Carbamazepine versus phenytoin monotherapy for epilepsy (Review)

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[Intervention Review]

Carbamazepine versus phenytoin monotherapy for epilepsy

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 2, 2002.

Worldwide, carbamazepine and phenytoin are commonly used antiepileptic drugs. This review summarizes evidence from randomized controlled trials in which these two drugs have been compared.

Objectives

To review the best evidence comparing carbamazepine and phenytoin when used as monotherapy in people with partial onset seizures, or generalized onset tonic-clonic seizures with or without other generalized seizure types.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (November 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2009), and MEDLINE (1950 to week 2, November 2009). No language restrictions were imposed. We also contacted pharmaceutical companies, experts in the field, and trial investigators.

Selection criteria

Randomized controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. Trials must have included a comparison of carbamazepine monotherapy with phenytoin monotherapy.

Data collection and analysis

This was an individual patient data review. Outcomes were time to (a) withdrawal of allocated treatment; (b) 12 month remission; (c) six month remission and (d) first seizure post randomization. Data were analysed using a stratified logrank analysis with results expressed as hazard ratios (HR) and 95% confidence intervals (95% CI), where a HR greater than one indicates an event is more likely on phenytoin.

Main results

Individual patient data are available for 551 participants from three trials, representing 61% of the participants recruited into the nine trials that met our inclusion criteria. By convention, for the outcomes time to six and 12 month remission HR greater than one indicates a clinical advantage for phenytoin, whilst for time to withdrawal and first seizure HR greater than one indicates a clinical advantage for carbamazepine. Results (HRs) were: (i) time to withdrawal of allocated treatment 0.97 (95% CI 0.74 to 1.28); (ii) time to 12 month remission 1.00 (95% CI 0.78 to 1.29); (iii) time to six month remission 1.10 (95% CI 0.87 to 1.39) and (iv) time to first seizure 0.91 (95% CI 0.74 to 1.12). The results suggest no overall difference between carbamazepine and phenytoin for these outcomes.

Authors' conclusions

We have not found evidence that a significant difference exists between carbamazepine and phenytoin for the outcomes examined in this review. Confidence intervals are wide and the possibility of important differences existing has not been excluded.

PLAIN LANGUAGE SUMMARY

Carbamazepine versus phenytoin monotherapy for epilepsy

There is no evidence to suggest any difference between the drugs carbamazepine and phenytoin for the seizure types studied.

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Carbamazepine and phenytoin are considered first line treatments in many countries both for partial onset seizures and generalized tonic-clonic seizures. The review of trials found no difference between carbamazepine and phenytoin for the control of the seizure types studied.

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 2, 2002) on 'Carbamazepine versus phenytoin monotherapy for epilepsy'.

Carbamazepine and phenytoin are considered first line treatments in many countries both for partial seizures and generalized tonic-clonic seizures (Mattson 1985). In Europe, carbamazepine is used in preference to phenytoin (SIGN 1997), whereas phenytoin is more commonly used in the USA (Wilder 1995). To date, no trial has shown differences in efficacy between these two drugs, and the difference in the European and US approach relate to perceived differences in adverse effect profiles. Carbamazepine has superseded phenytoin in Europe, due to phenytoin being associated with long-term cosmetic changes including gum hypertrophy and acne (Mattson 1985). Both carbamazepine and phenytoin are associated with an allergic rash (Tennis 1997) in 5 to 10% of patients, which on rare occasions may be life threatening. Carbamazepine is associated with causing neural tube defects, and both drugs are associated with causing other congenital abnormalities (Gladstone 1992; Nulman 1997), where the risk is estimated to be two to three times that of the general population.

Carbamazepine and phenytoin have been compared in a number of randomized controlled trials (Callaghan 1985; Heller 1995; Kosteljanetz 1979; Mattson 1985; Ramsay 1983; Shakir 1980; de Silva 1996; Simonsen 1976; Troupin 1977). Although no difference in efficacy has been found, the confidence intervals generated by these studies are wide and important differences in efficacy have not been excluded.

Despite this lack of evidence, carbamazepine is being used in preference to phenytoin as a 'standard drug' to compare with new drugs in monotherapy trials in people with partial seizures (Brodie 1995; Chadwick 1998; Reunanen 1996).

Our aim in this systematic review is to overview existing evidence for the comparative efficacy and tolerability of phenytoin and carbamazepine. There are however difficulties undertaking a systematic review of epilepsy monotherapy trials, as the important efficacy outcomes are time to event outcomes (eg. time to 12 month remission), and as such require survival type analysis. Although methods have been developed to synthesize survival type data using aggregate data (Parmar 1998), they require one to make assumptions with respect to censoring which may not necessarily hold. In addition, although similar seizure data have been collected in most epilepsy monotherapy trials, differing outcome definitions, approaches to analysis and lack of uniformity in the reporting of

outcomes (eg. trials may report time to 12 month remission but not time to first seizure or vice versa) all complicate attempts to use published aggregate data. In view of these difficulties, we decided to proceed with an individual patient data approach which allows a thorough analysis of time to event data. This review is one in a series investigating individual monotherapy comparisons.

OBJECTIVES

To review the effects of phenytoin compared to carbamazepine when used as monotherapy in subjects with partial onset seizures (simple/complex partial with or without secondarily generalization) or generalized onset tonic-clonic seizures (with or without other generalized seizure types).

METHODS

Criteria for considering studies for this review

Types of studies

(1) Randomized parallel group monotherapy trials which include a comparison of phenytoin with carbamazepine in subjects with epilepsy.
(2) The studies may be double blind, single blind or unblinded.
(3) The studies should have either adequate (eg. sealed opaque envelopes) or quasi methods (eg. allocation by date of birth) of randomization.

Types of participants

(1) Children or adults with partial onset seizures (simple partial, complex partial, or secondarily generalized tonic-clonic seizures) or generalized onset tonic-clonic seizures (with or without other generalized seizure types).
(2) Individuals treated with monotherapy.

Types of interventions

Phenytoin or carbamazepine as monotherapy.

Types of outcome measures

Below is a list of outcomes investigated in this review. Reporting of these outcomes in the original trial report was not an eligibility requirement for this review.
(1) Time to withdrawal of allocated treatment (retention time) was chosen as the primary outcome. This is a combined outcome reflecting both efficacy and tolerability as treatment may be withdrawn due to continued seizures, side effects, non-compliance or if additional add-on treatment was initiated (ie allocated treatment had failed). This is an outcome to which the patient makes a contribution, and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Commission 1998).
(2) Time to achieve 12 month remission (seizure free period).
(3) Time to achieve six month remission.
(4) Time to first seizure post randomization.

Search methods for identification of studies

We searched the Epilepsy Group's Specialized Register (16 November 2009, using the search term 'phenytoin AND carbamazepine'). This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant reports are also identified by handsearching selected journals and conference proceedings. A more detailed description of this activity is given in the 'Specialized register' section of the Cochrane Epilepsy Group module. In addition, we carried out searching as follows:

(1) Electronic databases

We searched the following databases. There were no language restrictions.
(a) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2009) using the search strategy outlined in Appendix 1.
(b) MEDLINE (Ovid) (1950 - week 2, November 2009) was searched using the search strategy outlined in Appendix 2.

(2) References from published studies

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

(3) Other sources

We contacted Novartis (manufacturers of carbamazepine), Parke-Davis (manufacturers of phenytoin), experts in the field and original investigators of relevant trials found.

Data collection and analysis

Trial assessment and data collection

All identified trials were assessed for inclusion independently by two of the review authors (Catrin Tudur Smith and Tony Marson). Authors were approached with a view to obtaining their co-operation in providing individual patient data (IPD). Each group was asked to provide IPD on date of randomization, drug allocated and dose, age, sex, presence of neurological signs, seizure types at randomization, number of seizures pre-randomization (with dates), EEG results, CT/MRI results, dates of follow up, dates of dose changes, dates of all seizures (any type) post randomization or seizure frequency data, date of treatment withdrawal and

reasons for treatment withdrawal. In addition, we asked for the following methodological data: method of generation of random list; method of concealment of randomization; stratification factors and blinding methods.

For each trial for which IPD were not obtained, we carried out an assessment to see whether any relevant aggregate level data could be extracted from reports for the outcomes of interest.

Data checking

For each trial where IPD were supplied we performed the following checks.

(1) Range and consistency checks: missing data; errors and inconsistencies were followed up with a nominated individual.

(2) Trial details were cross checked against any published report of the trial. All possible results from the trial reports were reproduced using the provided IPD.

(3) Review of the chronological randomization sequence. Missing allocation numbers were followed up with the nominated individual. The balance of prognostic factors was checked, taking account of factors stratified for in the randomization procedure.

Data manipulation

In one study (Mattson 1985), seizure data were provided in terms of the number of seizures recorded between each follow-up visit rather than specific dates of seizures. To enable time to event outcomes to be calculated, linear interpolation was applied to approximate dates of seizures between follow-up visits. For example, if four seizures were recorded between two visits which occurred on 01/03/90 and 01/05/90 (interval of 61 days), then date of first seizure would be approximately 13/03/90. This allowed an estimate of the time to six month remission, 12 month remission and the time to first seizure to be computed. Time to six and 12 month remission was calculated from the date of randomization to the date (or estimated date) the individual had first been free of seizures for six or 12 months respectively. Time to first seizure was calculated from the date of randomization 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 follow up ceased prior to the occurrence of the event of interest. These methods had been used for the remaining two trials (Heller 1995; de Silva 1996) for which outcome data were provided directly.

For two trials (Heller 1995; de Silva 1996) the date of and reason for treatment withdrawal were extracted from study case report forms by two review authors (Tony Marson and Paula Williamson). Both review authors independently extracted data from all case report forms, and disagreements were resolved by re-reviewing the case report forms at conference. For the remaining trials, data on length of time spent in trial and reason for withdrawal of allocated treatment were provided directly. For the analysis of time to withdrawal of allocated treatment, an event was defined to be the withdrawal of allocated treatment due to poor seizure control or side effects or both, non-compliance, or the addition of another antiepileptic drug. The outcome was censored if treatment was withdrawn because the individual achieved a period of remission or if the individual was still on allocated treatment at the end of follow up.

Data analysis

(1) We carried out our analysis on an intention-to-treat basis. The analysis included all randomized individuals analysed in the treatment group to which they were allocated, irrespective of which treatment they actually received.

(2) As all the data were 'time-to-event' in nature, a logrank analysis, stratified by trial to preserve the within trial randomization, was used to obtain study-specific and overall estimates of **h**azard **r**atios (HR) with 95% **c**onfidence **i**ntervals (CIs). We used the information provided by the stratified logrank test to investigate the main effect of drug and to assess evidence of heterogeneity in drug effect between trials (EBCTCG 1990).

Results are expressed as a HR and 95% CI and by convention a HR greater than one indicates that an event is more likely on phenytoin. Hence, for time to withdrawal of allocated treatment or time to first seizure a HR greater than one indicates a clinical advantage for carbamazepine (eg. HR = 1.1 would suggest a 10% increase in risk of withdrawal from phenytoin compared to carbamazepine) and for time to six and 12 month remission a HR greater than one indicates a clinical advantage for phenytoin.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified a total of 26 trial reports as potentially eligible for this systematic review. Of these, we excluded 11 trial reports, referring to seven trials, for reasons which are summarized in the 'table of characteristics of excluded studies' (Bird 1966; Bittencourt 1993; Dodrill 1977; Kosteljanetz 1979; Meador 1990; Shakir 1980; Simonsen 1975; Simonsen 1976; Troupin 1975; Troupin 1977; Wilkus 1978). A total of 15 trial reports in which individuals had been randomized to carbamazepine or phenytoin were identified as eligible for this review. Due to duplicate publications (Berg 1993; Berger 1981; Callaghan 1983; Pulliainen 1995; Smith 1987), there were in fact only 10 relevant trials (Callaghan 1985; Cereghino 1974; Czapinski 1997; Forsythe 1991; Heller 1995; Mattson 1985; Pulliainen 1994; Rajotte 1967; Ramsay 1983; de Silva 1996).

Original IPD were no longer available for six of these trials (Callaghan 1985; Cereghino 1974; Forsythe 1991; Pulliainen 1994; Rajotte 1967; Ramsay 1983) in which a total of 292 had been randomized to either carbamazepine or phenytoin. One recently completed study, only published in abstract form

(Czapinski 1997), randomized 60 participants with newly diagnosed epilepsy with partial complex seizures to either phenytoin or carbamazepine. At the time of writing, IPD have been pledged, but not received. Although none of these trials examined the time-to-event outcomes investigated in this systematic review, one trial (Forsythe 1991) presented IPD relating to time at which allocated drug was withdrawn and reason for withdrawal within the actual trial publication. Hence, this trial could be incorporated into the analysis of time to withdrawal of allocated treatment. Subject level or aggregate data could not be incorporated from any other trial regardless of outcome considered. Full details of outcomes considered and summary of results in each eligible trial for which individual patient data were not available can be found in Table 1.

IPD were available for the remaining three trials which recruited a total of 551 participants, representing 61% of individuals from all identified eligible trials (total of 903 participants). Computerized data were provided directly in one trial (Mattson 1985) and a combination of both (although mostly computerized) were supplied by the authors of two trials (Heller 1995; de Silva 1996). Of these three trials for which IPD were provided, one recruited children only (de Silva 1996) and two recruited adults only (Heller 1995; Mattson 1985). All three trials recruited people with newly diagnosed epilepsy. One trial (Mattson 1985) recruited participants with partial onset seizures only and the remaining two trials recruited participants with partial onset seizures (simple/complex partial or secondarily generalized tonic-clonic) and participants with generalized tonic-clonic seizures.

Data were available for the following subject characteristics (percentage of participants with data available): sex (100%), seizure type (100%), age at randomization (100%), number of seizures in six months prior to randomization (99%), time since first seizure to randomization (99%). The results of neurological examinations were computerized in two trials (Heller 1995; de Silva 1996) (42%) whilst EEG and CT data were only computerized in one trial (Mattson 1985).

Risk of bias in included studies

(1) Trials for which IPD are provided

The three trials used adequate methods of concealment of randomization (sealed opaque envelopes). One trial was double blinded (Mattson 1985) by using blank tablets in addition to randomized drug. The two remaining trials were unblinded (Heller 1995; de Silva 1996).

(2) Trials for which no IPD were provided

One trial (Forsythe 1991) used quota allocation which was considered an inadequate method of concealment as the choice of allocation may be left to the interviewer subject to 'quota controls'. Adequate methods were used in the trial by Callaghan 1985 (using an independent person to carry out the randomization) and the double blinded trial by Ramsay 1983 (using a placebo drug given in addition to active drug). Although two further trials were double-blinded (Rajotte 1967), details regarding method of concealment of allocation were not available for either trial and the method of generation of randomization list was only available in one trial (Cereghino 1974) who used random number tables. The method of concealment of allocation was not mentioned in the remaining trials (Czapinski 1997; Pulliainen 1994). Two trials were single blinded (Forsythe 1991; Pulliainen 1994) and the remaining trials were unblinded (Callaghan 1985; Czapinski 1997).

For further details, *see* table of 'characteristics of included studies'.

Effects of interventions

Details regarding the number of participants contributing to each analysis are given in Table 2. All results are summarized in Table 3 and MetaView. In the context of the MetaView plots produced in this review, the 'Peto OR' label is equivalent to 'HR'. As plots for time to event outcomes cannot currently be published on *The Cochrane Library*, the hazard ratio and survival curve plots produced using SCHARP 3 can be found on the Cochrane Epilepsy Group website at http://www.epilepsy.cochrane.org/Files/cbzphy.pdf.

(1) Time to withdrawal of allocated treatment

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

Time to withdrawal of allocated treatment and reason for withdrawal were available for 548 participants from three trials (99% of participants from three trials providing IPD). Although two participants withdrew from allocated treatment (one in each group) in one trial (de Silva 1996), a reason for withdrawal was not available and could not be determined from the case notes. For one participant in another trial (Heller 1995) no follow-up information following randomization was available. Sufficient IPD were available in the published report for a further 43 participants from one trial (Forsythe 1991). Therefore a total of 591 participants from four trials were available for the analysis of this outcome.

There was no evidence of statistical heterogeneity between trials (chi squared = 3.29, df = 3, p = 0.35).

The overall pooled HR of 0.97 (95% CI 0.74 to 1.28) suggests no clear clinical advantage for either drug.

(2) Time to achieve 12 month remission

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

Data for 551 participants (100% of those providing IPD) from three trials were available for the analysis of this outcome.

There was no evidence of statistical heterogeneity between trials (chi squared = 1.38, df = 2, p = 0.50).

The overall pooled HR of 1.00 (95% CI 0.78 to 1.29) suggests no clear clinical advantage for either drug.

(3) Time to achieve six month remission

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

Data for 551 participants (100% of those providing IPD) from three trials were available for the analysis of this outcome.
There was no evidence of statistical heterogeneity between trials (chi squared = 0.35, df = 2, p = 0.84).
The overall pooled HR of 1.10 (95% CI 0.87 to 1.39) suggests no clear clinical advantage for either drug.

(4) Time to first seizure post randomization

For this outcome, a HR greater than one indicates a clinical advantage for carbamazepine.
Data for 551 participants (100% of those providing IPD) from three trials were available for the analysis of this outcome.
There was no evidence of statistical heterogeneity between trials (chi squared = 2.84, df = 2, p = 0.24).
The overall pooled HR of 0.91 (95% CI 0.74 to 1.12) suggests no clear clinical advantage for either drug.

DISCUSSION

We have gratefully received IPD from the authors of three trials (551 participants) which included a comparison of phenytoin with carbamazepine for the treatment of epilepsy. Although 10 trials were identified as meeting the inclusion criteria of this review, there is only hope of collecting IPD from one further trial (Czapinski 1997) as data for the remaining five trials have been lost or no seizure data were originally recorded. The analyses included in this review will be updated when additional data become available or further trials are identified.

An important limitation is that, of the three trials providing full IPD, none of the trials collected data on specific generalized seizure types other than generalized tonic-clonic seizures. Hence, the results for seizure outcomes (time to 12 month remission, time to six month remission and time to first seizure), apply only to generalized tonic-clonic seizures, despite the fact that participants may have been experiencing other generalized seizure types such as absence or myoclonic seizures. Given the suspicion that carbamazepine and phenytoin may exacerbate myoclonus and absence seizures (Liporace 1994), it is unlikely that this issue will be addressed in future trials.

We have not demonstrated a statistically significant effect in favour of either carbamazepine or phenytoin for the primary global outcome 'time to withdrawal of allocated treatment'. This outcome is influenced by both the relative efficacy of the two drugs, as well as differences in tolerability and safety. Because 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. The confidence intervals for this outcome are too wide to confirm equivalence, as clinically important differences have not been excluded.

Similar results were obtained for the analysis of 'time to 12 month remission', 'time to six month remission', and 'time to first seizure', concluding that although no statistically significant differences were found between carbamazepine and phenytoin, the confidence intervals are too wide to confirm equivalence.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review do not provide evidence of a difference between carbamazepine and phenytoin given as monotherapy for the treatment of epilepsy.

Implications for research

Finding overall differences between these standard antiepileptic drugs has proved elusive. If overall differences do exist across heterogeneous populations of participants such as those studied here, those differences are likely to be small, and in order to be clinically useful, future comparative antiepileptic drug studies will need to be powered accordingly. It has been argued that future comparative antiepileptic drug studies be powered to establish equivalence (Jones 1996).

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REFERENCES

References to studies included in this review

Callaghan 1985 *{published data only}*
Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry* 1985;**48**(7):639–44.

Cereghino 1974 *{published data only}*
Cereghino JJ, Brock JJ, Van Meter JC, Penry JK, Smith LD, White BG. Carbamazepine for epilepsy. A controlled prospective evaluation. *Neurology* 1974;**24**(5):401–10.

Czapinski 1997 *{published data only}*
Czapinski P, Terczynski A, Czapinska E. Randomised 36-month comparative study of valproic acid, phenytoin, phenobarbital and carbamazepine efficacy in patients with newly diagnosed epilepsy with partial complex seizures. *Epilepsia* 1997;**38 Suppl**(3):42.

de Silva 1996 *{published data only}*
de Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, et al.Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 1996;**347**:709–13.

Forsythe 1991 *{published data only}*
Forsythe I, Butler R, Berg I, McGuire R. Cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate. *Developmental Medicine and Child Neurology* 1991;**33**: 524–34.

Heller 1995 *{published data only}*
Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AL, et al.Phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *Journal of Neurology, Neurosurgery, and Psychiatry* 1995;**58**(1):44–50.

Mattson 1985 *{published data only}*
Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, et al.Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondary generalized tonic-clonic seizures. *New England Journal of Medicine* 1985;**313**(3):145–51.

Pulliainen 1994 *{published data only}*
Pulliainen V, Jokelainen M. Effects of phenytoin and carbamazepine on cognitive functions in newly diagnosed epileptic patients. *Acta Neurologica Scandinavica* 1994;**89**: 81–6.

Rajotte 1967 *{published data only}*
Rajotte P, Jilek W, Jilek L, Perales A, Giard N, Bordeleau J, et al.The anti-epileptic and psychotropic properties of carbamazepine (Tegretol) [Proprietes antiepileptiques et psychotropes de la carbamazepine (Tegretol)]. *L'Union Med du Canada* 1967;**10**:1200–6.

Ramsay 1983 *{published data only}*
Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;**33**(7):904–10.

References to studies excluded from this review

Berg 1993 *{published data only}*
Berg I, Butler A, Ellis M, Foster J. Psychiatric aspects of epilepsy in childhood treated with carbamazepine, phenytoin or sodium valproate: a random trial. *Developmental Medicine and Child Neurology* 1993;**35**: 149–57.

Berger 1981 *{published data only}*
* Berger JR, Ramsay RE, Wilder BJ, Bruni J. A double-blind study comparing carbamazepine to phenytoin as initial seizure therapy. *Neurology* 1981;**31**(4 Pt 2):159.

Bird 1966 *{published data only}*
Bird CAK, Griffin BP, Miklaszewska JM, Galbraith AW. Tegretol (carbamazepine): a controlled trial of new anti-convulsant. *British Journal of Psychiatry* 1966;**112**:737–42.

Bittencourt 1993 *{published data only}*
Bittencourt PRM, Antoniuk SA, Bigarella MM, da Costa JC, Doro MP, Ferreira AS, et al.Carbamazepine and phenytoin in epilepsies refractory to barbiturates: efficacy, toxicity and mental function. *Epilepsy Research* 1993;**16**: 147–55.

Callaghan 1983 *{published data only}*
Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A comparative study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *British Journal of Clinical Practice* 1983;**27**:7–9.

Dodrill 1977 *{published data only}*
Dodrill CB, Troupin AS. Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. *Neurology* 1977;**27**:1023–8.

Kosteljanetz 1979 *{published data only}*
Kosteljanetz M, Christiansen J, Dam AM, Hansen BS, Pedersen H, Dam M. Carabamazepine vs phenytoin. A controlled clinical trial in focal motor and generalized epilepsy. *Archives of Neurology* 1979;**36**(1):22–4.

Meador 1990 *{published data only}*
Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. *Neurology* 1990;**40**:391–4.

Pulliainen 1995 *{published data only}*
Pulliainen V, Jokelainen M. Comparing the cognitive effects of phenytoin and carbamazepine in long-term monotherapy: a two-year follow-up. *Epilepsia* 1995;**36**(12): 1195–202.

Shakir 1980 *{published data only}*
Shakir RA. Sodium valproate, phenytoin and carbamazepine as sole anticonvulsants. The place of sodium valproate

in the treatment of epilepsy. Royal Society of Medicine International Congress and Symposium No. 30. London: Academic Press Inc (London) Ltd and the Royal Society of Medicine, 1980:7–16.

Simonsen 1975 *{published data only}*
Simonsen N, Olsen PZ, Kuhl V, Lund M, Wendelboe J. A double blind study of carbamazepine and diphenylhydantoin in temporal lobe epilepsy. *Acta Neurologica Scandinavica* 1975;**60**:39–42.

Simonsen 1976 *{published data only}*
Simonsen N, Olsen PZ, Kuhl V, Lund M, Wendelboe J. A comparative controlled study between carbamazepine and diphenylhydantoin in psychomotor epilepsy. *Epilepsia* 1976;**17**(2):169–76.

Smith 1987 *{published data only}*
Smith DB, Mattson RH, Cramer JA, Collins JF, et al.Results of a nationwide Veterans Administration Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone. *Epilepsia* 1987; **28**(Suppl 3):S50–S58.

Troupin 1975 *{published data only}*
Troupin AS, Green JR, Halpern LM. Carbamazepine (Tegretol) as an anticonvulsant. A controlled double-blind comparison with diphenylhydantoin (Dilantin). *Acta Neurologica Scandinavica Supplement* 1975;**75**:13–26.

Troupin 1977 *{published data only}*
Troupin A, Ojemann LM, Halpern L, Dodrill C, Wilkus R, Friel P, et al.Carbamazepine: a double blind comparison with phenytoin. *Neurology* 1977;**27**(6):511–9.

Wilkus 1978 *{published data only}*
Wilkus RJ, Dodrill CB, Troupin AS. Carbamazepine and the electroencephalogram of epileptics: a double blind study in comparison to phenytoin. *Epilepsia* 1978;**19**:283–91.

Additional references

Brodie 1995
Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995;**345**(8948):476–9.

Chadwick 1998
Chadwick DW, Anhut H, Greiner MJ, Alexander J, Murray GH, Garofalo EA, et al.A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77. *Neurology* 1998;**51**(5):1282–8.

Commission 1998
ILAE commission on antiepileptic drugs. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia* 1998;**39**(7): 799–803.

EBCTCG 1990
Early Breast Cancer Trialists' Collaborative Group. *Treatment of early breast cancer, worldwide evidence 1985-90*. Vol. **1**, Oxford: Oxford University Press, 1990.

Gladstone 1992
Gladstone DJ, Bologa M, Maguire C, Pastuszak A, Koren G. Course of pregnancy and fetal outcome following maternal exposure to carbamazepine and phenytoin: a prospective study. *Reproductive Toxicology* 1992;**6**(3):257–61.

Higgins 2005
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. The Cochrane Collaboration. Chichester: John Wiley & Sons, Ltd.

Jones 1996
Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *British Medical Journal* 1996;**313**(7048):36–9.

Liporace 1994
Liporace JD, Sperling MR, Dichter MA. Absence seizures and carbamazepine in adults. *Epilespia* 1994;**35**(5):1026–8.

Nulman 1997
Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *American Journal of Medical Genetics* 1997;**68**(1):18–24.

Parmar 1998
Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival end-points. *Statistics in Medicine* 1998;**17**: 2815–34.

Reunanen 1996
Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Research* 1996;**23** (2):149–55.

SIGN 1997
Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Epilepsy in Adults [Web Page]. http://pc47.cee.hw.ac.uk/sign/html/html21.htm November 1997.

Tennis 1997
Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 1997;**49**(2): 542–6.

Wilder 1995
Wilder BJ. Phenytoin: clinical use. *Antiepileptic drugs*. 4th Edition. New York: Raven Press, 1995:339–44.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Callaghan 1985

Methods	Randomization based on 2 latin squares. An independent person selected drug from randomization list. Unblinded.
Participants	Previously untreated, recently diagnosed. Number randomized: PHT = 58, CBZ = 59. 44% partial epilepsy. 52% male. Age range: 4 to 75 years. Duration of treatment (range in months): 3 to 47
Interventions	Monotherapy with PHT or CBZ. Mean daily dose achieved: PHT = 5.4 mg/kg, CBZ = 10.9 mg/kg
Outcomes	Seizure control: excellent (seizure free); good(> 50% reduction); poor(< 50% reduction)
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cereghino 1974

Methods	Randomly allocated using random number tables. Method of allocation concealment not stated. Double-blind achieved using additional placebo capsules
Participants	People with uncontrolled seizures on current medication. Number randomized: PHY = 15, CBZ = 15. 91% partial epilepsy in 3 drug groups; CBZ, PHY or PHB. 62% male in 3 drug groups. Age range: 18 to 51 years
Interventions	Monotherapy with PHY or CBZ. Daily dose: PHY = 300 mg/day, or CBZ = 1200 mg/day.
Outcomes	Behaviour outcomes. Adverse effects. Seizure frequency.
Notes	Cross-over trial. Outcomes chosen for this review were not reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Czapinski 1997

Methods	Method of generation of random list and allocation concealment not stated. Unblinded
Participants	People with newly diagnosed epilepsy. Number randomized: PHT = 30, CBZ = 30. 100% partial epilepsy. Percentage male and range of follow up not mentioned. Age range: 18 to 40 years
Interventions	Monotherapy with PHT or CBZ. Dose achieved not stated.
Outcomes	Proportion achieving 24 month remission at 3 years and exclusions after randomization due to adverse effects or no efficacy
Notes	Abstract only. Outcomes chosen for this review were not reported. IPD pledged but not yet received

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

de Silva 1996

Methods	Allocation concealed using sealed opaque envelopes. Random list generated using random permuted blocks. Unblinded
Participants	Newly diagnosed. Number randomized: PHT = 54, CBZ = 54. 55% partial epilepsy. 59% male. Age range: 3 to 16 years. Range of follow up (months): 3 to 88
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 175 mg/day, CBZ = 400 mg/day
Outcomes	Time to first seizure recurrence after start of therapy, Time to 12 month remission from all seizures, side effects
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Forsythe 1991

Methods	Participants randomly allocated using quota allocation. Single-blinded (for cognitive tests)
Participants	Newly diagnosed. Number randomized: PHT = 20, CBZ = 23. No information on epilepsy type, sex or range of follow-up. Age range: 5 to 14 years
Interventions	Monotherapy with PHT or CBZ. Mean dose: PHT = 6.1 mg/day, CBZ = 17.9 mg/day

Forsythe 1991 (*Continued*)

Outcomes	Cognitive assessments. Summary of withdrawals from randomized drug	
Notes	Outcomes chosen for this review were not reported. IPD not available, but could be constructed from the publication for the outcome 'time to withdrawal of allocated drug'	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Heller 1995

Methods	Allocation concealed using sealed opaque envelopes. Random list generated using random permuted blocks. Unblinded	
Participants	Newly diagnosed. Number randomized: PHT = 63, CBZ = 61. 42% partial epilepsy. 52% male. Age range:13 to 72 years. Range of follow-up (months): 1 to 91	
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 300 mg/day, CBZ = 600 mg/day	
Outcomes	Time to first seizure recurrence after start of therapy, time to 12 month remission from all seizures, side effects	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mattson 1985

Methods	Method of generation of random list and allocation concealment not stated. Double blind study achieved by providing additional blank tablet
Participants	People with previously untreated or undertreated partial seizures. Number randomized: PHT = 165, CBZ = 155. 100% partial epilepsy. 87% male. Age range: 18 to 82 years. Range of follow up (months) 1 to 177
Interventions	Monotherapy with PHT or CBZ. Median daily dose achieved: PHT = 400 mg/day, CBZ = 800 mg/day
Outcomes	Patient retention (length of time patient continued to take randomized drug), composite scores, total seizure control, seizure rates, incidence of side effects
Notes	

Mattson 1985 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Pulliainen 1994

Methods	Method of generation of random list and allocation concealment not stated. Single blind study achieved by providing additional blank tablet
Participants	Newly diagnosed. Number randomized: PHT = 20, CBZ = 23. 23% partial epilepsy. 47% male. Mean age (SD) years: PHT = 31.5 (11.3), CBZ = 26.8 (13.2). *See Notes*
Interventions	Monotherapy with PHT or CBZ. Dose information not reported.
Outcomes	Cognitive assessments.
Notes	59 participants were randomized but 16 were subsequently excluded. Results for these patients are not presented in the study report

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Rajotte 1967

Methods	Cross-over study. Method of generation of random list and allocation concealment not stated. Double blind study
Participants	Chronic institutionalized epileptic patients with behavior disorders. 24 individuals randomized to PHT or CBZ for 6 months before crossing over to the other group
Interventions	Monotherapy with PHT or CBZ. Dose information not reported.
Outcomes	Number of seizures and severity of personality disorders.
Notes	Limited information available as manuscript is not written in English

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Ramsay 1983

Methods	Method of generation of random list and allocation concealment not stated. Double blind study achieved by providing additional blank tablet
Participants	People previously untreated with anticonvulsants. Number randomized: PHT = 45, CBZ = 42. 63% partial epilepsy. 69% male. Overall mean age (range) 37.4 (18 to 77) years.
Interventions	Monotherapy with PHT or CBZ. Mean daily dose achieved: PHT = 5.35 mg/kg/day, CBZ = 9.32 mg/kg/day
Outcomes	Laboratory measures, side effects, treatment failure.
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

CBZ: carbamazepine
IPD: individual patient data
PHT: phenytoin
PHB: phenobarbitone

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 Forsythe 1991 publication
Berger 1981	Reports the same trial as Ramsay 1983.
Bird 1966	Unclear whether trial is randomized and unclear whether patients received either CBZ or PHT as monotherapy
Bittencourt 1993	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. Participants were given phenobarbital initially which was later withdrawn whilst either CBZ or PHT was also introduced
Callaghan 1983	Reports the same trial as Callaghan 1985.
Dodrill 1977	Reports the same trial as Troupin 1975.

(*Continued*)

Kosteljanetz 1979	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. All medication except phenobarbital and primidone were discontinued gradually whilst dose of randomized drug CBZ or PHT was increased
Meador 1990	Comparison between CBZ monotherapy and PHT monotherapy cannot be made. Cross over trial but some participants were receiving treatment at the start of the first period which had to be withdrawn slowly
Pulliainen 1995	Reports a subset of participants included in the trial reported by Pulliainen 1994
Shakir 1980	Direct comparison between CBZ and PHT not available. The publication reports two separate randomized studies, the first compares VPS and PHT and the second compares VPS and CBZ
Simonsen 1975	Reports the same trial as Simonsen 1976.
Simonsen 1976	Randomized participants were slowly withdrawn from their previous treatment as part of the trial and therefore a comparison between CBZ and PHT monotherapy cannot be made
Smith 1987	Reports the same trial as Mattson 1985.
Troupin 1975	All patients received PHT for two months prior to entering a randomized cross over period. It is unclear whether a comparison between CBZ and PHT monotherapy could be made
Troupin 1977	Reports the same trial as Troupin 1975.
Wilkus 1978	Reports the same trial as Troupin 1975.

CBZ: carbamazepine
PHT: phenytoin
VPS: sodium valproate

DATA AND ANALYSES

Comparison 1. Carbamazepine versus phenytoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to withdrawal of allocated treatment	4	591	Peto Odds Ratio (95% CI)	0.97 [0.74, 1.28]
2 Time to achieve 12 month remission	3	551	Peto Odds Ratio (95% CI)	1.00 [0.78, 1.29]
3 Time to achieve six month remission	3	551	Peto Odds Ratio (95% CI)	1.10 [0.87, 1.39]
4 Time to first seizure post randomization	3	551	Peto Odds Ratio (95% CI)	0.91 [0.74, 1.12]

Analysis 1.1. Comparison 1 Carbamazepine versus phenytoin, Outcome 1 Time to withdrawal of allocated treatment.

Review: Carbamazepine versus phenytoin monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenytoin

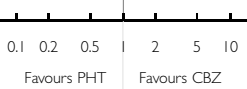
Outcome: 1 Time to withdrawal of allocated treatment

Study or subgroup	Phenytoin n/N	Carbamazepine n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
de Silva 1996	17/53	21/53		17.8 %	0.91 [0.48, 1.73]
Forsythe 1991	6/20	9/23		6.9 %	0.68 [0.24, 1.91]
Heller 1995	12/63	17/60		13.7 %	0.59 [0.28, 1.22]
Mattson 1985	73/165	56/154		61.6 %	1.16 [0.82, 1.64]
Total (95% CI)				**100.0 %**	**0.97 [0.74, 1.28]**

Heterogeneity: Chi^2 = 3.29, df = 3 (P = 0.35); I^2 =9%

Test for overall effect: Z = 0.18 (P = 0.85)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Carbamazepine versus phenytoin, Outcome 2 Time to achieve 12 month remission.

Review: Carbamazepine versus phenytoin monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenytoin

Outcome: 2 Time to achieve 12 month remission

Study or subgroup	Phenytoin n/N	Carbamazepine n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
de Silva 1996	48/54	45/54		35.2 %	1.23 [0.81, 1.88]
Heller 1995	47/63	40/61		29.6 %	0.91 [0.58, 1.45]
Mattson 1985	60/165	49/154		35.2 %	0.89 [0.58, 1.36]
Total (95% CI)				**100.0 %**	**1.00 [0.78, 1.29]**

Heterogeneity: Chi^2 = 1.38, df = 2 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Carbamazepine versus phenytoin, Outcome 3 Time to achieve six month remission.

Review: Carbamazepine versus phenytoin monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenytoin

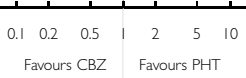
Outcome: 3 Time to achieve six month remission

Study or subgroup	Phenytoin n/N	Carbamazepine n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
de Silva 1996	48/54	47/54		31.3 %	1.14 [0.75, 1.72]
Heller 1995	54/63	48/61		31.3 %	0.99 [0.66, 1.50]
Mattson 1985	77/165	64/154		37.4 %	1.16 [0.80, 1.70]
Total (95% CI)				**100.0 %**	**1.10 [0.87, 1.39]**

Heterogeneity: Chi^2 = 0.35, df = 2 (P = 0.84); I^2 =0.0%

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable

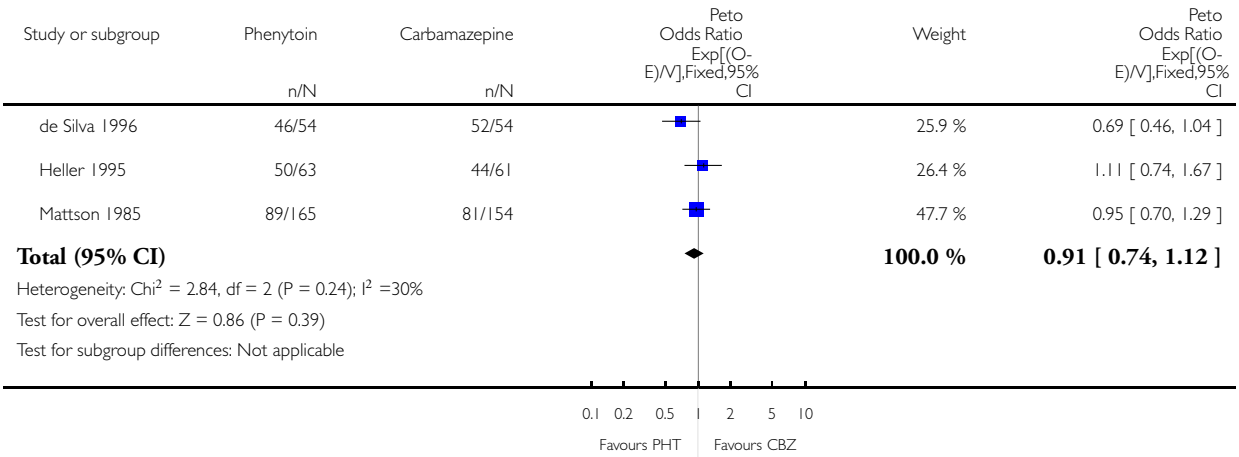


Analysis 1.4. Comparison 1 Carbamazepine versus phenytoin, Outcome 4 Time to first seizure post randomization.

Review: Carbamazepine versus phenytoin monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenytoin

Outcome: 4 Time to first seizure post randomization



ADDITIONAL TABLES

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

Trial	Outcomes reported	Summary of results
Callaghan 1985	1. Seizure control: excellent (seizure free); good (>50% reduction); poor (<50% reduction). 2. Side effects.	PHT CBZ 67% 37% 12% 37% 21% 25% 10% 8%
Czapinski 1997	1.Proportion achieving 24 month remission at 3 years. 2.Proportion excluded after randomization due to adverse effects or no efficacy	PHT CBZ 59% 62% 23% 30%
Forsythe 1991	1.Cognitive assessments. 2. Withdrawals from randomized drug. .	PHT CBZ 30% 39%

Table 1. Outcomes considered and summary of results for trials with no IPD (*Continued*)

Pulliainen 1994	1. Cognitive functions.	Compared to CBZ, patients on PHT became slower and their visual memory decreased. There was an equal decrease in negative mood on PHT and CBZ
Ramsay 1983	1. Side effects. 2. Seizure control.	Incidence of major side effects, minor side effects and complete seizure control was the same on PHT and CBZ
Rajotte 1967	1. Seizure frequency. 2. Severity of personality disorders.	No significant difference was found between the two drugs as to their antiepileptic properties. Carbamazepine reduces the severity of personality disorders in this population
Cereghino 1974	1. Behavior measured with rating scale modified from the Ward Behavior Rating Scale. 2. Seizure control 3. Side effects	Results in trial publication include all patients who received each drug in the three cross-over periods used in this study. In this population CBZ was equal in efficacy to PHY in controlling seizure frequency and side effects were minimal

Table 2. Number of participants contributing to each analysis

Trial	Number randomized	Time to withdrawal	Time to 12 month	Time to 6 month	Time to 1st seizure
de Silva 1996	Total=108 PHT=54; CBZ=54	Total=106 PHT=53; CBZ=53	Total=108 PHT=54; CBZ=54	Total=108 PHT=54; CBZ=54	Total=108 PHT=54; CBZ=54
Heller 1995	Total=124 PHT=63; CBZ=61	Total=123 PHT=63; CBZ=60	Total=124 PHT=63; CBZ=61	Total=124 PHT=63; CBZ=61	Total=124 PHT=63; CBZ=61
Mattson 1985	Total=319 PHT= 165; CBZ=154	Total=319 PHT= 165; CBZ=154	Total=319 PHT= 165; CBZ=154	Total=319 PHT= 165; CBZ=154	Total=319 PHT= 165; CBZ=154
Forsythe 1991	Total=43 PHT=20; CBZ=23	Total=43 PHT=20; CBZ=23	0 (information not available)	0 (information not available)	0 (information not available)

Table 3. Logrank analysis

Test for:	Statistic:	Time to withdrawal	Time to 12 month	Time to 6 month	Time to 1st seizure
Homogeneity	Chi square	(df=3) 3.29	(df=2) 1.38	(df=2) 0.35	(df=2) 2.84
	p-value	0.35	0.50	0.84	0.24
Overall effect	Chi square	(df=1) 0.18	(df=1) 0.04	(df=1) 0.80	(df=1) 0.86

Table 3. Logrank analysis (*Continued*)

	p-value	0.90	1.00	0.40	0.40
Hazard Ratio (95% CI)		0.97(0.74 to 1.28)	1.00(0.78 to 1.29)	1.10(0.87 to 1.39)	0.91 (0.74-1.12)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 (phenytoin)
#2 MeSH descriptor Phenytoin explode all trees
#3 carbamazepine
#4 MeSH descriptor Carbamazepine explode all trees
#5 ((#1 OR #2) AND (#3 OR #4))
#6 MeSH descriptor Epilepsy explode all trees
#7 MeSH descriptor Seizures explode all trees
#8 epilep* or seizure* or convulsion*
#9 (#6 OR #7 OR #8)
#10 (#5 AND #9)

Appendix 2. MEDLINE search strategy

The following search is based on the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE as set out in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.4, updated March 2005) (Higgins 2005).
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trials/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. clinical trial.pt.
8. Clinical Trial/
9. (clin$ adj trial$).ab,ti.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ab,ti.
11. exp PLACEBOS/
12. placebo$.ab,ti.
13. random$.ab,ti.
14. exp Research Design/
15. or/1-14
16. (animals not humans).sh.
17. 15 not 16

18. carbamazepin$.tw.
19. exp Carbamazepine/
20. phenytoin.tw. or exp Phenytoin/
21. (18 or 19) and 20
22. (epilep$ or seizure$ or convulsion$).tw.
23. exp Epilepsy/
24. exp Seizures/
25. 22 or 23 or 24
26. 17 and 21 and 25

WHAT'S NEW

Last assessed as up-to-date: 18 January 2010.

Date	Event	Description
1 November 2010	New search has been performed	Searches updated 1st November 2009; no new trials identified

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 2, 2002

Date	Event	Description
12 August 2009	Amended	Copyedits made at editorial base.
23 September 2008	Amended	Converted to new review format.
26 September 2007	New search has been performed	Searches updated 27th July 2007; no new trials identified.

CONTRIBUTIONS OF AUTHORS

Catrin Tudur Smith assessed eligibility and methodological quality of individual studies, organized and cleaned the individual patient data sets, performed data validation checks and statistical analyses and co-wrote the review.

Tony Marson collected individual patient data, liaised with original trialists, assessed eligibility and methodological quality of individual studies, extracted data from case notes, provided clinical guidance and co-wrote the review.

Helen Clough helped organize and clean the individual patient data sets, performed data validation checks and performed some preliminary statistical analyses.

Paula Williamson extracted data from case notes, supervised Catrin Tudur Smith and Helen Clough, provided statistical support and advice, and commented on each draft of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS Research & Development Programme, UK.

External sources

- Medical Research Council, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Carbamazepine [*therapeutic use]; Epilepsy [*drug therapy]; Phenytoin [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans