Carbamazepine versus phenobarbitone monotherapy for epilepsy (Review)

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[Intervention Review]

Carbamazepine versus phenobarbitone monotherapy for epilepsy

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Editorial group: Cochrane Epilepsy Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2009.
Review content assessed as up-to-date: 30 September 2006.

Citation: Tudur Smith C, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001904. DOI: 10.1002/14651858.CD001904.

ABSTRACT

Background

In developing countries, phenobarbitone is commonly used but its use in Europe and the USA has decreased due to concerns over adverse effects. Carbamazepine is recommended as the drug of choice for partial onset seizures, and there is concern that it may worsen some generalized onset seizure types. We report a review using individual patient data in which carbamazepine and phenobarbitone are compared.

Objectives

To review the effects of carbamazepine compared to phenobarbitone monotherapy for people with partial onset seizures or generalized onset tonic-clonic seizures.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (October 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2006) and MEDLINE (Ovid, 1950 to August 2006). We contacted experts in the field, original trial investigators, and the manufacturers of carbamazepine.

Selection criteria

Randomized or quasi-randomized, blinded or unblinded controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures.

Data collection and analysis

Outcome measures were (i) time to withdrawal of allocated treatment, (ii) time to 12-month remission, and (iii) time to first seizure. Data were analysed using a stratified logrank analysis with results expressed as hazard ratios (HR) and 95% confidence intervals (CIs), where a HR>1 indicates an event is more likely on phenobarbitone. A test for interaction between treatment and seizure type (partial versus generalized onset) was also undertaken.

Main results

Data are available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met our inclusion criteria. The main overall results (HR 95% CI) adjusted for seizure type were, (i) time to withdrawal 1.63(1.23 to 2.15), (ii) time to 12-month remission 0.87 (0.65 to 1.17), (iii) time to first seizure 0.85 (0.68 to 1.05). The review suggests that time to withdrawal is significantly improved with carbamazepine compared to phenobarbitone. No overall difference between drugs is identified for the outcomes 'time to 12-month remission' and 'time to first seizure'. Statistical heterogeneity was not encountered. An interaction between treatment and seizure type, confirmed statistically, was identified for time to first seizure, where phenobarbitone was favoured for partial onset seizures and carbamazepine for generalized onset tonic-clonic seizures.

Authors' conclusions

We found no overall difference between carbamazepine and phenobarbitone for time to 12-month remission or time to first seizure, however, subgroup analyses for time to first seizure suggest an advantage with phenobarbitone for partial onset seizures and a clinical advantage with carbamazepine for generalized onset tonic-clonic seizures. Phenobarbitone is significantly more likely to be withdrawn, indicating that it is less well tolerated than carbamazepine.

PLAIN LANGUAGE SUMMARY

Carbamazepine versus phenobarbitone monotherapy for epilepsy

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Carbamazepine and phenobarbitone are commonly used antiepileptic drugs. The review of trials found that carbamazepine is better tolerated than phenobarbitone. No reliable evidence was found of a difference in the overall seizure control between these two drugs. For the seizure types investigated, time to first seizure was longer for people with partial onset seizures taking phenobarbitone whilst carbamazepine tended to be better for people with generalized onset seizures.

BACKGROUND

Worldwide, carbamazepine and phenobarbitone are commonly used antiepileptic drugs. In Europe and the USA, carbamazepine is considered a drug of first choice for people with a partial onset to their seizures (SIGN 1997). Phenobarbitone is commonly used as a first line drug in developing countries since it is much cheaper.

In the USA and much of Europe, phenobarbitone is no longer considered a first line drug due to worries over its short and long term tolerability. In the largest reported randomized controlled trial investigating phenobarbitone as monotherapy in adults with partial seizures (Mattson 1985), no difference was found with respect to seizure control when compared with phenytoin and carbamazepine. However, for the compound outcome 'time to treatment withdrawal' phenobarbitone fared significantly worse implying that it was less well tolerated. In children, there is concern about behavioural disturbance caused by phenobarbitone. In one paediatric study in the UK (de Silva 1996) the phenobarbitone arm of the trial was withdrawn due to concerns about behavioural problems and because of difficulties getting paediatricians to randomize individuals. However, another study in rural India (Pal 1998) comparing phenobarbitone with phenytoin found no such problem, and the authors concluded that phenobarbitone was a suitable first line drug in this setting.

Carbamazepine is recommended as the drug of choice for partial onset seizures (SIGN 1997), and there is concern that it may worsen certain generalized onset seizure types such as myoclonus (Shields 1983, Snead 1985). However, a meta-analysis comparing carbamazepine with valproate (Marson 2000) found no hard evidence to support this view, finding only a trend in favour of carbamazepine for partial onset seizures. This meta-analysis also failed to find evidence to support the recommended use of valproate for generalized seizure types. Phenobarbitone is thought to be effective for both partial and generalized seizure types, and no single trial has found convincing differences in effect on seizures between carbamazepine and phenobarbitone. However, confidence intervals around estimates have been wide and equivalence cannot be inferred. The aim of this review is to summarize data from existing trials, and to investigate the presence of an interaction between

drug and seizure type (partial onset versus generalized onset seizure types).

There are however difficulties in undertaking a systematic review of epilepsy monotherapy trials, as the recommended outcomes (ILAE Commission 1998) require analysis of time to event data (eg time to 12-month remission). Although methods have been developed to synthesize time to event data using summary information (Parmar 1998), it was unlikely that all trials would report appropriate data for the outcomes and subgroups of interest. We therefore collected individual patient data.

