysis in reviews of monotherapy trials impossible. Where trial authors cannot or will not make IPD available for analysis, we are left with no choice but to exclude a proportion of relevant evidence from the review, which may impact upon the interpretation of the results of the review and the applicability of the evidence and conclusions. The International League Against Epilepsy recommends that trials of a monotherapy design should adopt a primary effectiveness outcome of time to treatment failure (i.e. 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Callaghan 1985

Methods	Parallel study design, outpatient setting Study conducted in Eire (Republic of Ireland) Randomisation based on two Latin squares and the preference of drug for the participant An independent person selected "drug of first preference" from randomisation list	
Participants	Adults and children with a minimum of 2 untreated generalised or focal seizures in the 6 months preceding the trial Number randomised: PHT = 58; SV = 64 48 participants (39%) with focal epilepsy. 67 (55%) men Age range: 5-71. Duration of treatment (range in months):3-48	
Interventions	Monotherapy with PHT or SV Mean daily dose achieved: PHT: 5.4 mg/kg; SV: 15.6 mg/kg	
Outcomes	Seizure control: excellent (complete freedom of seizures) good (> 50% reduction in seizure frequency) poor (< 50% reduction in seizure frequency)	
Notes	Outcomes chosen for this review were not reported. IPD not available	
<i>Risk of bias</i>		
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) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided

Callaghan 1985 (Continued)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT approach taken, all randomised participants analysed
Selective reporting (reporting bias)	Low risk	Primary outcomes (seizure control) and secondary outcomes (side effects) reported sufficiently. No protocol available, outcomes for this review not reported
Other bias	Low risk	No other bias detected

Craig 1994

Methods	Parallel study design Study conducted in the UK Participants randomised using computerised stratified minimisation programme by age group, sex and seizure type Allocation was pharmacy-controlled The main investigator performing cognitive testing was blinded to allocation. Participants and personnel unblinded
Participants	Participants over 60 years of age with newly onset seizures (1 or more generalised tonic-clonic seizures or 2 or more focal seizures) Number randomised: PHT = 81; SV = 85 80 participants (48%) with focal epilepsy, 71 (44%) men Mean age (range): 78 (61-95 years). Range of follow-up: 1-20 months
Interventions	Monotherapy with PHT or SV Starting doses: PHT: 200 mg/day, SV: 400 mg/day Median daily dose achieved: PHT 247 mg (range 175-275); SV: 688 mg (range 400-1000)
Outcomes	Psychological tests (cognitive function, anxiety and depression) Adverse event frequency Seizure control
Notes	Trial paper reports on a subset of 38 participants. Full IPD set provided and used for this review includes all 166 participants randomised in the trial. IPD provided for 3/4 outcomes of this review ('time to treatment failure' not available)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised stratified minimisation programme, stratified for age group, gender and seizure type

Craig 1994 (Continued)

Allocation concealment (selection bias)	Low risk	Pharmacy-controlled allocation, prescription disclosed to general practitioner and consultant
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main investigator performing cognitive testing was blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis undertaken with all randomised participants from IPD (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcome measures reported in published report or provided in IPD (see footnote 2)
Other bias	Low risk	No other bias detected

Czapinski 1997a

Methods	36-month randomised comparative trial Parallel study design Study conducted in Poland Method of generation of random list and allocation concealment not stated	
Participants	Adults with newly diagnosed epilepsy Number randomised: PHT = 30; SV = 30 100% focal epilepsy, age range: 18 to 40 years Percentage men and range of follow-up not mentioned	
Interventions	Monotherapy with PHT or SV Starting doses: PHT: 200 mg/day, SV: 600 mg/day. Dose achieved not stated	
Outcomes	Proportion achieving 24-month remission at 3 years Exclusions after randomisation due to adverse events or no efficacy	
Notes	Abstract only. Outcomes chosen for this review were not reported. IPD pledged but not received	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Czapinski 1997a (Continued)

Random sequence generation (selection bias)	Unclear risk	Trial “randomised” but no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Exclusion rates” (interpreted as treatment withdrawal rates) reported for all treatment groups, no further information provided
Selective reporting (reporting bias)	Unclear risk	No protocol available and trial reported only in abstract form; outcomes for this review not available
Other bias	Unclear risk	Insufficient detail provided in abstract to allow judgement

De Silva 1996

Methods	Parallel study design, outpatient setting Study conducted at two centres in the UK Random list generated using random permuted blocks Allocation concealed using sealed opaque envelopes Unblinded
Participants	Children with newly diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the trial) Number randomised: PHT = 54; SV = 49 55 children (53%) with focal epilepsy. 52 (50%) boys Mean age (range): 10 (3-16) years. Range of follow-up (months): 3-88
Interventions	Monotherapy with PHT or SV Median daily dose achieved: PHT: 175 mg/day, SV: 600 mg/day
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse events and treatment withdrawals due to adverse events
Notes	IPD provided for all outcomes of this review
<i>Risk of bias</i>	

De Silva 1996 (Continued)

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 via 4 batches of sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, authors state masking of treatment would not be "practicable or ethical" and would "undermine compliance"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded, authors state masking of treatment would not be "practicable or ethical" and would "undermine compliance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	No other bias detected

Forsythe 1991

Methods	Parallel study design, outpatient setting Study conducted in the UK Patients randomly allocated using quota allocation allowing for gender, age, seizure type and current treatment Outcome assessors were single-blinded for cognitive testing
Participants	Children with at least 3 newly diagnosed generalised or focal seizures within a period of 6 months Number randomised: PHT = 20; SV = 21 No information on epilepsy type, gender or range of follow-up Age range: 5-14 years. Trial duration: 12 months
Interventions	Monotherapy with PHT or SV Mean dose achieved: PHT: 6.1 mg/day, SV: 25.3 mg/day
Outcomes	Cognitive assessments Summary of withdrawals from randomised drug

Forsythe 1991 (Continued)

Notes	Outcomes chosen for this review were not reported. IPD not available, but could be constructed from the publication for the outcome 'time on allocated drug' (without stratification by seizure type)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quota allocation by gender, 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) All outcomes	High risk	Personnel and participants (and parents) unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors single-blinded for cognitive testing
Incomplete outcome data (attrition bias) All outcomes	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	Cognitive outcomes described in methods section well reported in results section. Adverse events 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	Parallel study design, outpatient setting Study conducted at two centres in the UK Random list generated using random permuted blocks Allocation concealed using sealed opaque envelopes Unblinded
Participants	Adults with newly diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the trial) Number randomised: PHT = 63; SV = 61

Heller 1995 (Continued)

	53 participants (43%) with focal epilepsy. 62 (48%) men Mean age (range): 33 (14-72) years Range of follow-up (months): 1-91	
Interventions	Monotherapy with PHT or SV Median daily dose achieved: PHT: 300 mg/day, SV: 800 mg/day	
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse events and treatment withdrawal due to adverse events	
Notes	IPD provided for all outcomes of this review	
Risk of bias		
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 via 4 batches of concealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, authors state masking of treatment would not be "practical" and would have "introduced bias due to a very large drop-out rate"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded, authors state masking of treatment would not be "practical" and would have "introduced bias due to a very large drop-out rate"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	No other bias detected

Ramsay 1992

Methods	Parallel trial Study conducted at 16 centres in the USA Participants assigned via randomisation tables within each centre in a 2:1 ratio (SV: PHT) Method of allocation concealment not stated Unblinded
Participants	Participants with at least 2 newly diagnosed and previously untreated primary generalised tonic-clonic seizures within 14 days of starting the trial Number randomised: PHT = 50; SV = 86 0% participants with focal epilepsy, 73 (54%) men Mean age (range): 21 (3-64 years). Participants followed up for up to 6 months
Interventions	Monotherapy with PHT or SV Starting doses PHT: 3-5 mg/kg/day, SV: 10-15 mg/kg/day, doses gradually increased Doses achieved not stated
Outcomes	Time to first generalised tonic-clonic seizure 6-month seizure recurrence rates Adverse events
Notes	IPD provided for 3/4 outcomes of this review (maximum follow-up 6 months, therefore trial cannot contribute to outcome 'time to achieve 12-month remission')

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised on a 2:1 ratio SV: PHT using randomisation tables in each centre (information provided by trial author)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial; authors state that differences in adverse events of PHT and SV would "quickly unblind" the trial anyway
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial; authors state that differences in adverse events of PHT and SV would "quickly unblind" the trial anyway
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)

Ramsay 1992 (Continued)

Other bias	Low risk	No other bias detected
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Rastogi 1991

Methods	Parallel study design, outpatient setting Study conducted in Meerut, India No information provided on method of generation of random list, allocation concealment or blinding
Participants	Participants with at least 2 focal or generalised tonic-clonic seizures per month Unclear if participants were newly diagnosed Number randomised: PHT = 45; SV = 49 27 participants (29%) focal epilepsy, 70 (74%) men Age range: PHT: 12-42 years; SV: 8-52 years Participants were evaluated after 4, 12 and 24 weeks of treatment No information on range of follow-up
Interventions	Monotherapy with PHT or SV Average daily dose achieved: PHT: 5.6 mg/kg/day, SV: 18.8 mg/kg/day
Outcomes	Reduction in frequency of seizures: excellent (100% reduction) good (75% - 99% reduction) fair (50% - 74% reduction) poor (< 50% reduction) Adverse effects Seizure control
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants "randomly allocated irrespective of seizure type," no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Rastogi 1991 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Frequency of seizures reported for all randomised participants, no information provided on treatment withdrawal rates/attrition rates etc
Selective reporting (reporting bias)	Low risk	Frequency of seizures during treatment well reported, most common adverse events reported No protocol available to compare with a priori analysis plan, outcomes for this review not reported
Other bias	Low risk	No other bias detected

Shakir 1981

Methods	Parallel study design, outpatient setting Study conducted in two centres (Glasgow, Scotland and Wellington, New Zealand) Participants allocated using telephone randomisation within the two centres (information provided by trial author) No information provided on method of allocation concealment or blinding	
Participants	21 (64%) participants previously untreated, 12 (36%) participants continued to have seizures on previous drug therapies Original treatments gradually withdrawn before PHT or SV treatment introduced Number randomised: PHT = 15; SV = 18 19 participants (58%) with focal epilepsy, 12 (36%) men Mean age (range): 23 (7-55 years). Mean follow-up (range): 30 (9-48 months)	
Interventions	Monotherapy with PHT or SV Starting doses: PHT: < 12 years 150 mg/day, older participants: 300 mg/day SV: < 12 years 300-400 mg/day, older participants: 800-1200 mg/day. Doses achieved not stated	
Outcomes	Seizures during treatment Adverse events	
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'	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants "randomly divided", using telephone randomisation (information provided by trial author)

Shakir 1981 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomised participants, time on treatment reported for all randomised participants. No losses to follow-up reported
Selective reporting (reporting bias)	Low risk	No protocol available, outcomes chosen for this review not reported. Seizure outcomes and adverse events well reported
Other bias	Low risk	No other bias detected

Thilothammal 1996

Methods	Parallel study design, outpatient setting Study conducted in Madras (Chennai), India Random list generated using computer-generated random numbers Method of concealment not mentioned Double-blind achieved by providing additional placebo tablets	
Participants	Children with more than 1 previously untreated generalised tonic-clonic (afebrile) seizure Number randomised: PHT = 52; SV = 48 0% focal epilepsy. 52 (52%) men. Age range: 4-12 years Range of follow-up (months): 22-36	
Interventions	Monotherapy with PHT or SV Starting doses: PHT: 5-8 mg/kg/day, SV: 15-50 mg/kg/day Dose achieved not stated	
Outcomes	Proportion with recurrence of seizures Adverse events	
Notes	Outcomes chosen for this review were not reported. IPD not available	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Thilothammal 1996 (Continued)

Random sequence generation (selection bias)	Low risk	Participants randomised via a computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded using additional placebo tablets; unclear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinded using additional placebo tablets; unclear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed
Selective reporting (reporting bias)	Low risk	No protocol available; outcomes chosen for this review not reported
Other bias	Low risk	No other bias detected

Turnbull 1985

Methods	Parallel study design, outpatient setting Study conducted in the UK Participants allocated to treatment stratified by age group, gender and seizure type No information provided on method of generation of random list, allocation concealment or blinding	
Participants	Participants with 2 or more focal or generalised tonic-clonic seizure in the past 3 years Participants were previously untreated but started on antiepileptic drug treatment within 3 months of their most recent seizure Number randomised: PHT = 70; SV = 70 63 participants (45%) with focal onset seizures, 73 (52%) men Mean age (range): 35 (14-70 years). Range of follow-up: 24-48 months	
Interventions	Monotherapy with PHT or SV Starting doses: PHT 300 mg/day, SV 600 mg/day. Dose achieved not stated	
Outcomes	Time to 2-year remission Time to first seizure Adverse events	
Notes	IPD provided for all outcomes included in this review	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Turnbull 1985 (Continued)

Random sequence generation (selection bias)	Unclear risk	Participants randomised with stratification for age group, gender and seizure type. Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	No other bias detected

¹ Abbreviations:

IPD: individual participant data; ITT: intention-to-treat; PHT: phenytoin; SV: sodium valproate.

² For studies which provided IPD, attrition and reporting bias are reduced as attrition rates and unpublished outcome data are requested (Craig 1994; De Silva 1996; Heller 1995; Ramsay 1992; Turnbull 1985).

³ See Figure 2 and Figure 3 for 'Risk of bias' summary and graph.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Berg 1993	Reports the same trial as Forsythe 1991 , but more relevant information given in the Forsythe publication
Callaghan 1981	Abstract only. Preliminary results of the trial reported in Callaghan 1985
Callaghan 1983	Abstract only. Preliminary results of the trial reported in Callaghan 1985
Callaghan 1984	Preliminary results of the trial reported in Callaghan 1985
Craig 1993	Abstract only. Preliminary results of the trial reported in Craig 1994
Czapinski 1997b	Reports the same abstract as Czapinski 1997a

(Continued)

Czapinski 1997c	Reports the same abstract as Czapinski 1997a
Goggin 1984	Abstract only. Preliminary results of the trial reported in Callaghan 1985
Goggin 1986	Reports the same trial as Callaghan 1985 , but more relevant information given in the Callaghan publication
Jannuzzi 2000	No randomised comparison of valproate and phenytoin (participants randomised to a dose adjustment method rather than to a treatment)
Kaminow 2003	No randomised comparison of valproate and phenytoin (study of lamotrigine versus 'standard' antiepileptic drug treatment)
Sabers 1995	Not fully randomised: "The treatment was chosen at random unless the individual diagnoses required a specific drug"
Schmidt 2007	No randomised comparison of valproate and phenytoin (post hoc analysis of 5 studies of oxcarbazepine versus another antiepileptic drug)
Shakir 1980	Reports the same trial as Shakir 1981 . There are some differences between the results in the 2 publications. The reason for this could not be established
Tallis 1994a	Abstract only. Reports the same trial as Craig 1994
Tallis 1994b	Abstract only. Reports the same trial as Craig 1994
Turnbull 1982	Preliminary results of the trial reported in Turnbull 1985
Wilder 1983	Preliminary results of the trial reported in Turnbull 1985
Zeng 2010	Not randomised

DATA AND ANALYSES

Comparison 1. Sodium valproate versus phenytoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to treatment failure (any reason related to the treatment)	6	569	Hazard Ratio (Fixed, 95% CI)	0.94 [0.67, 1.32]
2 Time to treatment failure due to adverse events	4	495	Hazard Ratio (Fixed, 95% CI)	0.68 [0.40, 1.17]
3 Time to treatment failure due to lack of efficacy	6	569	Hazard Ratio (Fixed, 95% CI)	1.23 [0.77, 1.97]
4 Time to treatment failure (any reason related to the treatment) - by epilepsy type	5	528	Hazard Ratio (Fixed, 95% CI)	0.88 [0.61, 1.27]
4.1 Focal onset seizures	4	187	Hazard Ratio (Fixed, 95% CI)	0.83 [0.50, 1.38]
4.2 Generalised onset seizures (tonic-clonic only)	5	341	Hazard Ratio (Fixed, 95% CI)	0.94 [0.55, 1.61]
5 Time to treatment failure due to adverse events - by epilepsy type	4	418	Hazard Ratio (Fixed, 95% CI)	0.77 [0.44, 1.37]
5.1 Focal onset seizures	3	168	Hazard Ratio (Fixed, 95% CI)	0.75 [0.35, 1.60]
5.2 Generalised onset seizures (tonic-clonic only)	3	250	Hazard Ratio (Fixed, 95% CI)	0.81 [0.34, 1.90]
6 Time to treatment failure due to lack of efficacy - by epilepsy type	5	451	Hazard Ratio (Fixed, 95% CI)	1.16 [0.71, 1.89]
6.1 Focal onset seizures	4	187	Hazard Ratio (Fixed, 95% CI)	1.01 [0.55, 1.85]
6.2 Generalised onset seizures (tonic-clonic only)	4	264	Hazard Ratio (Fixed, 95% CI)	1.51 [0.66, 3.45]
7 Time to first seizure	5	639	Hazard Ratio (Fixed, 95% CI)	1.04 [0.85, 1.28]
8 Time to first seizure - by epilepsy type	5	639	Hazard Ratio (Fixed, 95% CI)	1.08 [0.88, 1.33]
8.1 Focal onset seizures	4	244	Hazard Ratio (Fixed, 95% CI)	1.20 [0.90, 1.60]
8.2 Generalised onset seizures (tonic-clonic only)	5	395	Hazard Ratio (Fixed, 95% CI)	0.97 [0.72, 1.30]
9 Time to first seizure - epilepsy type reclassified to focal for generalised and age of onset > 30 years	5	639	Hazard Ratio (Fixed, 95% CI)	1.05 [0.86, 1.29]
9.1 Focal onset seizures	5	416	Hazard Ratio (Fixed, 95% CI)	1.23 [0.96, 1.57]
9.2 Generalised onset seizures (tonic-clonic only)	4	223	Hazard Ratio (Fixed, 95% CI)	0.72 [0.50, 1.05]
10 Time to first seizure - epilepsy type reclassified to uncertain for generalised and age of onset > 30 years	5	649	Hazard Ratio (Fixed, 95% CI)	1.06 [0.86, 1.30]
10.1 Focal onset seizures	4	255	Hazard Ratio (Fixed, 95% CI)	1.20 [0.90, 1.60]

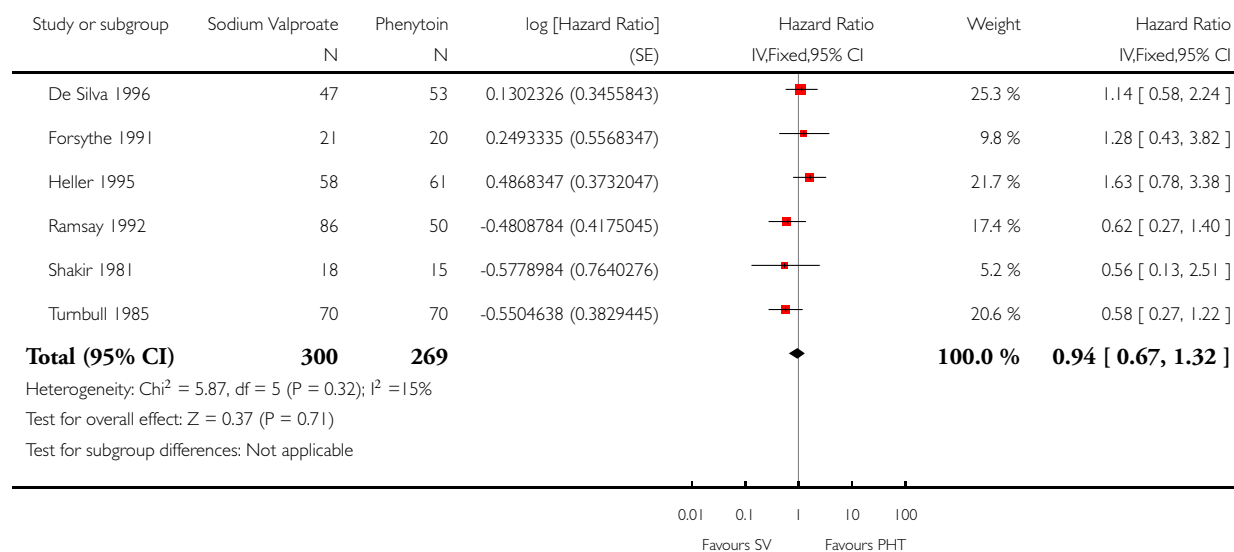
10.2 Generalised onset seizures (tonic-clonic only)	4	223	Hazard Ratio (Fixed, 95% CI)	0.72 [0.50, 1.05]
10.3 Uncertain seizure type	4	171	Hazard Ratio (Fixed, 95% CI)	1.35 [0.85, 2.14]
11 Time to achieve 12-month remission	4	514	Hazard Ratio (Fixed, 95% CI)	1.03 [0.82, 1.29]
12 Time to achieve 12-month remission - by epilepsy type	4	514	Hazard Ratio (Fixed, 95% CI)	1.02 [0.81, 1.28]
12.1 Focal onset seizures	4	244	Hazard Ratio (Fixed, 95% CI)	1.11 [0.78, 1.60]
12.2 Generalised onset seizures (tonic-clonic only)	4	270	Hazard Ratio (Fixed, 95% CI)	0.96 [0.71, 1.29]
13 Time to achieve six-month remission	5	639	Hazard Ratio (Fixed, 95% CI)	1.08 [0.89, 1.30]
14 Time to achieve six-month remission - by epilepsy type	5	639	Hazard Ratio (Fixed, 95% CI)	1.05 [0.86, 1.27]
14.1 Focal onset seizures	4	244	Hazard Ratio (Fixed, 95% CI)	1.00 [0.73, 1.35]
14.2 Generalised onset seizures (tonic-clonic only)	5	395	Hazard Ratio (Fixed, 95% CI)	1.08 [0.84, 1.38]

Analysis 1.1. Comparison 1 Sodium valproate versus phenytoin, Outcome 1 Time to treatment failure (any reason related to the treatment).

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 1 Time to treatment failure (any reason related to the treatment)

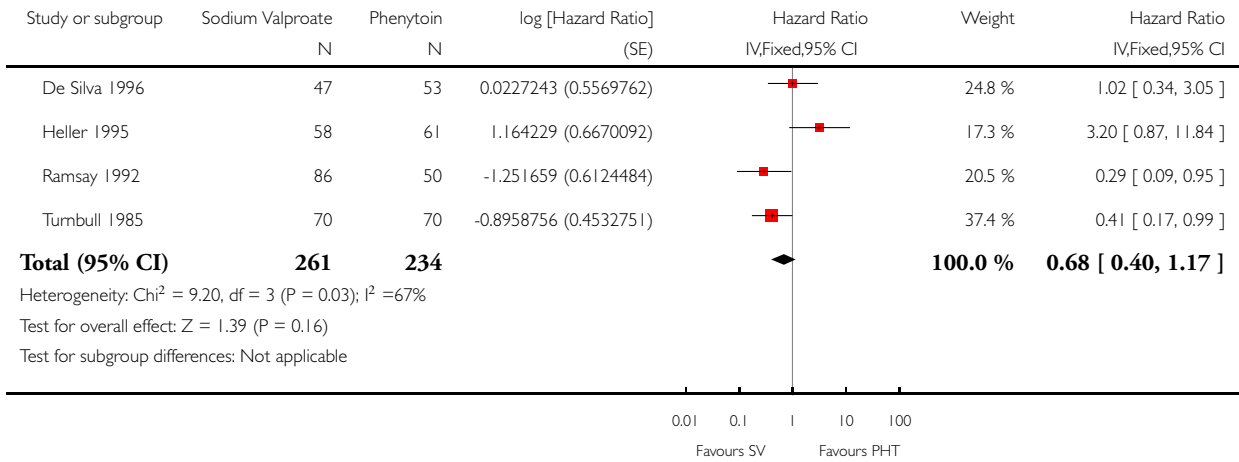


Analysis 1.2. Comparison 1 Sodium valproate versus phenytoin, Outcome 2 Time to treatment failure due to adverse events.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 2 Time to treatment failure due to adverse events

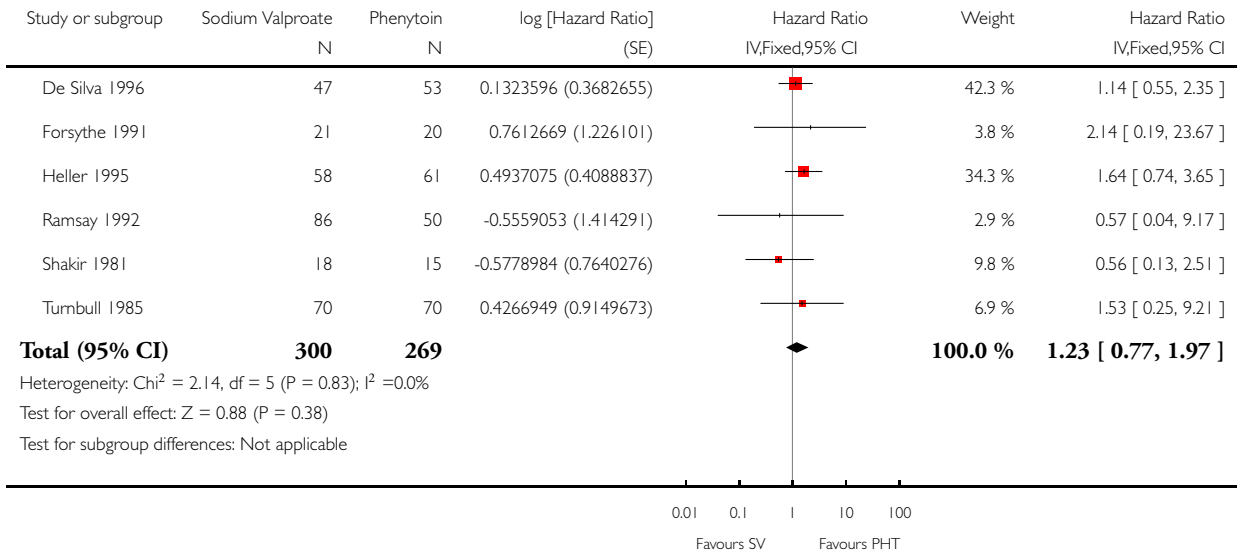


Analysis 1.3. Comparison 1 Sodium valproate versus phenytoin, Outcome 3 Time to treatment failure due to lack of efficacy.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 3 Time to treatment failure due to lack of efficacy

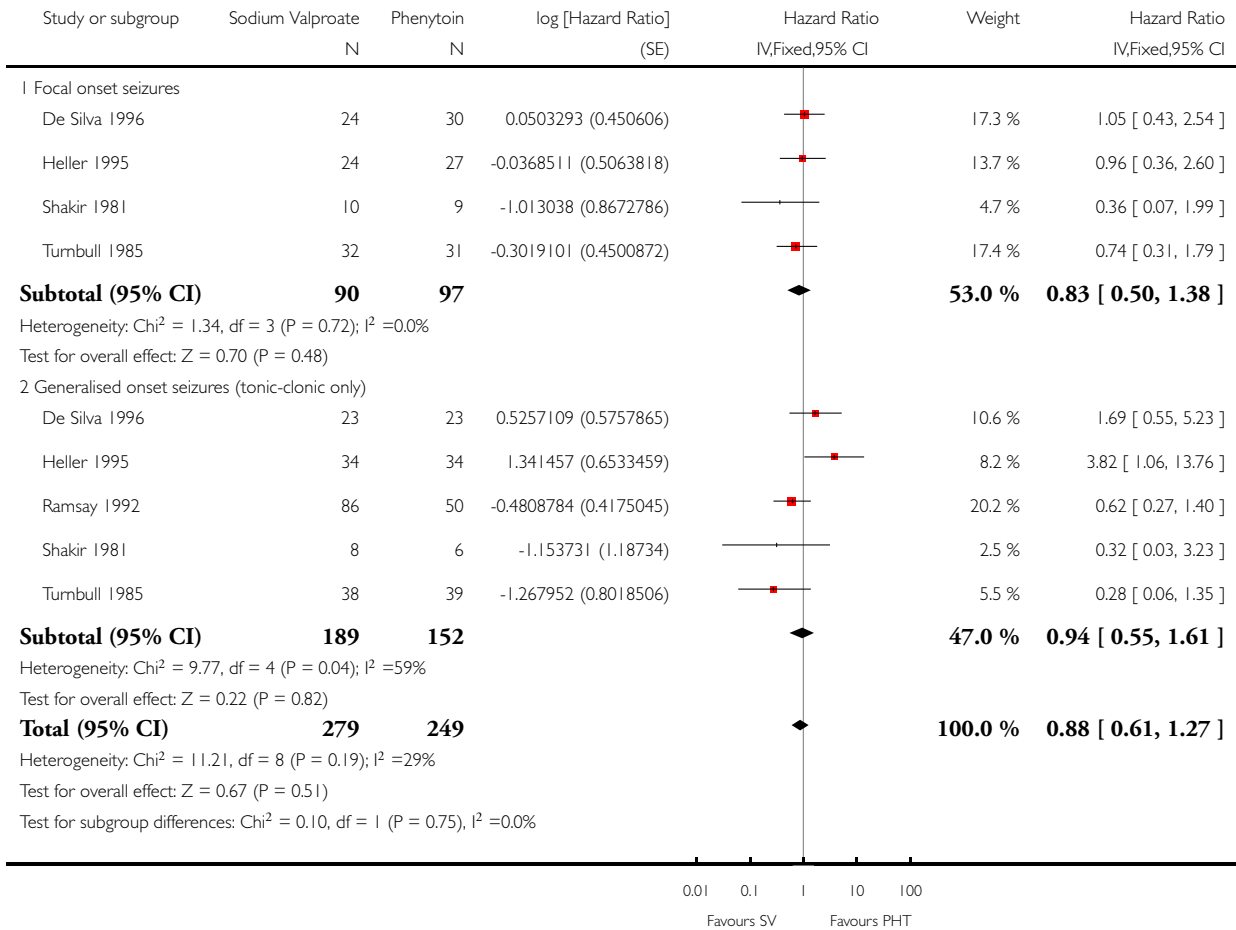


Analysis 1.4. Comparison 1 Sodium valproate versus phenytoin, Outcome 4 Time to treatment failure (any reason related to the treatment) - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 4 Time to treatment failure (any reason related to the treatment) - by epilepsy type

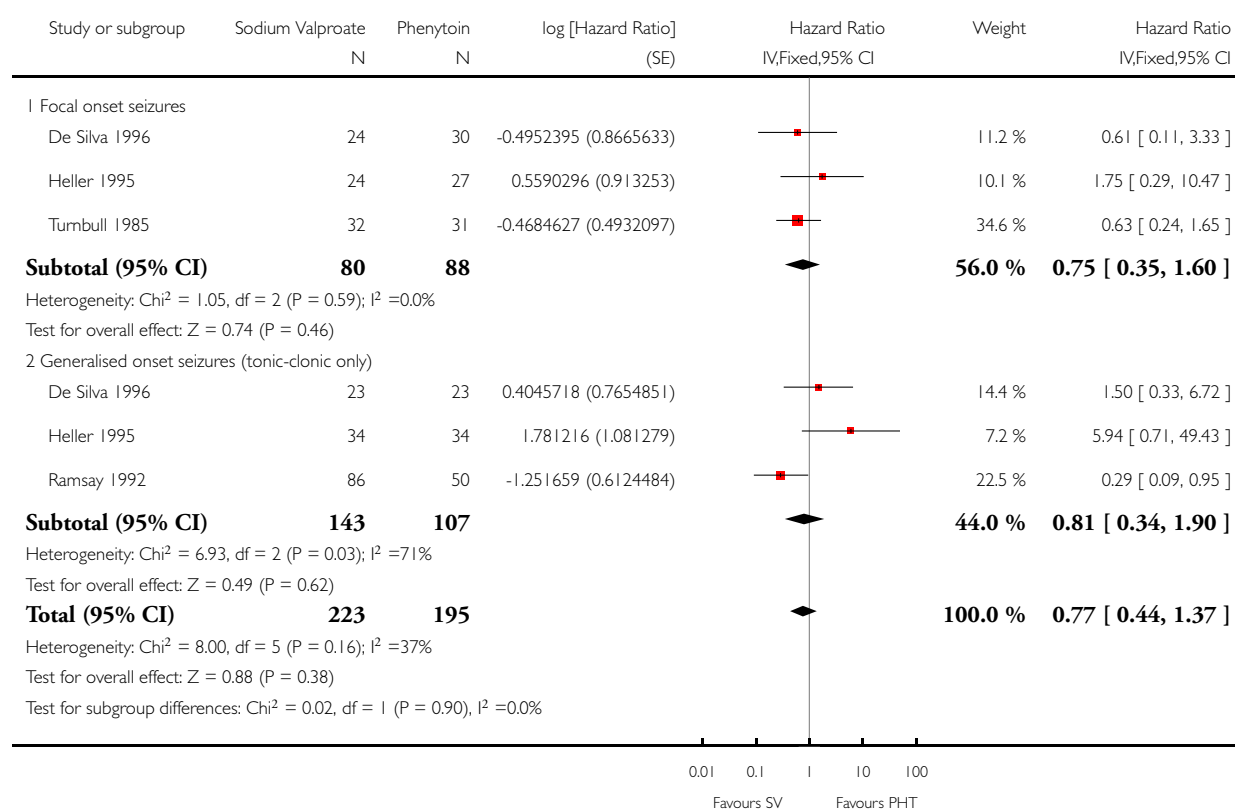


Analysis 1.5. Comparison 1 Sodium valproate versus phenytoin, Outcome 5 Time to treatment failure due to adverse events - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 5 Time to treatment failure due to adverse events - by epilepsy type

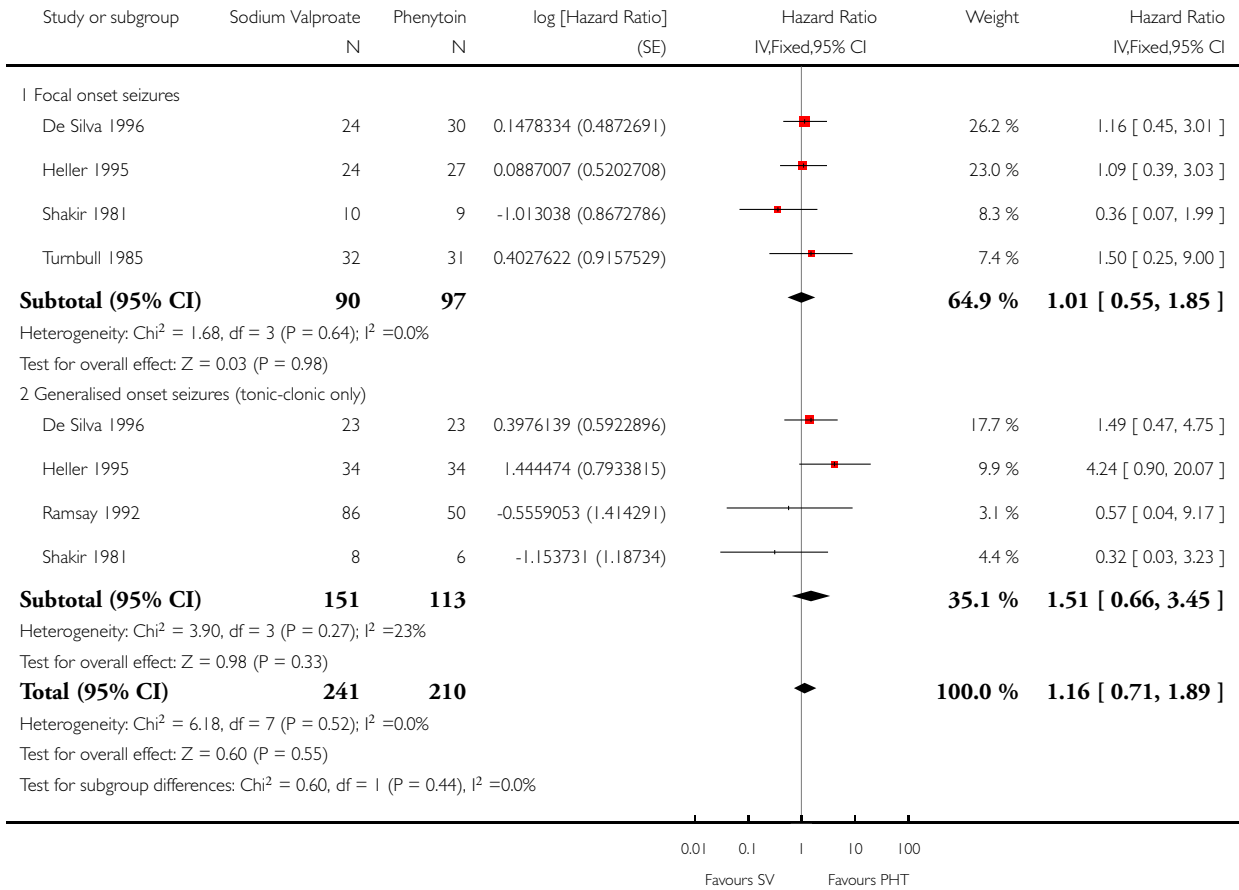


Analysis 1.6. Comparison 1 Sodium valproate versus phenytoin, Outcome 6 Time to treatment failure due to lack of efficacy - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 6 Time to treatment failure due to lack of efficacy - by epilepsy type

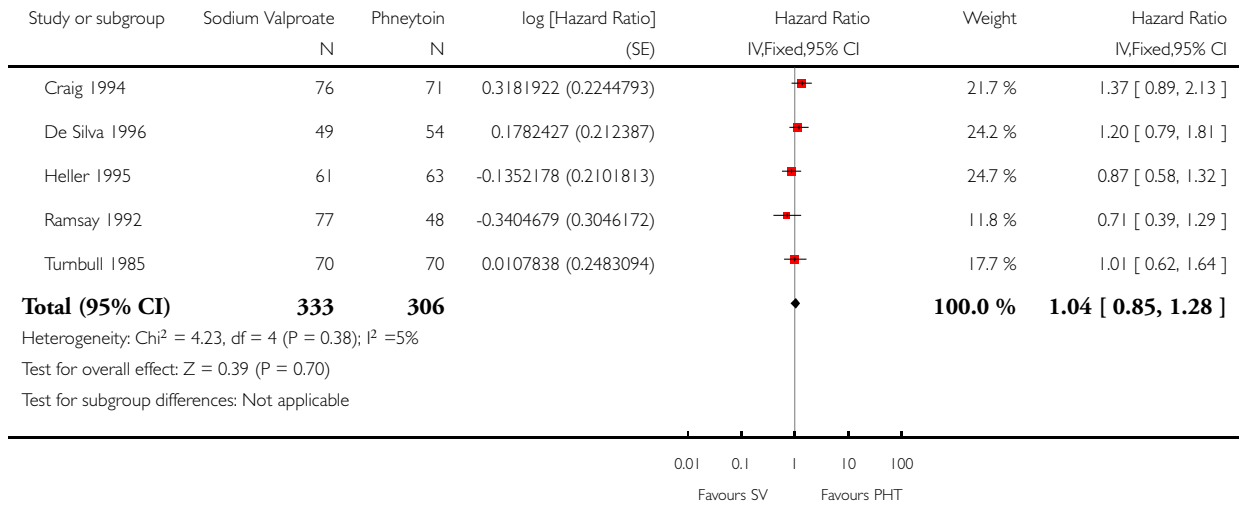


Analysis 1.7. Comparison 1 Sodium valproate versus phenytoin, Outcome 7 Time to first seizure.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 7 Time to first seizure

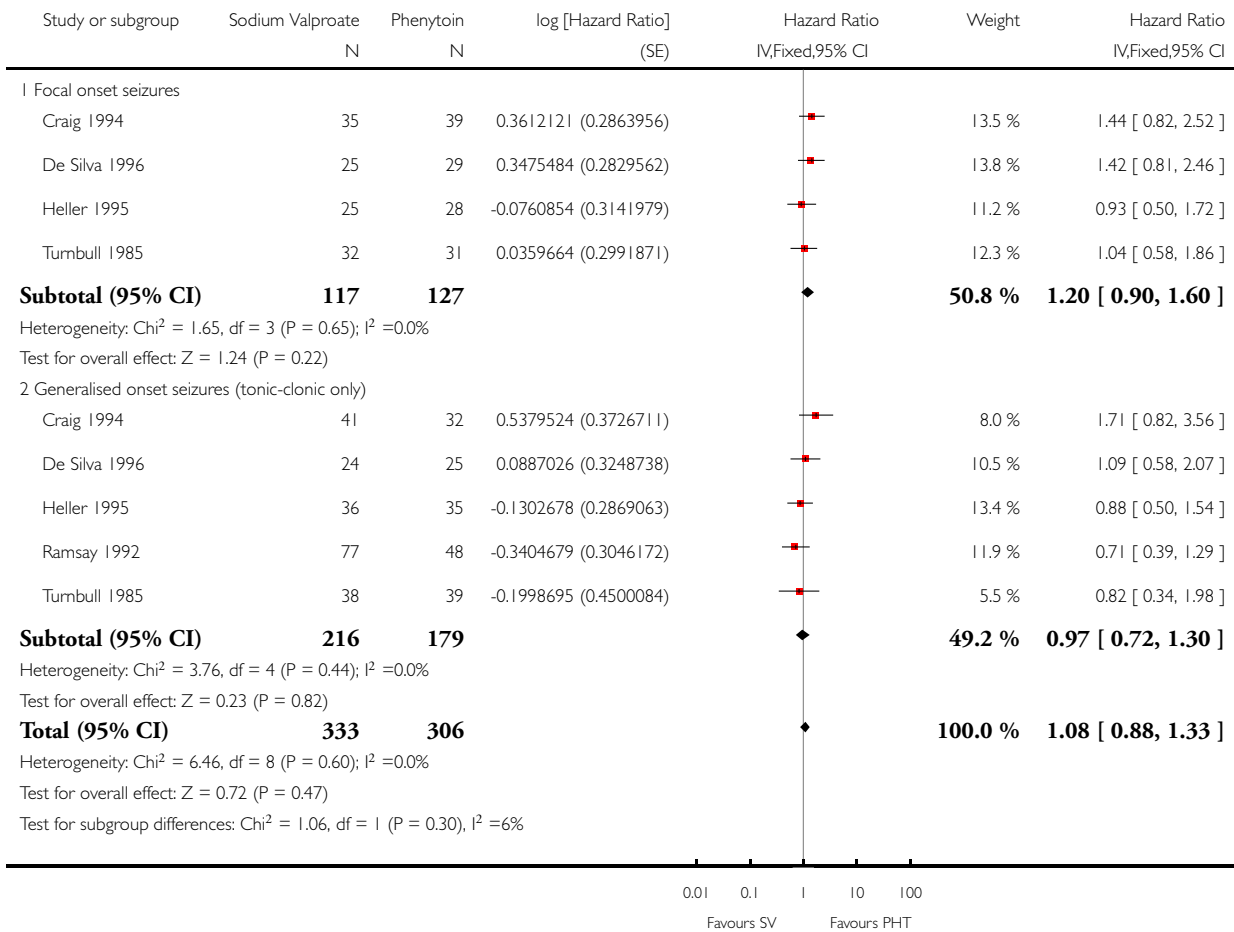


Analysis 1.8. Comparison 1 Sodium valproate versus phenytoin, Outcome 8 Time to first seizure - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 8 Time to first seizure - by epilepsy type

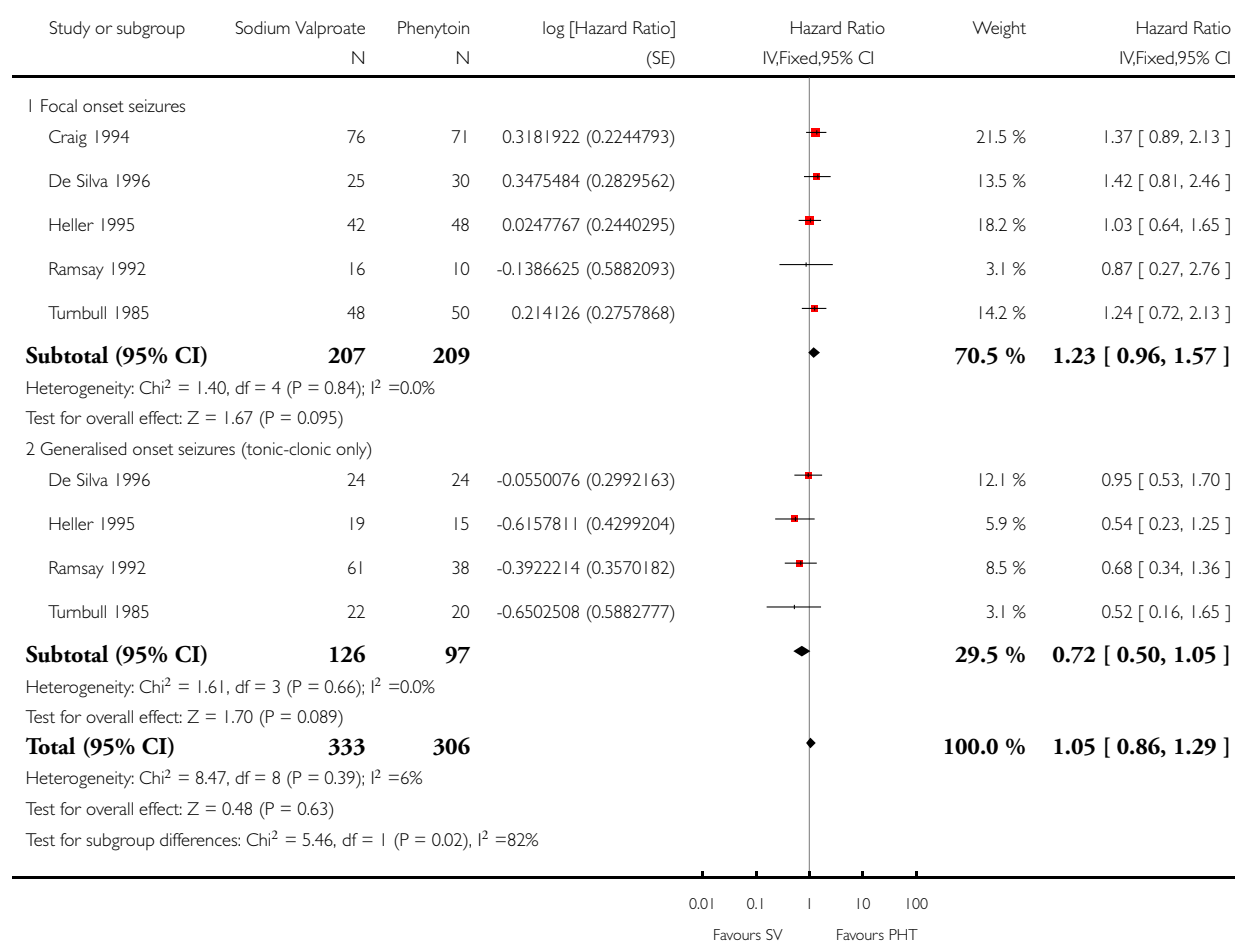


Analysis 1.9. Comparison 1 Sodium valproate versus phenytoin, Outcome 9 Time to first seizure - epilepsy type reclassified to focal for generalised and age of onset > 30 years.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 9 Time to first seizure - epilepsy type reclassified to focal for generalised and age of onset > 30 years

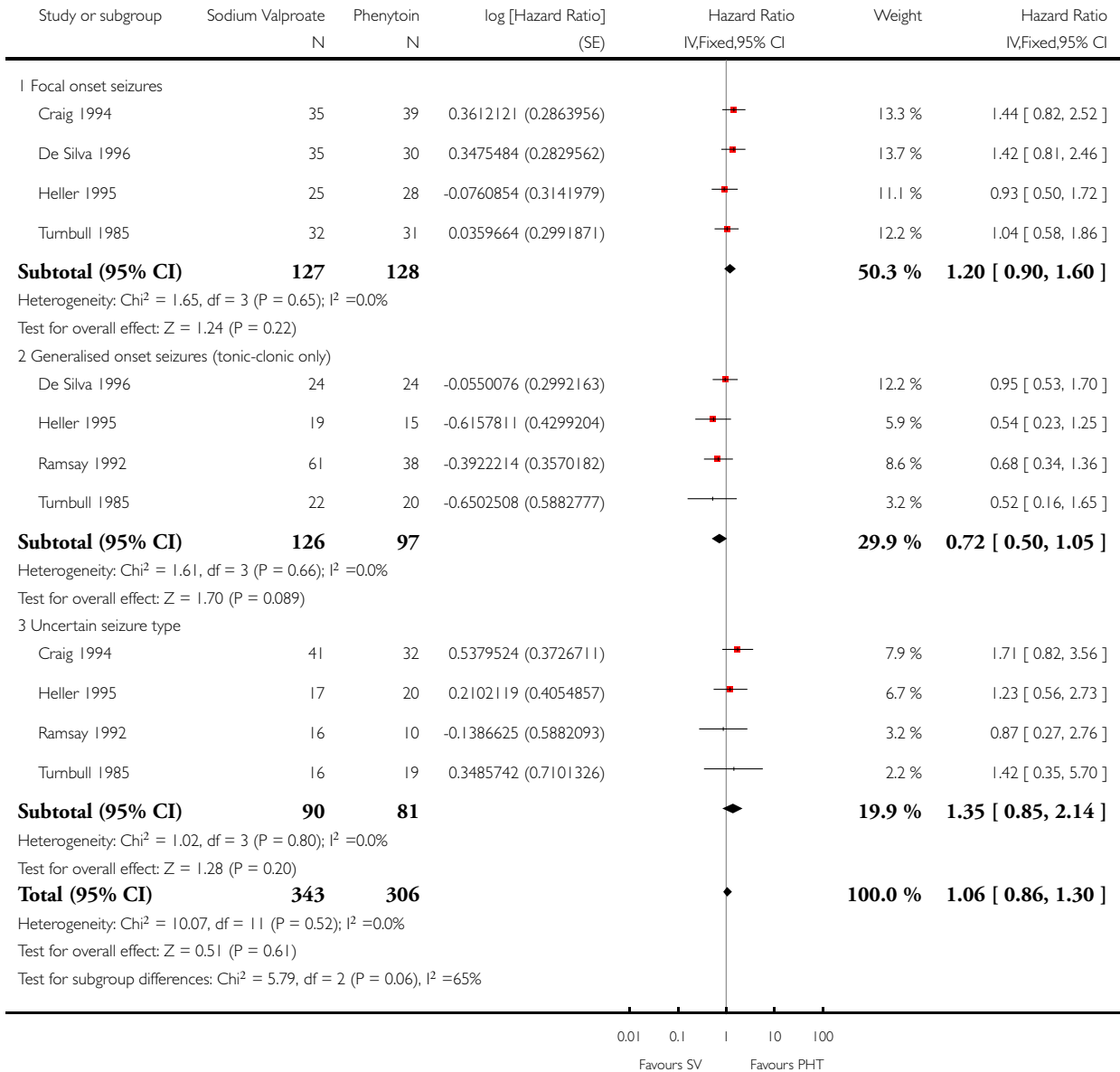


Analysis 1.10. Comparison 1 Sodium valproate versus phenytoin, Outcome 10 Time to first seizure - epilepsy type reclassified to uncertain for generalised and age of onset > 30 years.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 10 Time to first seizure - epilepsy type reclassified to uncertain for generalised and age of onset > 30 years

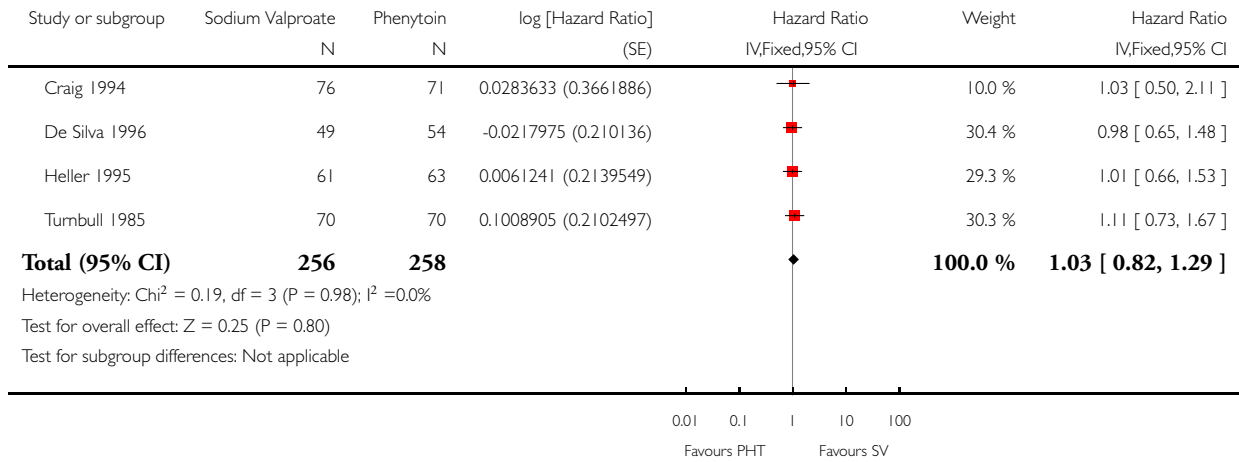


Analysis 1.11. Comparison 1 Sodium valproate versus phenytoin, Outcome 11 Time to achieve 12-month remission.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 11 Time to achieve 12-month remission

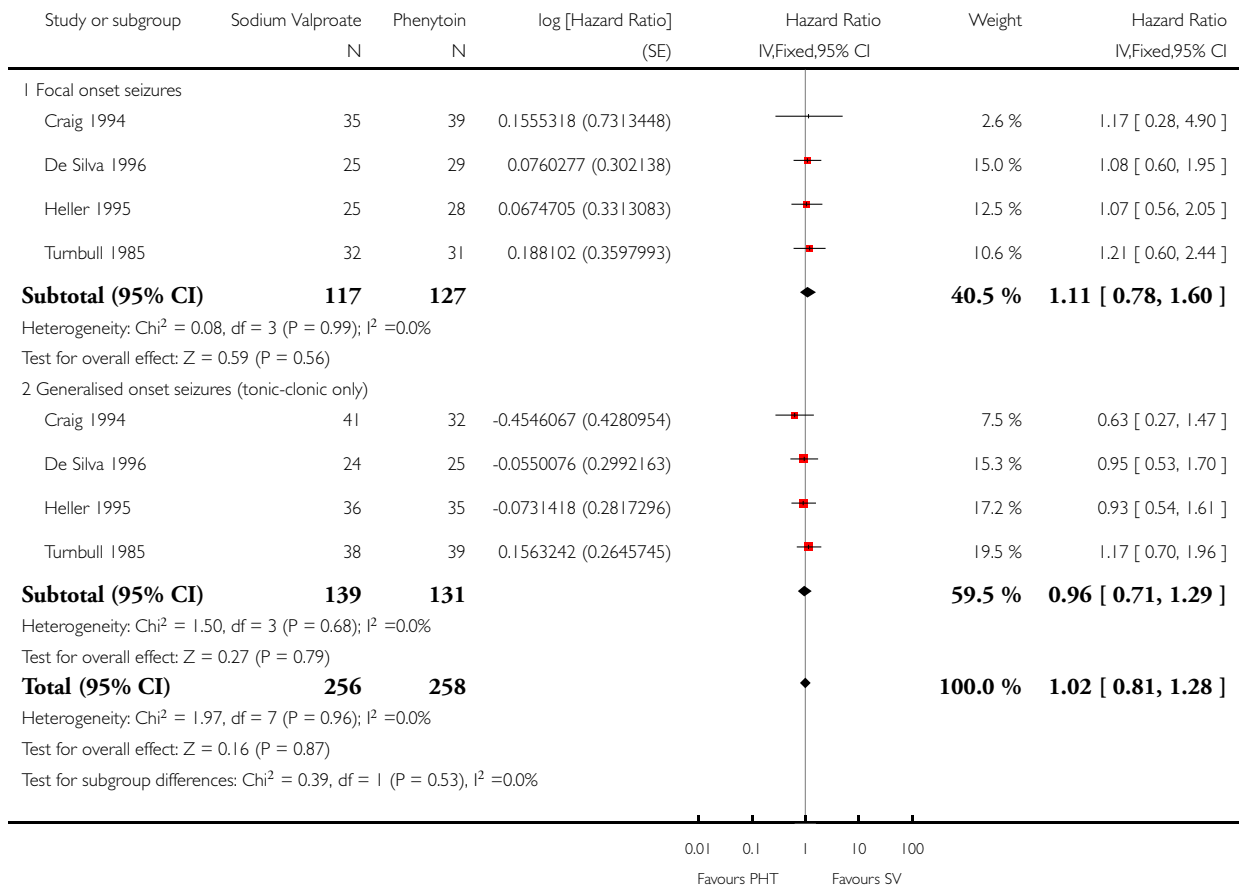


Analysis 1.12. Comparison 1 Sodium valproate versus phenytoin, Outcome 12 Time to achieve 12-month remission - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 12 Time to achieve 12-month remission - by epilepsy type

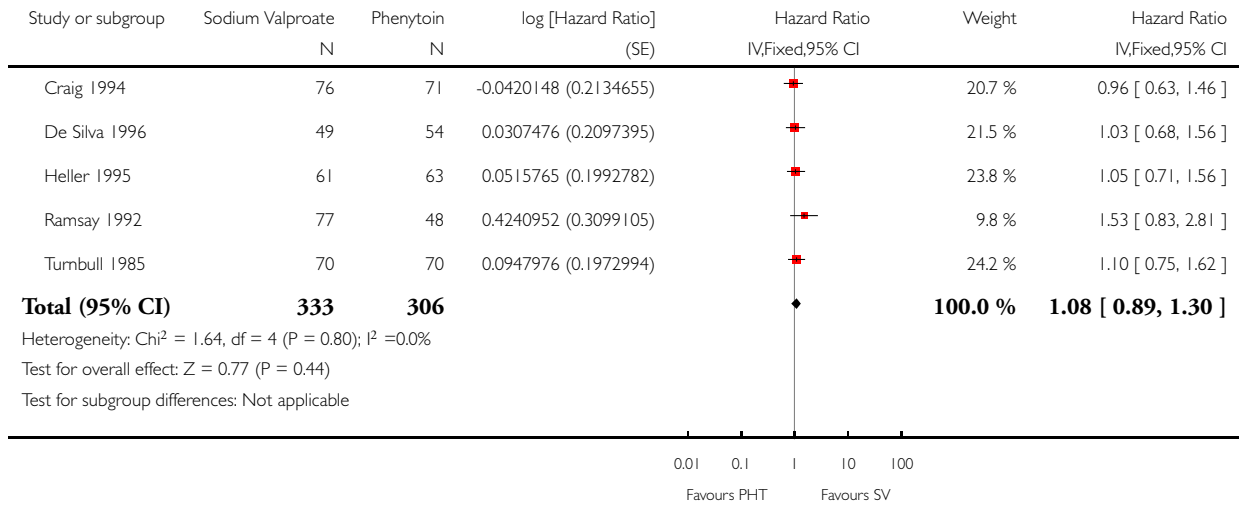


Analysis 1.13. Comparison 1 Sodium valproate versus phenytoin, Outcome 13 Time to achieve six-month remission.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: 1 Sodium valproate versus phenytoin

Outcome: 13 Time to achieve six-month remission

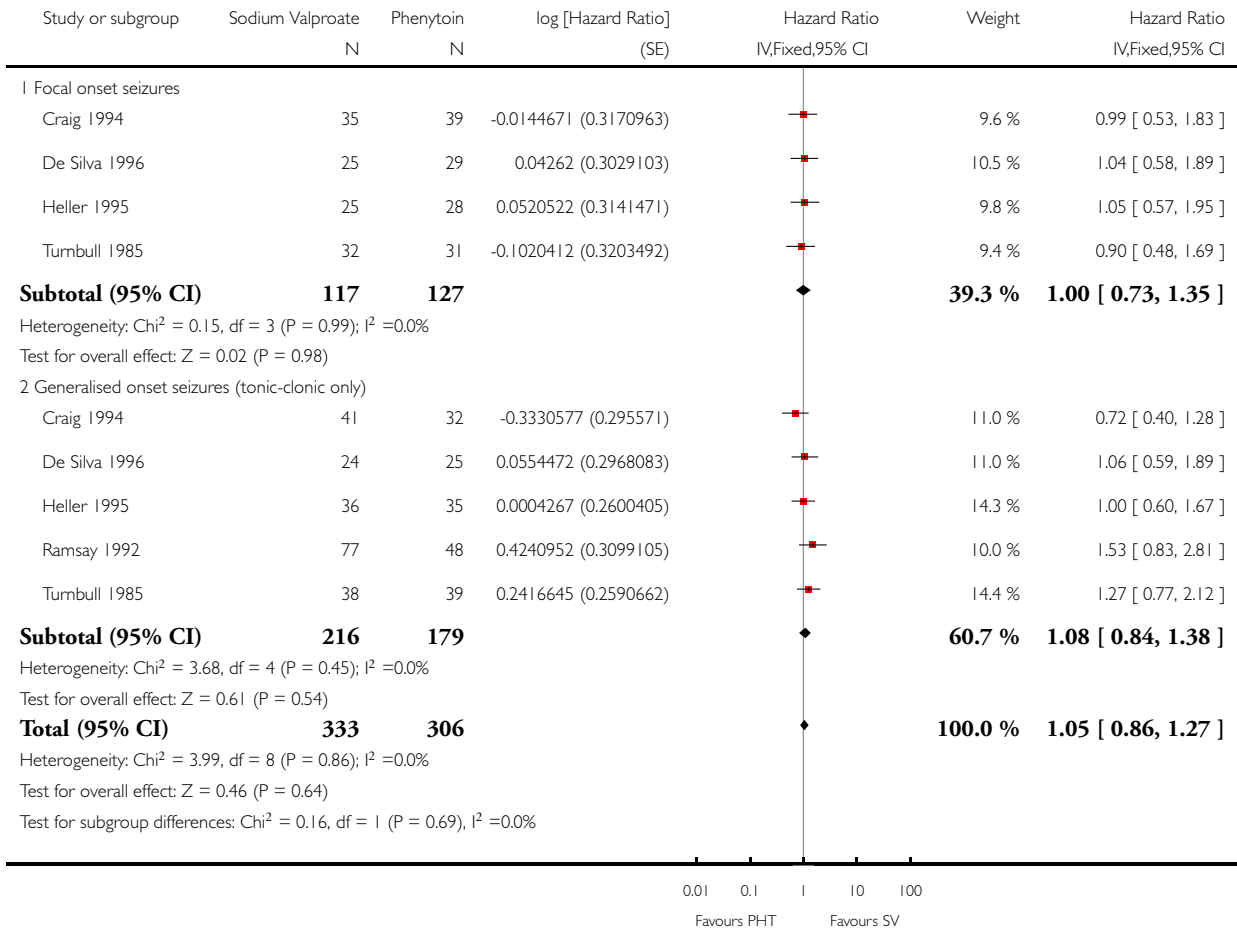


Analysis I.14. Comparison I Sodium valproate versus phenytoin, Outcome I4 Time to achieve six-month remission - by epilepsy type.

Review: Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review

Comparison: I Sodium valproate versus phenytoin

Outcome: I4 Time to achieve six-month remission - by epilepsy type



ADDITIONAL TABLES

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

	Focal seizures: n (%)			Male gender: n (%)			Age at entry (years): Mean (SD), range			Aged > 30 years and generalised seizures: n (%)			Epilepsy duration (years): mean (SD), range			Number of seizures in prior 6 months: median (range)		
	SV	PHT	Miss- ing	SV	PHT	Miss- ing	SV	PHT	Miss- ing	SV	PHT	Miss- ing	SV	PHT	Miss- ing	SV	PHT	Miss- ing
Craig 1994	37 (44%)	43 (53%)	0	38 (46%)	33 (41%)	3	77.6 (7.2), 61 to 95	78.7 (7.0), 64 to 95	3	46	38	0	NA	NA	166	2 (0 to 60)	3 (1 to 99)	3
De Silva 1996	25 (51%)	30 (56%)	0	18 (37%)	34 (63%)	0	11.3 (3.2), 2 to 15	9.5 (3.4), 3 to 15	0	0	0	0	1.2 (1.5), 0 to 4.9	1.0 (2.1), 0 to 13.7	0	3 (1 to 900)	3 (1 to 404)	0
Heller 1995	25 (41%)	28 (44%)	0	28 (46%)	34 (54%)	0	32.0 (15.6), 14 to 67	33.5 (14.3), 14 to 72	2	17	20	0	2.6 (3.9), 0 to 17.9	3.8 (5.4), 0 to 24.3	2	2 (1 to 181)	2 (1 to 575)	2
Ram- say 1992	0 (0%)	0 (0%)	0	48 (56%)	25 (50%)	0	21.1 (14.4), 3 to 64	20.6 (14.0), 4 to 63	0	16	10	0	0.1 (0.3), 0 to 1.9	0.2 (0.5), 0 to 3.0	15	NA	NA	136
Turn- bull 1985	32 (46%)	31 (44%)	0	34 (49%)	39 (56%)	0	35.1 (16.5), 14 to 69	35.3 (15.9), 16 to 70	0	16	19	0	2.2 (2.9), 0 to 11.0	2.1 (4.2), 0 to 30.0	0	2 (0 to 60)	2 (1 to 60)	0

SV= sodium valproate; PHT= Phenytoin; n = number of participants; NA = not available; SD = standard deviation. Proportions (%) are calculated based on non-missing data.

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

	EEG normal: n (%)			CT scan normal: n (%)			Neurological exam normal: n (%)		
	SV	PHT	Missing	SV	PHT	Missing	SV	PHT	Missing
Craig 1994	20 (30%)	8 (16%)	64	NA	NA	166	NA	NA	166
De Silva 1996	NA	NA	103	NA	NA	103	43 (88%)	48 (89%)	0
Heller 1995	NA	NA	124	NA	NA	124	56 (95%)	54 (86%)	2
Ramsay 1992	NA	NA	136	NA	NA	136	NA	NA	136
Turnbull 1985	30 (46%)	38 (54%)	0	6 (50%)	11 (73%)	43	NA	NA	70

EEG = electroencephalographic; SV= sodium valproate; PHT= Phenytoin; n = number of participants; NA = not available. Proportions (%) are calculated based on non-missing data.

Table 3. Outcomes considered and summary of results for trials with no individual participant data (IPD)

Trial	Outcomes reported	Summary of results
Callaghan 1985	<ul style="list-style-type: none"> Seizure control <ul style="list-style-type: none"> excellent (seizure-free) good (> 50% reduction) poor (< 50% reduction) Adverse events 	<ul style="list-style-type: none"> PHT (n = 58); SV (n = 64) <ul style="list-style-type: none"> 39 (67%); 34 (53%) 7 (12%); 16 (25%) 12 (21%); 14 (22%) 2.6 (10%); 7 (11%)
Czapinski 1997a	<ul style="list-style-type: none"> Proportion achieving 24-month remission at 3 years (PHT: 59%; SV: 64%) Proportion excluded after randomisation due to adverse events or no efficacy (PHT: 23%; SV: 23%) 	<ul style="list-style-type: none"> Proportion achieving 24-month remission at 3 years (PHT: 59%; SV: 64%) Proportion excluded after randomisation due to adverse events or no efficacy (PHT: 23%; SV: 23%)
Forsythe 1991	<ul style="list-style-type: none"> Cognitive assessments Withdrawals from randomised drug 	<ul style="list-style-type: none"> Significant difference favouring SV test of speed of information processing (P < 0.01) No significant differences between treatment groups for any other cognitive tests PHT: 6/20 (30%); SV: 7/21 (33%)
Rastogi 1991	<ul style="list-style-type: none"> Reduction in frequency of seizures at 24 weeks <ul style="list-style-type: none"> excellent (100% reduction) good (75% - 99% reduction) fair (50% - 74% reduction) poor (< 50% reduction) 	<ul style="list-style-type: none"> PHT (n = 45); SV (n = 49) <ul style="list-style-type: none"> 23 (51%); 24 (49%) 13 (24%); 17 (35%) 8 (18%); 5(10%) 1 (2%); 3 (6%)

Table 3. Outcomes considered and summary of results for trials with no individual participant data (IPD) (Continued)

	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> All reported adverse events were minor <ul style="list-style-type: none"> PHT: gum hyperplasia (18%), nystagmus (13%), gastrointestinal symptoms (4%), drowsiness (4%), ataxia (2%) SV: gastrointestinal symptoms (12%), drowsiness (6%), weight gain (2%)
Shakir 1981	<ul style="list-style-type: none"> Seizures during treatment Adverse events 	<ul style="list-style-type: none"> PHT: 5 (33%); SV: 7 (39%) PHT: 1 case of ataxia, 5 cases of acne SV: 2 cases of gastrointestinal symptoms, 2 cases of hair loss, 4 cases of weight gain
Thilothammal 1996	<ul style="list-style-type: none"> Recurrence of seizures Adverse events 	<ul style="list-style-type: none"> PHT: 14/52 (27%)/SV: 10/48 (21%) PHT: 33/52 (63%)/SV: 15/48 (31%)

n = number of participants; PHT: phenytoin; SV: sodium valproate.

Table 4. Number of individuals contributing to each analysis

Trial	Number randomised			Time to treatment failure (for any reason related to treatment)			Time to achieve 12-month remission			Time to achieve 6-month remission			Time to first seizure		
	PHT	SV	Total	PHT	SV	Total	PHT	SV	Total	PHT	SV	Total	PHT	SV	Total
Craig 1994 ^a	81	85	166	0	0	0	71	76	147	71	76	147	71	76	147
De Silva 1996	54	49	103	53	47	100	54	49	103	54	49	103	54	49	103
Forsyth 1991 ^b	20	21	41	20	21	41	0	0	0	0	0	0	0	0	0
Heller 1995	63	61	124	61	58	119	63	61	124	63	61	124	63	61	124
Ramsey 1992 ^c	50	86	136	50	86	136	0	0	0	48	77	125	48	77	125

Table 4. Number of individuals contributing to each analysis (Continued)

Turnbull 1985	70	70	140	70	70	140	70	70	140	70	70	140	70	70	140
Shakir 1981 ^b	15	18	33	15	18	33	0	0	0	0	0	0	0	0	0
Total	353	390	743	269	300	569	258	256	514	306	333	639	306	333	639

^aTreatment failure information not provided for [Craig 1994](#), so cannot contribute to 'time to treatment failure'.

^bData extracted from [Forsythe 1991](#) and [Shakir 1981](#) publications to calculate time to treatment failure. Insufficient published data to calculate other outcomes.

^cFollow-up for [Ramsay 1992](#) is less than 12 months so cannot contribute to 'time to achieve 12-month remission'.

PHT: phenytoin; SV: sodium valproate.

Table 5. Reasons for premature discontinuation (treatment failure)

Reason for early termination (and classification in time-to-event analysis)	De Silva 1996 ^b		Heller 1995 ^{b,c}		Ramsay 1992		Turnbull 1985		Forsythe 1991		Shakir 1981 ^d		Total ^a		
	SV	PHT	SV	PHT	SV	PHT	SV	PHT	SV	PHT	SV	PHT	SV	PHT	All
Adverse events (event)	2	2	4	1	4	8	6	14	0	1	0	0	16	26	42
Lack of efficacy (event)	11	10	9	8	1	1	2	0	2	1	3	6	28	26	54

Table 5. Reasons for premature discontinuation (treatment failure) (Continued)

Both adverse events and lack of efficacy (event)	4	5	6	2	0	0	1	2	0	0	0	0	11	9	20
Non-compliance/ protocol violation (event)	0	0	0	0	7	2	2	2	5	4	0	0	14	8	22
Illness or death (not treatment-related, censored) ^e	0	0	0	0	1	1	3	3	0	0	0	0	4	4	8
Participant went into remission (censored)	16	24	13	14	0	0	0	0	0	0	0	0	29	38	67
Lost to follow-up (cen-	0	0	0	0	10	3	7	7	0	0	0	0	17	10	27

Table 5. Reasons for premature discontinuation (treatment failure) (Continued)

sored)															
Other (censored) ^f	0	0	0	0	3	0	0	0	0	0	0	0	3	0	3
Completed the study (censored)	14	12	26	38	60	35	49	42	14	14	15	9	178	150	328
Total	47	53	58	63	86	50	70	70	21	20	18	15	300	271	571

PHT: phenytoin; SV: sodium valproate

^aIPD for 'time to treatment failure' was not provided for [Craig 1994](#).

^bThree participants for [Heller 1995](#) (all SV) and three for [De Silva 1996](#) (one PHT and two SV) have missing reasons for treatment failure.

^cFour participants from [Heller 1995](#) had missing treatment failure times and did not contribute to analysis but reasons for treatment failure are given.

^dNine participants in [Shakir 1981](#) were listed as having started on a second drug due to 'failure to respond.' This reason was classified as treatment failure due to lack of efficacy.

^eDeath due to reasons not related to the study drug.

^fOther reasons from [Ramsay 1992](#) - two participants withdrew due to pregnancy and one for personal reasons.

Table 6. Sensitivity analysis - epilepsy type misclassification

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 (95% CI) fixed-effects	HR	Test subgroup differences	of	Pooled (95% CI) fixed-effects	HR	Test subgroup differences	of	Pooled (95% CI) fixed-effects	HR	Test subgroup differences	of
Time to treatment failure (for any reason related to treatment) ^a	F: 0.83 (0.50 to 1.38) G: 0.94 (0.55 to 1.61) O: 0.88 (0.61 to 1.27)		Chi ² = 0.10, df = 1 (P = 0.75), I ² = 0%		F: 0.95 (0.59 to 1.52) G: 0.77 (0.42 to 1.41) O: 0.88 (0.60 to 1.27)		Chi ² = 0.29, df = 1 (P = 0.59), I ² = 0%		F: 0.83 (0.50 to 1.38) G: 0.77 (0.42 to 1.41) U: 6.83 (0.82 to 57.16) O: 0.86 (0.59 to 1.27)		Chi ² = 3.80, df = 2 (P = 0.15), I ² = 47.3%	

Table 6. Sensitivity analysis - epilepsy type misclassification (Continued)

Time to treatment failure due to adverse events ^b	F: 0.75 (0.35 to 1.60) G: 0.81 (0.34 to 1.90) O: 0.77 (0.44 to 1.37)	Chi ² = 0.02, df = 1 (P = 0.90), I ² = 0%	F: 0.87 (0.42 to 1.80) G: 0.64 (0.26 to 1.59) O: 0.77 (0.44 to 1.36)	Chi ² = 0.26, df = 1 (P = 0.61), I ² = 0%	Not calculated ^b	Not calculated ^b
Time to treatment failure due to lack of efficacy ^b	F: 1.01 (0.55 to 1.85) G: 1.51 (0.66 to 3.45) O: 1.16 (0.71 to 1.89)	Chi ² = 0.60, df = 1 (P = 0.44), I ² = 0%	F: 1.00 (0.51 to 1.96) G: 1.73 (0.56 to 5.35) O: 1.16 (0.65 to 2.06)	Chi ² = 0.66, df = 1 (P = 0.42), I ² = 0%	Not calculated ^b	Not calculated ^b
Time to first seizure ^c	F: 1.20 (0.90 to 1.60) G: 0.97 (0.72 to 1.30) O: 1.08 (0.88 to 1.33)	Chi ² = 1.06, df = 1 (P = 0.30), I ² = 5.6%	F: 1.23 (0.96 to 1.57) G: 0.72 (0.50 to 1.05) O: 1.05 (0.86 to 1.29)	Chi ² = 5.46, df = 1 (P = 0.02), I ² = 81.7%	F: 1.20 (0.90 to 1.60) G: 0.72 (0.50 to 1.05) U: 1.35 (0.85 to 2.14) O: 1.06 (0.86 to 1.30)	Chi ² = 5.79, df = 2 (P = 0.06), I ² = 65.5%
Time to 12-month remission ^d	F: 1.11 (0.78 to 1.60) G: 0.96 (0.71 to 1.29) O: 1.02 (0.81 to 1.28)	Chi ² = 0.39, df = 1 (P = 0.53), I ² = 0%	F: 0.99 (0.75 to 1.32) G: 1.07 (0.72 to 1.59) O: 1.02 (0.81 to 1.28)	Chi ² = 0.10, df = 1 (P = 0.75), I ² = 0%	F: 1.11 (0.78 to 1.60) G: 1.07 (0.72 to 1.59) U: 0.74 (0.46 to 1.18) O: 0.99 (0.79 to 1.25)	Chi ² = 2.07, df = 2 (P = 0.36), I ² = 3.3%
Time to 6-month remission ^e	F: 1.00 (0.73 to 1.35) G: 1.08 (0.84 to 1.38) O: 1.05 (0.86 to 1.27)	Chi ² = 0.16, df = 1 (P = 0.69), I ² = 0%	F: 1.00 (0.79 to 1.26) G: 1.14 (0.80 to 1.61) O: 1.04 (0.85 to 1.26)	Chi ² = 0.38, df = 1 (P = 0.54), I ² = 0%	F: 1.00 (0.73 to 1.35) G: 1.14 (0.80 to 1.61) U: 0.90 (0.62 to 1.31) O: 1.01 (0.83 to 1.23)	Chi ² = 0.80, df = 2 (P = 0.67), I ² = 0%

Chi²: Chi² statistic; df: degrees of freedom of Chi² distribution; F: focal epilepsy; G: generalised epilepsy; O: overall (all participants);

U: uncertain epilepsy; P: P value (< 0.05 are classified as statistically significant).

^a 100 participants reclassified to focal epilepsy or uncertain epilepsy type for outcome 'time to treatment failure (for any reason related to treatment)'; see [Analysis 1.4](#) for original analysis.

^b 100 participants reclassified to focal epilepsy or uncertain epilepsy type for outcomes 'time to treatment failure due to adverse events' and 'time to treatment failure due to lack of efficacy'; see [Analysis 1.5](#) and [Analysis 1.6](#) for original analyses. Forest plots not presented for sensitivity analysis for generalised and age at onset > 30 years reclassified as focal epilepsy as results were numerically similar and

conclusions are unchanged. Sensitivity analysis for generalised and age at onset > 30 years reclassified as uncertain epilepsy type not performed due to small numbers of participants failing treatment for these reasons in the uncertain epilepsy type groups in each trial.
^c171 participants reclassified to focal epilepsy or uncertain epilepsy type for outcome 'time to first seizure'; see [Analysis 1.8](#) for original analysis and see [Analysis 1.10](#) and [Analysis 1.9](#) for forest plots of 'time to first seizure' sensitivity analyses for generalised and age at onset > 30 years reclassified as focal epilepsy and uncertain epilepsy type, respectively.

^d145 participants reclassified to focal epilepsy or uncertain epilepsy type for outcome 'time to achieve 12-month remission', see [Analysis 1.12](#) for original analysis. As results were numerically similar and conclusions are unchanged, forest plots are not presented.

^e171 participants reclassified to focal epilepsy or uncertain epilepsy type for outcome 'time to achieve 6-month remission', see [Analysis 1.14](#) for original analysis. As results were numerically similar and conclusions are unchanged, forest plots are not presented.

Table 7. Adverse event data (narrative report)

Trial	Adverse event data ^a	Summary of reported results	
		Phenytoin (PHT)	SV (sodium valproate)
Callaghan 1985	All adverse events developed (by drug) and adverse events leading to discontinuation of treatment	PHT (n = 58): gum hypertrophy (n = 2), rash (n = 2), ataxia (n = 2)	SV (n = 64): weight gain (n = 4: all discontinued treatment), drowsiness (n = 2), aggressive behaviour (n = 1: discontinued treatment)
Craig 1994	Adverse event frequency (spontaneous reports) ^b Discontinuations due to adverse events ^c	PHT (n = 25): unsteadiness (n = 9), sleepiness (n = 7), drowsiness (n = 2), impaired concentration (n = 2), confusion (n = 1), constipation (n = 1), diarrhoea (n = 1), dysarthria (n = 1), lethargy (n = 1), nystagmus (n = 1), rash (n = 1), tired legs (n = 1) PHT discontinuations (n = 6): rash (n = 1), diarrhoea (n = 1), confusion (n = 1), unsteadiness (n = 1), constipation (n = 1), sleepiness (n = 1)	SV (n = 17): unsteadiness (n = 2), sleepiness (n = 3), tremor (n = 5), oedema (n = 3), alopecia (n = 2), depression (n = 2), weight gain (n = 2) SV discontinuations (n = 2): weight gain and depression (n = 1), unsteadiness (n = 1)
Czapinski 1997a	"Exclusions" due to adverse events or no efficacy ^d	Proportion "excluded": PHT: 33.3%	Proportion "excluded": SV: 23.3%
De Silva 1996	"Unacceptable" adverse events leading to drug withdrawal ^e	PHT (n = 54): drowsiness (n = 2), skin rash (n = 1) blood dyscrasia (n = 1), hirsutism (n = 1)	SV (n = 49): behavioural (n = 1), tremor (n = 1)
Forsythe 1991	No adverse event data reported (treatment withdrawal data only reported)	1 participant (PHT) withdrew from the study due to depression and anorexia	No adverse event data (or treatment withdrawals due to adverse events) reported
Heller 1995	"Unacceptable" adverse events leading to drug withdrawal ^e	PHT (n = 63): myalgia (n = 1), irritability (n = 1)	SV (n = 61): dizziness (n = 2) abnormal liver function test (n = 1)

Table 7. Adverse event data (narrative report) (Continued)

Ramsay 1992	Most common adverse events (by treatment group) ^f	PHT (n = 50): dyspepsia (n = 1), nausea (n = 2), dizziness (n = 2), somnolence (n = 5), tremor (n = 2), rash (n = 4)	SV (n = 86): dyspepsia (n = 7), nausea (n = 10), dizziness (n = 5), somnolence (n = 8), tremor (n = 5), rash (n = 3)
Rastogi 1991	Commonest adverse events (reported as percentages by treatment group) ^f	PHT (n = 45): gum hyperplasia (17.7%), nystagmus (13.33%), ataxia (2.2%), gastrointestinal disturbances (4.44%), drowsiness (4.44%)	SV (n = 49): gastrointestinal disturbances (12%), drowsiness (6.12%), weight gain (2.04%)
Shakir 1981	Adverse events (narrative description) ^b	PHT (n = 15): 1 case of ataxia, 5 cases of acne	SV (n = 18): 2 cases of gastrointestinal symptoms, 2 cases of hair loss, 4 cases of weight gain
Thilothammal 1996	Assessment of adverse events ^b	PHT (n = 52): 33 participants reported at least one side effect Reported frequencies: gingival hypertrophy (n = 30), ataxia (n = 13), sedation (n = 12), nausea and vomiting (n = 1) Other reported adverse events (no frequencies): nystagmus, confusion	SV (n = 48): 15 participants reported at least one side effect Reported frequencies: hyperactivity (n = 6), impaired school performance (n = 4), severe skin allergy (n = 1)
Turnbull 1985	Treatment withdrawals due to dose-related and idiosyncratic adverse events	PHT (n = 70): 11 treatment withdrawals due to dose-related adverse events (nystagmus, ataxia, tremor, diplopia and mental change) 5 treatment withdrawals due to idiosyncratic adverse events (skin eruption, erythroderma and jaundice)	SV (n = 70): 9 treatment withdrawals due to dose-related adverse events (tremor, irritability, restlessness and alopecia) No treatment withdrawals due to idiosyncratic adverse events

^aAdverse event data, as reported narratively in the publications. Adverse event data were not requested in original IPD requests 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; Ramsay 1992; Turnbull 1985) see Table 5.

^bParticipants may report more than one adverse event.

^cThe published paper, Craig 1994, reports on a subset of 38 participants, so the adverse event data summary applies only to this subset. IPD were provided for 166 participants (no additional adverse event data provided).

^dCzapinski 1997a is an abstract only so very little information is reported.

^eParticipants may have withdrawn due to adverse event alone or a combination of adverse events and poor efficacy (seizures).

^fMost commonly reported adverse events only, no indication of overall frequency of all adverse events.

APPENDICES

Appendix 1. Cochrane Epilepsy Group's Specialized Register search strategy

1. MeSH DESCRIPTOR Phenytoin Explode All AND INREGISTER
2. phenytoin or Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin AND INREGISTER
3. #1 OR #2 AND INREGISTER
4. MeSH DESCRIPTOR Valproic Acid Explode All AND INREGISTER
5. Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epject or Episenta or Epival or Valpro* or Orlept or Orfiril or Selenica or Convulex or Depakote AND INREGISTER
6. #4 OR #5 AND INREGISTER
7. #3 AND #6 AND INREGISTER
8. (adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*):TI AND INREGISTER
9. #7 NOT #8 AND INREGISTER
10. MeSH DESCRIPTOR Phenytoin Explode All AND CENTRAL:TARGET
11. phenytoin or Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin AND CENTRAL:TARGET
12. #10 OR #11 AND CENTRAL:TARGET
13. MeSH DESCRIPTOR Valproic Acid Explode All AND CENTRAL:TARGET
14. Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epject or Episenta or Epival or Valpro* or Orlept or Orfiril or Selenica or Convulex or Depakote AND CENTRAL:TARGET
15. #13 OR #14 AND CENTRAL:TARGET
16. #12 AND #15 AND CENTRAL:TARGET
17. (adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*):TI AND CENTRAL:TARGET
18. #16 NOT #17 AND CENTRAL:TARGET
19. #9 OR #18

Appendix 2. CENTRAL search strategy

- #1 MeSH descriptor: [Phenytoin] explode all trees
- #2 Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin:ti,ab,kw (Word variations have been searched)
- #3 #1 or #2
- #4 MeSH descriptor: [Valproic Acid] explode all trees
- #5 Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epject or Episenta or Epival or Valpro* or Orlept or Orfiril or Selenica or Convulex or Depakote:ti,ab,kw (Word variations have been searched)
- #6 #4 or #5
- #7 #3 and #6
- #8 (adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*):ti (Word variations have been searched)
- #9 #7 not #8
- #10 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)
- #11 MeSH descriptor: [Epilepsy] explode all trees
- #12 MeSH descriptor: [Seizures] explode all trees
- #13 (#10 or #11 or #12) in Trials
- #14 #9 and #13

Appendix 3. MEDLINE search strategy

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

1. exp phenytoin/ or (Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin).mp.
2. exp Valproic Acid/ or (Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epiject or Episenta or Epival or Valpro\$ or Orlept or Orfiril or Selenica or Convulex or Depakote).mp.
3. ((adjunct\$ or “add-on” or “add on” or adjuvant\$ or combination\$ or polytherap\$) not (monotherap\$ or alone or singl\$)).ti.
4. (1 and 2) not 3
5. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Epilepsy/
12. exp Seizures/
13. (epilep\$ or seizure\$ or convuls\$).tw.
14. 11 or 12 or 13
15. exp *Pre-Eclampsia/ or exp *Eclampsia/
16. 14 not 15
17. 4 and 10 and 16
18. remove duplicates from 17

Earlier versions of this review used the following search, based on the previous Cochrane Highly Sensitive Search Strategy for MEDLINE as set out in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.4, updated March 2005) (Higgins 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trials/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. clinical trial.pt.
8. Clinical Trial/
9. (clin\$ adj trial\$).ab,ti.
10. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ab,ti.
11. exp PLACEBOS/
12. placebo\$.ab,ti.
13. random\$.ab,ti.
14. exp Research Design/
15. or/1-14
16. (animals not humans).sh.
17. 15 not 16
18. phenytoin/ or (phenytoin or diphenylhydantoin).tw.
19. valproic acid/ or valpro\$.tw.
20. exp epilepsy/ or epilep\$.tw.
21. exp seizures/ or seizure\$.tw.
22. convulsion\$.tw.
23. 18 and 19
24. 20 or 21 or 22
25. 23 and 24
26. 17 and 25

Appendix 4. SCOPUS search strategy

((TITLE(phenytoin or Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin) or ABS(phenytoin or Epanutin or Phenytek or Dilantin or Eptoin or Diphenin or Dipheninum or Diphenylhydantoin)) and (TITLE(Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epiject or Episenta or Epival or Valpro* or Orlept or Orfiril or Selenica or Convulex or Depakote) or ABS(Depakene or Depacon or Depakine or Valparin or Stavzor or Epilim or Epiject or Episenta or Epival or Valpro* or Orlept or Orfiril or Selenica or Convulex or Depakote))) and not (TITLE-ABS-KEY((adjunct* OR "add-on" OR "add on") AND NOT monotherap*)) and (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel-group" OR "parallel group" OR crossover OR cross-over OR "cross over" OR cluster OR "head to head" 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 "parallel group" OR crossover OR cross-over OR "cross over" OR cluster OR "head to head" OR "head-to-head") PRE/2 (trial OR method OR procedure OR study))) 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))))

WHAT'S NEW

Last assessed as up-to-date: 19 February 2018.

Date	Event	Description
26 June 2018	New citation required but conclusions have not changed	Review updated; conclusions are unchanged
19 February 2018	New search has been performed	<p>Updated search on 19 February 2018; no new studies included</p> <p>The title was changed in line with the titles of other pairwise monotherapy comparisons in the series (i.e. 'monotherapy for epilepsy' instead of 'for partial onset seizures and generalised onset tonic-clonic seizures') and in line with Cochrane guidelines of intervention (i.e. valproate) first and comparator (i.e. phenytoin) second</p> <p>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).</p> <p>Lead author, previously known as Sarah Nolan is now Sarah Nevitt</p>

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 4, 2001

Date	Event	Description
26 April 2017	Amended	Declarations of interest section updated
19 May 2015	New search has been performed	No new studies included; conclusions unchanged
19 May 2015	New citation required but conclusions have not changed	Searches updated on 19 May 2015
13 August 2013	New citation required but conclusions have not changed	Conclusions unchanged
21 February 2013	New search has been performed	Searches updated February 2013. Analyses and text updated. 'Risk of bias' assessments and 'Summary of findings' table added
23 September 2008	Amended	Converted to new review format
27 July 2007	New search has been performed	We reran our searches on 27 July 2007 and identified one new study and added it to the 'Characteristics of studies awaiting classification' section; we will assess it for inclusion in the review at a later date

CONTRIBUTIONS OF AUTHORS

SJ Nevitt assessed studies for inclusion in the review update, obtained individual participant data (IPD) from trial investigators for the review update, assessed risk of bias in all included studies, performed analyses in Stata version 14, added survival plots and a 'Summary of findings' table, and updated the text of the review.

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

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

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

DECLARATIONS OF INTEREST

SJ Nevitt has no declarations of interest.

AG Marson: A consortium of pharmaceutical companies (GSK, Eisai, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to 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).

J Weston has no declarations of interest.

C Tudur Smith has no declarations of interest.

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- Walton Centre for Neurology and Neurosurgery, UK.

External sources

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

This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2018 update: we changed the title in line with the titles of other pair-wise monotherapy comparisons in the series (i.e. 'monotherapy for epilepsy' instead of 'for focal onset seizures and generalised onset tonic-clonic seizures) and in line with Cochrane Style guidelines of intervention (i.e. sodium valproate) first and comparator (i.e. phenytoin) second.

We redefined 'time to withdrawal of allocated treatment' 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 antiepileptic monotherapy.

We conducted additional analyses of 'time to treatment failure' (due to lack of efficacy and due to adverse events) following feedback on published antiepileptic drug monotherapy reviews that these suboutcomes would be useful for clinical practice.

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

We presented adverse event information as a separate secondary outcome, 'incidence of adverse events' in line with other Cochrane IPD reviews investigating pair-wise monotherapy comparisons.

In December 2014, we changed the title to specify that the review uses individual participant data (IPD).

For the 2013 update, in a post hoc change, we added 'Summary of findings' tables to the review.

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.

We added the outcome 'time to six-month remission' for consistency with the other reviews in the series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons and removed the outcome 'quality of Life' which was found to not be readily available in an analysable format from early IPD requests.

NOTES

The protocol for this review was published with Catrin Tudur as the contact review author. Catrin is now known as Catrin Tudur Smith.

Sarah J Nolan (lead author of the 2013 and 2016 update) is now Sarah J Nevitt.

Jennifer Pulman (author of the 2013 update) is now Jennifer Weston.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Epilepsies, Partial [*drug therapy]; Epilepsy, Generalized [drug therapy]; Epilepsy, Tonic-Clonic [*drug therapy]; Phenytoin [*therapeutic use]; Randomized Controlled Trials as Topic; Seizures [drug therapy]; Valproic Acid [*therapeutic use]

MeSH check words

Humans