The use of individual patient data also helps to overcome a number of other problems. Firstly, despite the fact that the same seizure data have been collected in epilepsy monotherapy trials, there has been no uniformity in the reporting of outcomes. For example, trials may report time to 12-month remission but not time to first seizure or vice versa. Secondly, trialists have had differing approaches to analysis, particularly with respect to censoring of time to event data. Thirdly, we are interested in the interaction between seizure type and treatment, but not all trials have reported separate results for people with partial and generalized onset seizures. An individual patient data approach allows a thorough analysis of time to event data, and treatment covariate interactions. This review is one in a series investigating individual monotherapy comparisons.

OBJECTIVES

To review the effects of carbamazepine compared to phenobarbitone when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalized seizures) 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 controlled monotherapy studies comparing carbamazepine and phenobarbitone in people with epilepsy.
(2) Studies may be double blind, single blind or unblinded.
(3) Studies should have either adequate (eg random number tables) or quasi methods (eg by day of the week) of randomization.

Types of participants

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

Types of interventions

Carbamazepine or phenobarbitone 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). This is a compound outcome reflecting both effect on seizures as well as adverse effects, as treatment may be withdrawn due to continued seizures, adverse effects (or a combination of both continued seizures and adverse effects), non-compliance or if additional add-on treatment was initiated (ie allocated treatment had failed). This is an outcome to which the individual makes a contribution, and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE Commission 1998).
(2) Time to achieve 12-month remission (seizure free period).
(3) Time to first seizure post randomization.
(4) Quality of life measures if available.

Search methods for identification of studies

We searched the following databases:
(1) Cochrane Epilepsy Group's Specialized Register (October 2006) using the search terms 'carbamazepine AND phenobarbit*'.
(2) The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2006) using the strategy outlined in Appendix 1.
(3) MEDLINE (Ovid, 1950 to August 2006) using the strategy outlined in Appendix 2.
The Cochrane Epilepsy Group trials register has been compiled by searching MEDLINE (1966-2009) and handsearching *Epilepsia, Epilepsy Research, Seizure* and *Acta Neurologica Scandinavica* whilst other key neurology and general medical journals have been handsearched by other Cochrane groups. The identified publications were obtained to look for further cross references. Appropriate conference abstracts have also been searched. Articles identified by the search which were not in English were not excluded on that basis alone. We have also contacted Novartis (manufacturers of carbamazepine) and the original investigators of any relevant trials that we identified.

Data collection and analysis

Trial assessment and data collection

All identified trials were assessed for inclusion independently by two of the reviewers (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 individual patient data on date of randomization, drug allocated and dose, age, sex, presence of neurological signs, seizure types at randomization, number of seizures prerandomization (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 (recorded by patient/relatives/clinician), 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, an assessment was carried out 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 three studies (Feksi 1991; Mattson 1985; Placencia 1993), 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 12-month remission and the time to first seizure to be computed. Time to 12-month remission was calculated from the date of randomization to the date (or estimated date) the individual had first been free from seizures for 12 months. 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 already been used for two trials (de Silva 1996; Heller 1995) for which outcome data were provided directly.

For two trials (de Silva 1996; Heller 1995) the date of and reason for treatment withdrawal were extracted from study case report forms by two reviewers (Tony Marson and Paula Williamson). Both reviewers 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 date of withdrawal or 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 analyzed in the treatment group to which they were allocated, irrespective of which treatment they actually received. Therefore, for the outcomes 'time to 12-month remission' and 'time to first seizure' participants were not censored if treatment was withdrawn. For the outcome 'time to withdrawal of allocated treatment' participants who withdrew from treatment were censored if the reason for withdrawal was remission but otherwise were treated as an event (see detailed description above).

(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 hazard ratios with 95% confidence intervals (CIs). We used the information provided by the stratified logrank test to investigate the main effect of treatment, to investigate the presence of an interaction between treatment and seizure type (partial onset versus generalized onset seizure types), and to assess evidence for homogeneity in treatment effect between trials (EBCTCG 1990).

(3) Due to the clinical belief that carbamazepine is more effective in partial onset seizures while phenobarbitone is thought to be effective for both partial and generalized seizure types, all analyses are stratified by seizure type (partial onset versus generalized onset), according to the classification given by the original trialists.

(4) Due to drug related side effects the phenobarbitone arm was discontinued in one trial (de Silva 1996) after randomizing only 10 children to this drug. Following the removal of phenobarbitone, further randomization continued between phenytoin, carbamazepine and sodium valproate (remaining drugs examined in the trial). In order to assess whether this had any effect on the comparison between phenobarbitone and carbamazepine, sensitivity analyses have been undertaken for each outcome excluding those individuals who were randomized to carbamazepine after the removal of phenobarbitone in the de Silva 1996 trial.

(5) Sensitivity analyses are undertaken to assess the impact of inadequate concealment of treatment allocation.

Results are expressed as a hazard ratio (HR) and 95% CIs, and by convention a HR > 1 indicates that an event is more likely on phenobarbitone. Hence, for time to withdrawal of allocated treatment or time to first seizure a HR > 1 indicates a clinical advantage for carbamazepine (eg HR = 1.1 would suggest a 10% increase in risk of withdrawal from phenobarbitone compared to carbamazepine) and for time to 12-month remission a HR > 1 indicates a clinical advantage for phenobarbitone.

RESULTS

Description of studies

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

A total of 12 trial reports were identified as potentially eligible for this systematic review. Three trials were excluded as they did not meet the eligibility criteria for this review. For two of these trials a comparison between carbamazepine and phenobarbitone monotherapy was not made (Marjerrison 1968; Meador 1990), whilst for one study it was unclear whether randomization was used (Bird 1966) and we have been unable to contact the original author. Further details are given in the 'table of characteristics of excluded studies'. A total of eight trial reports in which individuals had been randomized to carbamazepine monotherapy or phenobarbitone monotherapy were identified as eligible for this review. The results of eight trials have been published and one is unpublished (Czapinski 1997).

Individual patient data (IPD) were not obtained for three trials as suitable seizure data for the outcomes examined in this systematic review were not recorded (Chen 1996; Mitchell 1987), or the authors no longer had a copy of the data (Cereghino 1974). A total of 114 participants were randomized to either carbamazepine or phenobarbitone in these three trials. One further study only published in abstract form (Czapinski 1997), randomized 60 participants with newly diagnosed epilepsy with partial complex seizures to either phenobarbitone or carbamazepine. At the time of writing, IPD have been pledged but not received. For a further trial (Feksi 1991) in which 302 participants were randomized, we were provided access to an IPD dataset, but this was not the final dataset used for the analysis published by the original authors. The final dataset was held by the pharmaceutical company that sponsored the trial, Ciba Geigy, who at that time held the product license for carbamazepine. Since the trial was undertaken there have been a number of mergers and restructures within the industry and the current owners of the data are Novartis. Unfortunately Novartis have been unable to locate the data for this trial. The dataset that we have for this trial contained a number of problems and inconsistencies and we therefore decided not to include this trial in the meta-analysis. If the final dataset is located or the problems with the dataset are overcome by another means, these data will be included in a future update of this review. None of these five trials examined the time-to-event outcomes investigated in this systematic review therefore subject individual or aggregate data could not be extracted from trial reports. Full details of outcomes considered and summary of results in each eligible trial for which IPD were not available, or could not be used, can be found in Table 1.

IPD were available for the remaining four trials which recruited a total of 684 participants, representing 59% of 1160 individuals from all nine identified eligible trials. Computerized data were provided directly in two trials (Mattson 1985; Placencia 1993) and a combination of both computerized and hard copy data (although mostly computerized) were supplied by the authors of two trials (de Silva 1996; Heller 1995). Of these four trials for which IPD were provided, one recruited children only (de Silva 1996), two recruited adults only (Heller 1995; Mattson 1985) and one recruited both adults and children (Placencia 1993). Three trials recruited people with newly diagnosed epilepsy (de Silva 1996; Heller 1995; Mattson 1985), and one trial recruited people with active seizures who were previously largely untreated (Placencia 1993). One trial (Mattson 1985) recruited people with partial onset seizures only and the remaining three trials included people with partial onset seizures (simple/complex partial or secondarily generalized onset tonic-clonic) and people with generalized tonic-clonic seizures.

For the trials providing IPD, data were available for the following individual characteristics (percentage of participants with data available): sex (100%); seizure type (100%); age at randomization (99%); number of seizures in six months prior to randomization (99%) and time since first seizure to randomization (99%). The results of neurological examinations were computerized in two trials (de Silva 1996; Heller 1995) (27%) whilst EEG and CT data were also only computerized in two trials (Mattson 1985, Placencia 1993) (73% and 69% respectively).

The table of 'characteristics of included studies' provides a detailed description of each study included in this systematic review.

Risk of bias in included studies

Trials for which individual patient data (IPD) were provided

Three trials (de Silva 1996; Heller 1995; Mattson 1985) used an adequate method of concealment of randomization (sealed opaque envelopes). The initial phase for the remaining trial (Placencia 1993) involved a large scale cross-sectional survey from which a randomization list based on each participant's survey number was generated. The randomized comparison of carbamazepine and phenobarbitone was undertaken in a separate second phase of the study. However, an imbalance in the number of participants in each drug group was detected following randomization of approximately 50 participants and sealed opaque envelopes were subsequently used. One trial was double blinded (Mattson 1985) achieved by using blank tablets in addition to randomized drug.

The three remaining trials were unblinded (de Silva 1996; Heller 1995; Placencia 1993).

Trials fo which no IPD were available

An adequate method of concealment of randomization (sealed opaque envelopes) was used in one trial (Feksi 1991). Details of methods used to conceal the allocation sequence were not provided in the remaining trials. One trial was double-blinded using placebo capsules (Cereghino 1974) and in one trial recruiting children only (Mitchell 1987), blinding of parents and the psychologist assessing cognitive outcomes was used. The physician involved with clinical follow-up assessments in this trial was aware of drug allocation. The two remaining trials (Chen 1996; Czapinski 1997) were unblinded.

For further details, see the 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 (see summary of analyses below). In the context of the MetaView plots produced in this review, the 'Peto odds ratio' label is equivalent to 'hazard ratio (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 3.05 can be found on the Cochrane Epilepsy Group website at http://www.epilepsy.cochrane.org/Files/cbzpb.pdf.

Time to withdrawal of allocated treatment

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

Time to withdrawal of allocated treatment and reason for withdrawal are available for 674 participants from four trials (99% of participants from four trials providing individual patient data (IPD)). One participant withdrew from carbamazepine in one trial (de Silva 1996) but a reason for withdrawal was not available for this individual and information regarding withdrawal was not available for four participants in another trial (Heller 1995). Furthermore, the information required could not be determined from the case notes in these two trials. In one further trial (Placencia 1993), seizure type classification was missing for four participants and date of withdrawal was unavailable for one participant.

In one trial (Placencia 1993) there are unresolved inconsistencies (between IPD dataset and published results) in the number of participants who withdrew from allocated treatment for certain reasons. These inconsistencies are as follows. Results from IPD dataset, 16 participants left area, 10 withdrew due to adverse effects, three withdrew for personal reasons, and one participant had a missing reason. Results in trial report, 18 participants left area, 5 withdrew due to adverse effects and seven withdrew for personal reasons. As the overall number censored is similar (results from IPD dataset, 40 censored, 13 events and results in trial report, 41 censored, 12 events) and as a sensitivity analysis excluding results of Placencia 1993 gave very similar results, we feel that these inconsistencies are minor and are unlikely to have a large impact on the overall results. However, if further information does become available this analysis will be updated accordingly. Overall, statistical heterogeneity between trials was not detected (chi squared = 5.54, df = 3, p = 0.14).

For participants with generalized onset seizures (155), the pooled HR (with 95% confidence intervals (CIs)) of 1.78 (95% CI 0.87 to 3.62) suggests a potentially clinically important advantage for carbamazepine but this advantage is not statistically significant. For participants with partial onset seizures (519), the pooled HR of 1.60 (95% CI 1.18 to 2.17) suggests a statistically significant and clinically important advantage for carbamazepine. Overall, the pooled HR (adjusted for seizure type) of 1.63 (95% CI 1.23 to 2.15) provides evidence of a statistically significant overall clinical advantage for carbamazepine for this outcome. No interaction between treatment and seizure type (generalized versus partial onset) was found (chi squared = 0.07, df = 1, p = 0.79).

The sensitivity analysis excluding participants randomized to carbamazepine following withdrawal of phenobarbitone arm in the de Silva 1996 trial gave similar results, with an estimated pooled hazard ratio of 1.53 (95% CI 1.15 to 2.03). Results within each seizure group were also similar with a pooled HR of 1.57 (95% CI 0.75 to 3.25) for participants with generalized seizures (134) and a pooled HR of 1.52 (95% CI 1.12 to 2.07) for participants with partial seizures (497).

Time to acheive 12-month remission

For this outcome, a HR > 1 indicates a clinical advantage for phenobarbitone.

Data for 680 participants (99% of those providing IPD) from four trials were available for the analysis of this outcome. Overall, statistical heterogeneity between trials was not detected (chi squared = 4.04, df= 3, p = 0.26).

For participants with generalized onset seizures (157), the pooled HR of 0.61(95% CI 0.36 to 1.03), suggests a potentially clinically important advantage for carbamazepine but this advantage is not statistically significant. For participants with partial onset seizures (523), the pooled HR of 1.03 (95% CI 0.72 to 1.49) suggests no clear clinical advantage for either drug. Overall, the pooled HR (adjusted for seizure type) of 0.87 (95% CI 0.65 to 1.17) suggests no clear overall advantage for either drug. No interaction between treatment and seizure type (generalized versus partial onset) was found (chi squared = 2.63, df = 1, p = 0.11).

The sensitivity analysis excluding participants randomized to carbamazepine following withdrawal of phenobarbitone arm in the de Silva 1996 trial gave similar results, with an estimated pooled hazard ratio of 0.84 (95% CI 0.62 to 1.14). Results within each seizure group were also similar with a pooled HR of 0.54 (95% CI 0.31 to 0.95) for participants with generalized seizures (136) and a pooled HR of 1.01 (95% CI 0.70 to 1.47) for participants with partial seizures (500).

Time to first seizure post randomisation

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

Data for 680 participants (99% of those providing IPD) from four trials are available for the analysis of this outcome. Overall, statistical heterogeneity between trials was not detected (ch squared = 1.08, df = 3, p = 0.78).

For participants with generalized onset seizures (157), the pooled HR of 1.50 (95% CI 0.95 to 2.35), suggests a potentially clinically important advantage for carbamazepine although this advantage is not statistically significant. For participants with partial onset seizures (523), a statistically significant and clinically important advantage for phenobarbitone is demonstrated by the pooled HR of 0.71 (95% CI 0.55 to 0.91). Overall, the pooled HR (adjusted for seizure type) of 0.85 (95% CI 0.68 to 1.05) suggests a potentially important advantage for phenobarbitone but this advantage is not statistically significant. Furthermore, a statistically significant interaction between treatment and seizure type (generalized versus partial onset) was detected (chi squared = 8.07, df = 1, p = 0.004) suggesting that carbamazepine is better for generalized onset seizures whilst phenobarbitone is better for partial onset seizures.

The sensitivity analysis excluding participants randomized to carbamazepine following withdrawal of phenobarbitone arm in the de Silva 1996 trial gave similar results, with an estimated pooled hazard ratio of 0.85 (95% CI 0.68 to 1.07). Results within each seizure group were also similar with a pooled HR of 1.47 (95% CI 0.93 to 2.33) for participants with generalized seizures (136) and a pooled HR of 0.72 (95% CI 0.56 to 0.93) for participants with partial seizures (500).

Quality of life outcomes

Quality of life outcomes were not recorded in any trial.

For each outcome sensitivity analyses following exclusion of the Placencia 1993 trial (due to inadequate concealment of treatment allocation) gave very similar results suggesting robustness.

DISCUSSION

Nine trials recruiting 1160 participants met the inclusion criteria for this review. We have gratefully received individual patient data (IPD) from the authors of five of these trials representing 85% of the potentially available data. However, inconsistencies and problems with the data obtained for one trial (Feksi 1991) have prevented us from including the results of this trial in the analyses presented in this review. This trial randomized 302 participants representing 26% of the total number in the nine eligible trials and 31% of the total number of participants from the trials for which IPD were obtained. We acknowledge that the Feksi 1991 trial results could potentially have a large impact on the meta-analyses presented in this review. With this in mind, the meta-analyses should be interpreted with caution.

Three of the trials (de Silva 1996; Heller 1995; Mattson 1985) for which IPD were available and included in the meta-analyses are considered good quality as they used sealed opaque envelopes to conceal treatment allocation. Some bias may have been introduced in the remaining trial (Placencia 1993) as the initial randomization list based on each participant's previously allocated survey number was not concealed. During the course of this trial sealed opaque envelopes replaced this original approach as an imbalance in treatment group sample size was detected. Our sensitivity analyses indicate that the meta-analysis results are generally robust to excluding this trial and would suggest that biases are likely to be minimal. Only one of the four trials used double blinding (Mattson 1985). Further biases may therefore exist in these analyses particularly for the outcome 'time on allocated treatment' due to the a priori expectation that adverse effects are more likely with phenobarbitone which may have increased awareness and influenced the decision to withdraw from this drug.

With respect to controlling seizures, for time to 12-month remission the overall results suggest no advantage for either drug. Subgroup results find no statistical evidence of an interaction between seizure type and treatment, but do show a trend in favour of carbamazepine for generalized onset seizures, hazard ratio (HR) (with 95% confidence intervals (CIs)) of 0.61(95% CI 0.36 to 1.03), and no difference for partial onset seizures HR 1.03 (95% CI 0.72 to 1.49). Results for time to first seizure show no overall advantage for either drug. Subgroup analyses show a significant interaction between treatment and seizure type with phenobarbitone favoured for partial onset seizures, HR 0.71(95% CI 0.55 to 0.91), and a trend in favour of carbamazepine for generalized onset seizures, HR 1.50 (95% CI 0.95 to 2.35). Hence, for both seizure outcomes there is a trend in favour of carbamazepine for generalized onset seizures. This is unexpected given anecdotal evidence that carbamazepine may worsen generalized onset seizure types such as absence or myoclonus (Shields 1983; Snead 1985). For time to first seizure the significant advantage for phenobarbitone for treating partial onset seizures is also unexpected, given that current guidelines recommend carbamazepine as the drug of choice (SIGN 1997; Wallace 1997). Despite these interesting findings, the results do not provide robust evidence upon which to base a choice between these two drugs in terms of seizure control.

For time on allocated treatment, the overall hazard ratio adjusted for seizure type suggests that patients taking phenobarbitone are significantly more likely to have treatment withdrawn compared to patients taking carbamazepine, HR 1.63 (95% CI 1.23 to 2.15). A general trend towards favouring carbamazepine for this outcome is indicated for both seizure types. Given that results for the seizure outcomes do not find a clear advantage for either drug, the advantage for carbamazepine for treatment withdrawal indicates that this drug was better tolerated than phenobarbitone.

AUTHORS' CONCLUSIONS

Implications for practice

Overall we found a clear advantage for carbamazepine for time to treatment withdrawal indicating that this drug is significantly better tolerated than phenobarbitone. For the seizure outcomes we found trends in favour of phenobarbitone for partial onset seizures and carbamazepine for generalized onset seizures. These however do not provide reliable evidence upon which to base a choice. Hence, overall results indicate that of the two drugs investigated, carbamazepine would be the better choice for people with either partial or generalized onset seizure types. However, given reports of carbamazepine worsening certain seizure types, it is not considered a drug of first choice for individuals with a generalized seizure disorder.

Implications for research

Further trials would be required to investigate the relative effects of these drugs upon particular seizure types (eg partial versus generalized onset). However, given that we have clear evidence that phenobarbitone is less well tolerated, it is unlikely that trials recruiting newly diagnosed individuals will be undertaken.

ACKNOWLEDGEMENTS

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

The MRC Clinical Trials Unit, meta-analysis group, for the use of, and advice on, their SCHARP meta-analysis software application, which was developed in collaboration with the Istituto "Mario Negri", Milan.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

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: PHB = 15, CBZ = 15. 91% partial epilepsy in 3 drug groups; CBZ, PHB or PHY. 62% male in 3 drug groups. Age range: 18 to 51 years
Interventions	Monotherapy with PHB or CBZ. Daily dose: PHB = 300 mg/day, or CBZ = 1200 mg/day.
Outcomes	Behaviour outcomes. Adverse effects. seizure frequency.
Notes	Outcomes chosen for this review were not reported.

Risk of bias

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

Chen 1996

Methods	Randomly allocated by simple randomization of block size 3. Method of allocation concealment not stated. Unblinded
Participants	People with newly diagnosed onset seizures. Number randomized: PHB = 25; CBZ = 26. 54% partial epilepsy. 52% male. Age range: 7 to 15 years
Interventions	Monotherapy with PHB or CBZ. Dose achieved not stated.
Outcomes	Cognitive outcomes.
Notes	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 epielpsy. Number randomized: PHB = 30; CBZ = 30. 100% partial epilepsy. Percentage male and range of follow-up not mentioned. Age range: 18 to 40 years
Interventions	Monotherapy with PHB 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: PHB = 10; CBZ = 54. 53% partial epilepsy. 53% male. Age range: 3 to 16 years. Range of follow-up 3 to 88 (months)
Interventions	Monotherapy with PHB or CBZ. Median daily dose achieved: PHB = not stated; CBZ = 400 mg/day
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12-month remission from all seizures. Adverse effects.
Notes	6 of the first 10 children assigned to PHB had unacceptable adverse effects so no further children were assigned to PHB

Risk of bias

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

Feksi 1991

Methods	Allocation concealed using sealed opaque envelopes. Unblinded	
Participants	Previously largely untreated cases. Number randomized: PHB = 150; CBZ = 152. 38% partial epilepsy. 57% male. Age range: 6 to 65 years	
Interventions	Monotherapy with PHB or CBZ. Dose achieved not stated.	
Outcomes	Seizure activity during therapy. Adverse experiences.	
Notes	IPD made available but not used due to inconsistencies and problems with data provided	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Heller 1995

Methods	Allocation concealed using sealed opaque envelopes. Random list generated using random permuted blocks. Unblinded	
Participants	People with newly diagnosed epilepsy. Number randomized: PHB = 58; CBZ = 61. 41% partial epilepsy. 54% male. Age range: 13 to 60 years. Range of follow-up 1 to 91 months	
Interventions	Monotherapy with PHB or CBZ. Median daily dose achieved: PHB = 105 mg/day; CBZ = 600 mg/day	
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12-month remission from all seizures. Adverse effects.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mattson 1985

Methods	Method of generation of random list not stated. Allocation concealed using sealed envelopes. Double blind study achieved by providing additional blank tablet
Participants	People with previously untreated or under treated partial seizures. Number randomized: PHB = 155; CBZ = 154. 100% partial epilepsy. 88% male. Age range: 18 to 82 years. Range of follow-up 1 to 177 months

Mattson 1985 (*Continued*)

Interventions	Monotherapy with PHB or CBZ. Median daily dose achieved: PHB = 160 mg/day; CBZ = 800 mg/day
Outcomes	Participant retention (length of time participants continued to take randomized drug). Composite scores. Total seizure control. Seizure rates Incidence of adverse effects.
Notes	

Risk of bias

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

Mitchell 1987

Methods	Randomly allocated by stratified randomization scheme. Method of allocation concealment not stated. Double blind for psychometric tests
Participants	Children with newly diagnosed epilepsy. Number randomized: PHB = 18; CBZ = 15. 100% partial epilepsy. 61% male. Mean age 7 years
Interventions	Monotherapy with PHB or CBZ.
Outcomes	Cognitive outcome. Compliance. Seizure control at 6 months. Seizure control at 12 months.
Notes	Outcomes chosen for this review were not reported.

Risk of bias

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

Placencia 1993

Methods	Allocation concealed using sealed opaque envelopes (method not used for all participants). Unblinded
Participants	Previously largely untreated cases. Number randomized: PHB = 97; CBZ = 95. 68% partial epilepsy. 57% male. Age range: 2 to 68 years
Interventions	Monotherapy with PHB or CBZ.

Placencia 1993 (*Continued*)

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

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

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

Study	Reason for exclusion
Bird 1966	Unclear whether trial is randomized and unclear whether participants received either CBZ or PHB as monotherapy
Marjerrison 1968	Comparison between CBZ monotherapy and PHB monotherapy cannot be made
Meador 1990	Comparison between CBZ monotherapy and PHB 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

CBZ: carbamazepine
PHB: phenobarbitone

DATA AND ANALYSES

Comparison 1. Carbamazepine versus phenobarbitone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time on allocated treatment	4	674	Peto Odds Ratio (95% CI)	1.63 [1.23, 2.15]
1.1 Generalized seizures	3	155	Peto Odds Ratio (95% CI)	1.78 [0.87, 3.62]
1.2 Partial onset	4	519	Peto Odds Ratio (95% CI)	1.60 [1.18, 2.17]
2 Time to 12-month remission	4	680	Peto Odds Ratio (95% CI)	0.87 [0.65, 1.17]
2.1 Generalized seizures	3	157	Peto Odds Ratio (95% CI)	0.61 [0.36, 1.03]
2.2 Partial onset	4	523	Peto Odds Ratio (95% CI)	1.03 [0.72, 1.49]
3 Time to first seizure	4	680	Peto Odds Ratio (95% CI)	0.85 [0.68, 1.05]
3.1 Generalized seizures	3	157	Peto Odds Ratio (95% CI)	1.50 [0.95, 2.35]
3.2 Partial onset	4	523	Peto Odds Ratio (95% CI)	0.71 [0.55, 0.91]

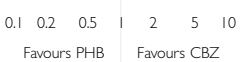
Analysis 1.1. Comparison 1 Carbamazepine versus phenobarbitone, Outcome 1 Time on allocated treatment.

Review: Carbamazepine versus phenobarbitone monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenobarbitone

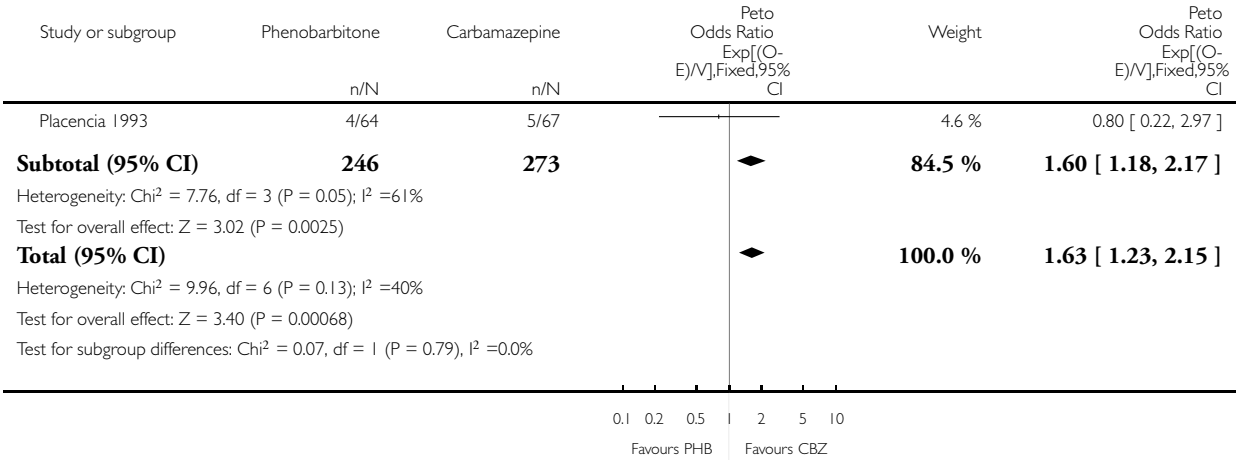
Outcome: 1 Time on allocated treatment

Study or subgroup	Phenobarbitone 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
1 Generalized seizures					
de Silva 1996	4/5	10/25		3.8 %	2.62 [0.62, 11.06]
Heller 1995	11/33	9/36		10.2 %	1.26 [0.52, 3.04]
Placencia 1993	3/30	0/26		1.5 %	6.55 [0.68, 63.00]
Subtotal (95% CI)	**68**	**87**		**15.5 %**	**1.78 [0.87, 3.62]**
Heterogeneity: Chi² = 2.14, df = 2 (P = 0.34); I² =6%					
Test for overall effect: Z = 1.58 (P = 0.11)					
2 Partial onset					
de Silva 1996	4/5	11/28		1.9 %	21.85 [2.93, 163.22]
Heller 1995	11/22	8/24		9.3 %	1.88 [0.75, 4.70]
Mattson 1985	79/155	56/154		68.6 %	1.52 [1.08, 2.13]



(*Continued* . . .)

(. . . *Continued*)

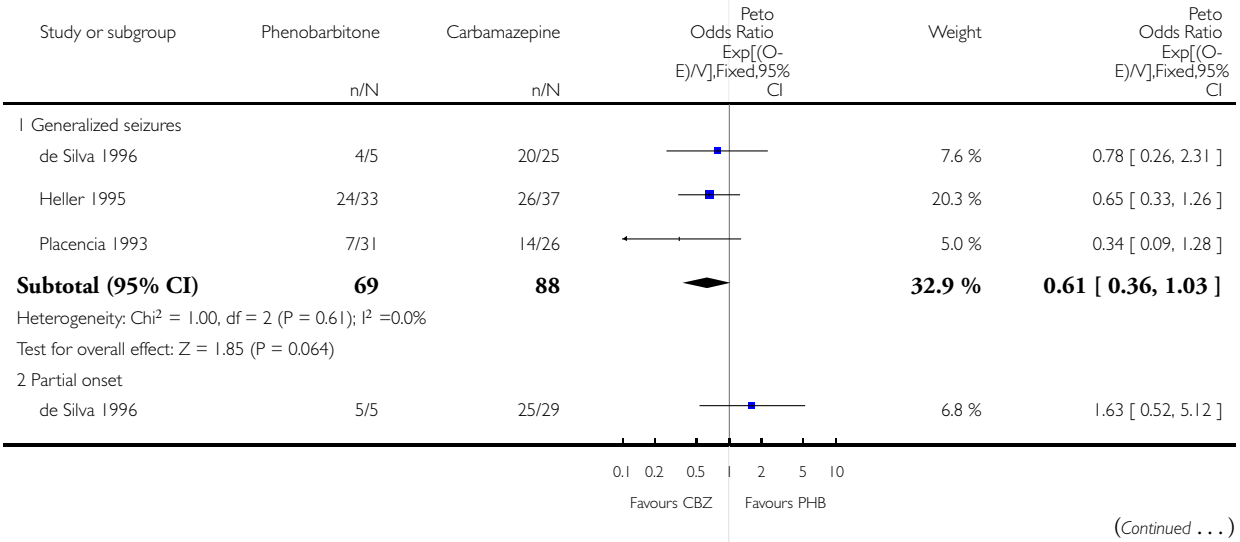


Analysis 1.2. Comparison 1 Carbamazepine versus phenobarbitone, Outcome 2 Time to 12-month remission.

Review: Carbamazepine versus phenobarbitone monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenobarbitone

Outcome: 2 Time to 12-month remission



(*Continued* . . .)

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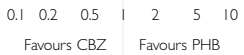
Study or subgroup	Phenobarbitone n/N	Carbamazepine n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Heller 1995	13/25	14/24		14.4 %	0.94 [0.43, 2.07]
Mattson 1985	40/155	49/154		35.6 %	0.68 [0.41, 1.12]
Placencia 1993	24/64	15/67		10.3 %	3.75 [1.48, 9.51]
Subtotal (95% CI)	**249**	**274**		**67.1 %**	**1.03 [0.72, 1.49]**
Heterogeneity: Chi² = 10.78, df = 3 (P = 0.01); I² =72%					
Test for overall effect: Z = 0.18 (P = 0.85)					
Total (95% CI)				**100.0 %**	**0.87 [0.65, 1.17]**
Heterogeneity: Chi² = 14.41, df = 6 (P = 0.03); I² =58%					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Chi² = 2.63, df = 1 (P = 0.11), I² =62%					

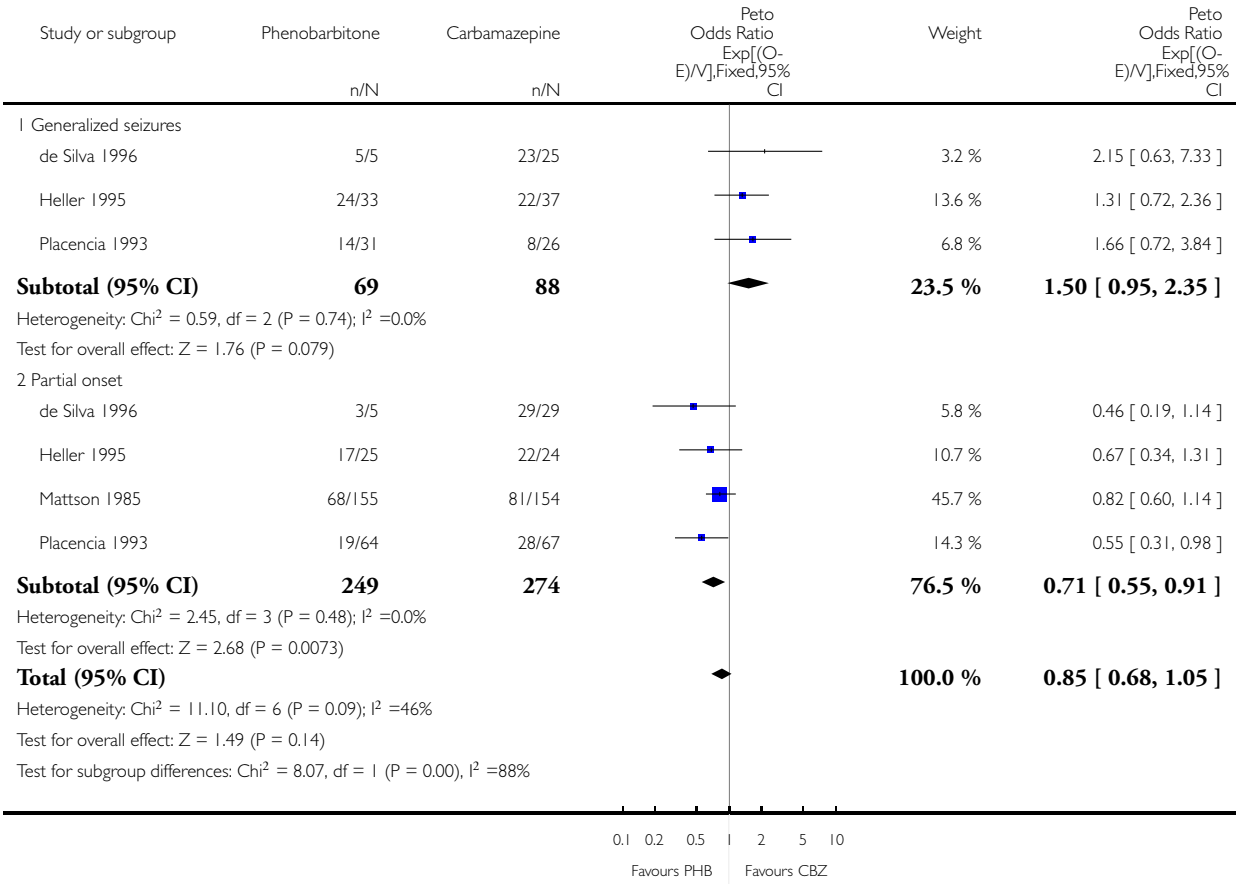


Analysis 1.3. Comparison 1 Carbamazepine versus phenobarbitone, Outcome 3 Time to first seizure.

Review: Carbamazepine versus phenobarbitone monotherapy for epilepsy

Comparison: 1 Carbamazepine versus phenobarbitone

Outcome: 3 Time to first seizure



ADDITIONAL TABLES

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

Trial	Outcomes reported	Summary of results
Chen 1996	1. IQ scores measured with WISC-R scale. 2. Time to complete the Bender-Gestalt test. 3. Auditory event related potentials	1. No significant differences. 2. No significant differences. 3. No significant difference.

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

Czapinski 1997	1. Proportion achieving 24 month remission at 3 years. 2. Proportion excluded after randomization due to adverse effects or no efficacy	PHB CBZ 60% 62% 33% 30%
Feksi 1991	1. Proportion of withdrawals before 12 months. 2. Seizure activity during therapy (patients completing 12 months follow up): seizure free decreased frequency no change in seizure frequency increased frequency 3. Adverse experiences (for patients completing 12 months follow-up): Proportion of patients Number of reported events	PHB CBZ 18% 17% 54% 52% 23% 29% 15% 13% 8% 6% 47% 37% 86 68
Mitchell 1987	1. Behaviour 2. Seizure control	1. No significant difference 2. No significant difference
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. CBZ was equal in efficacy to PHB in controlling seizure frequency and side effects were minimal

Table 2. Number of patients contributing to each analysis

Trial	Number randomised	Time to withdrawal	Time to 12 month	Time to 1st seizure
de Silva 1996	Total=64 PHB=10; CBZ=54	Total=63 PHB=10; CBZ=53	Total=64 PHB=10; CBZ=54	Total=64 PHB=10; CBZ=54
Heller 1995	Total=119 PHB=58; CBZ=61	Total=115 PHB=55; CBZ=60	Total=119 PHB=58; CBZ=61	Total=119 PHB=58; CBZ=61
Mattson 1985	Total=309 PHB=155; CBZ=154	Total=309 PHB=155; CBZ=154	Total=309 PHB=155; CBZ=154	Total=309 PHB=155; CBZ=154
Placencia 1993	Total=192 PHB=97; CBZ=95	Total=187 PHB=94; CBZ=93	Total=188 PHB=95; CBZ=93	Total=188 PHB=95; CBZ=93

Table 3. Results of Logrank analysis (heterogeneity, overall effect and interaction)

Test for:	Statistic:	Time to withdrawal	Time to 12 month	Time to 1st seizure
Heterogeneity	Chi square	(df=3) 5.54	(df=3) 4.04	(df=3) 1.08
	p-value	0.14	0.26	0.78

Table 3. Results of Logrank analysis (heterogeneity, overall effect and interaction) (*Continued*)

Overall effect	Chi square	(df=1) 11.44	(df=1) 0.86	(df=1) 2.06
	p-value	0.001	0.35	0.15
Interaction between treatment and seizure type	Chi square	(df=1) 0.07	(df=1) 2.63	(df=1) 8.07
	p-value	0.79	0.11	0.004
Overall Hazard Ratio (95% CI) adjusted for seizure type		1.63 (1.23 to 2.15)	0.87 (0.65 to 1.17)	0.85 (0.68 to 1.05)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 (phenobarbit*)
#2 MeSH descriptor Phenobarbital 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. exp Clinical Trials/
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. phenobarbit$.tw. or exp Phenobarbital/
19. carbamazepin$.tw.
20. exp Carbamazepine/
21. 18 and (19 or 20)
22. (epilep$ or seizure$ or convulsion$).tw.
23. exp Epilepsy/
24. exp Seizures/
25. 22 or 23 or 24
26. 21 and 25
27. 26 and 17

WHAT'S NEW

Last assessed as up-to-date: 30 September 2006.

Date	Event	Description
12 August 2009	Amended	Copyedits made at editorial base.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 1, 2003

Date	Event	Description
24 September 2008	Amended	Converted to new review format.
1 October 2006	New search has been performed	We re-ran our searches on 1st October 2006; no new studies were 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.

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

DECLARATIONS OF INTEREST

None known to the reviewers.

SOURCES OF SUPPORT

Internal sources

- NHS Research & Development Programme, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans