Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures (Review)

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[Intervention Review]

Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures

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ABSTRACT

Background

Phenytoin and valproate are commonly used antiepileptic drugs. It is generally believed that phenytoin is more effective for partial onset seizures, or generalized onset seizures with or without other generalized seizure types.

Objectives

To review the best evidence comparing phenytoin and valproate 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 (July 2007), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2007) and MEDLINE (1966 to July 2007). No language restrictions were imposed. We also contacted pharmaceutical companies and researchers in the field.

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 phenytoin monotherapy with valproate 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 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

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met our inclusion criteria. One important limitation is that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow up. Hence results apply only to generalized tonic-clonic seizures. The main overall results were as follows (HR, HR greater than one indicates a clinical advantage for phenytoin for both remission outcomes and a clinical advantage for valproate for the outcomes time to withdrawal and time to first seizure): (a) time to withdrawal of allocated treatment 1.10 (95% CI 0.79 to 1.54); (b) time to 12 month remission 1.04 (95% CI 0.78 to 1.38); (c) time to six month remission 0.89 (95% CI 0.71 to 1.11) and (d) time to first seizure 0.92 (95% CI 0.74 to 1.14). The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found.

Authors' conclusions

We have not found evidence that a significant difference exists between phenytoin and valproate for the outcomes examined in this review. Results do not apply to absence or myoclonus. No outright evidence was found to support or overthrow current treatment policies.

PLAIN LANGUAGE SUMMARY

Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures

No evidence to suggest any difference between the drugs phenytoin and valproate for the seizure types studied.

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Phenytoin and valproate are commonly used antiepileptic drugs. The review of trials found no difference between these two drugs for the seizure types studied. The review also found no evidence to support the policy of using valproate for generalized onset tonic-clonic seizures and phenytoin for partial onset seizures. We were unable to address the issue of preferring valproate for generalized onset seizure types other than tonic-clonic.

BACKGROUND

Phenytoin and valproate are commonly used antiepileptic drugs. Phenytoin is used as a first line drug in low and middle income countries since it is cheaper and can be given as a single daily dose. It is generally believed that valproate monotherapy is more effective than phenytoin monotherapy in generalized onset seizures (generalized tonic-clonic seizures, absence and myoclonus) while phenytoin monotherapy is more effective than valproate monotherapy in partial onset seizures (simple partial, complex partial and secondary generalized tonic-clonic seizures) (Chadwick 1994) although there is no hard evidence from individual randomized controlled trials to support this belief. Evidence in favour of valproate for generalized seizures comes predominantly from observational studies, suggesting a dramatic benefit with valproate in people with juvenile myoclonic epilepsy (Delgado-Escueta 1984; Penry 1989), and reports of efficacy of valproate against absence seizures (Bourgeois 1987; Jeavons 1977). Some animal models have suggested that phenytoin has either no effect in absence seizures or may in fact worsen seizures (Liporace 1994). There is also anecdotal evidence that phenytoin may cause paradoxical intoxication (increased seizure frequency with increased anticonvulsant dose) and encephalopathy (Troupin 1975; Vallarta 1974). Even if we accept that phenytoin should not be a drug of first choice for people experiencing absence, myoclonic and atonic seizures, we still have insufficient evidence from randomized controlled trials to guide a choice between phenytoin and valproate for people with generalized onset tonic-clonic seizures or people with partial onset seizures. We have therefore undertaken this systematic review and meta-analysis of existing relevant randomized controlled trials.

In this review the important outcomes recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Commission 1998) require analysis of time to event data (eg. time to 12 month remission). Although methods have been developed to synthesize survival type data using summary information (Parmar 1998), the majority of eligible trials had not reported sufficient information for the subgroups of in-

terest, therefore we collected individual patient data (original data collected for each participant from each trial).

The use of individual patient data should also help 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 particularly interested in the interaction between seizure type and treatment, but not all trials have reported separate results for people with partial onset 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 phenytoin compared to valproate when used as monotherapy in people 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 valproate in people with epilepsy.
(2) The studies may be double blind, single blind or unblinded.
(3) The studies should have either adequate or quasi methods (eg. 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) People treated with monotherapy.

Types of interventions

Phenytoin or valproate 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. Participants achieved this outcome if allocated treatment was withdrawn for poor seizure control, adverse effects, non-compliance or if additional add-on treatment was initiated (ie. allocated treatment had failed). This is a combined outcome reflecting both efficacy and tolerability and is an outcome to which the individual makes a contribution. It 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.
(5) Quality of life measures if available.

Search methods for identification of studies

We searched the Epilepsy Group's Specialized Register (27 July 2007). 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 3, 2007) using the search term 'phenytoin and valproate (or sodium valproate or valproic acid)' as free text and MeSH terms.
(b)MEDLINE (Ovid) (1966 - July 2007) using the search strategy outlined in Appendix 1.
(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 Sanofi (manufacturers of valproate in Europe), Abbott (manufacturers of valproate in the USA), Parke-Davis (manufacturers of phenytoin), and original investigators of relevant trials found.

Data collection and analysis

Trial assessment and data collection

All trials identified by the search strategy were assessed for inclusion independently by two review authors (Catrin Tudur Smith and Tony Marson). We then undertook a feasibility study, writing to original authors asking whether they would collaborate with an individual patient data (IPD) meta-analysis, and whether data from their trial could be made available. The response was favourable, and we proceeded to ask for the following participant data for each trial: date of randomization; drug allocated and dose; age; sex; presence of neurological signs; seizure types at randomization; number of seizures prior to 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 reason 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 individual patient data were not obtained, one review author (Catrin Tudur Smith) assessed whether sufficient aggregate data for the outcomes of interest had been reported.

Data checking

For each trial where individual patient data were supplied the following checks were performed.

(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

For three trials (Craig 1994; Ramsay 1992; Turnbull 1985) seizure data were provided in terms of the number of seizures recorded between clinic visits. Linear interpolation was applied to approximate the dates on which seizures occurred. 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. Time to six and 12 month remission was calculated from the date of randomization to the 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.

Withdrawal data were not available for one trial (Craig 1994). For two trials (Heller 1995; de Silva 1996) dates 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 either the withdrawal of allocated treatment due to poor seizure control or adverse 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 participants 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 hazard ratios (with 95% confidence intervals). We used the information provided by the stratified logrank test to investigate the main effects of drug and covariates, drug-covariate interactions and heterogeneity between trials (EBCTCG 1990).

(3) Due to the strong clinical belief that valproate is more effective in generalized onset seizures while phenytoin is more effective in partial onset seizures, all analyses are stratified by seizure type (partial onset versus generalized onset), according to the classification given by the original trialists at randomization.

(4) As misclassification of seizure type is a recognized problem in epilepsy, we investigated its potential impact on the results in a sensitivity analysis.

Results are expressed as a hazard ratio (HR) and 95% confidence interval, 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 valproate (eg. HR = 1.1 would suggest a 10% increase in risk of withdrawal from phenytoin compared to valproate) 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.

A total of 15 trial reports in which individuals had been randomized to phenytoin or valproate were identified as eligible. Due to duplicate publications (Berg 1993; Shakir 1980; Tallis 1994; Wilder 1983a), there were in fact only 11 relevant trials (Callaghan 1985; Craig 1994; Czapinski 1997; Forsythe 1991; Heller 1995; Ramsay 1992; Rastogi 1991; Shakir 1981; de Silva 1996; Thilothammal 1996; Turnbull 1985).

Individual patient data were no longer available for five of these trials (Callaghan 1985; Forsythe 1991; Rastogi 1991; Shakir 1981; Thilothammal 1996) in which a total of 392 individuals had been randomized to either phenytoin or valproate. None of these five trials reported the specific time-to-event outcomes chosen for this systematic review. One recently completed study, only published in abstract form (Czapinski 1997), randomized 60 individuals with partial onset seizures to either phenytoin or valproate. At the time of writing, individual patient data have been pledged, but not received. Although none of these trials analysed the outcomes investigated in this systematic review, two trials (Forsythe 1991; Shakir 1981) presented individual patient data relating to time at which allocated drug was withdrawn and reason for withdrawal in the trial publication. Hence, these two trials could be incorporated into the analysis of time to withdrawal of allocated treatment. Individual level or aggregate data could not be obtained from the trial publication in any other trial. Full details of outcomes considered and summary of results in each trial for which individual patient data were not available can be found in Table 1.

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

Of the five trials for which individual patient data were provided, one recruited individuals of all ages (Ramsay 1992), one recruited children only (de Silva 1996), two recruited adults only (Heller 1995; Turnbull 1985) and one trial recruited elderly people (Craig 1994). Newly diagnosed people were recruited in all five trials.

One trial (Ramsay 1992) recruited only people with generalized onset tonic-clonic seizures, some of whom were experiencing other generalized seizure types such as absence or myoclonus. All generalized seizure types were recorded during follow up for this trial. The remaining four trials recruited people with partial onset seizures (simple/complex partial or secondarily generalized tonic-clonic) and people with generalized onset tonic-clonic seizures. For the people with generalized onset tonic-clonic seizures recruited into these four trials, other generalized seizure types were not recorded during follow up. As a result, the majority of the data from the five trials does not address the treatment of generalized seizure types such as absence or myoclonus but applies only to generalized onset tonic-clonic seizures. In our analysis the most consistent approach was to use only the data for generalized onset tonic-clonic seizures. We also report a sensitivity analysis which includes data on all generalized seizure types from Ramsay 1992.

Data were available for the following participant 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 (79%); time since first seizure to randomization (73%). EEG data had been recorded for all five trials, but only computerized in two trials (Craig 1994; Turnbull 1985;). Similar difficulties were encountered with CT/MRI data, and neurological examination findings.

Risk of bias in included studies

(1) Trials for which individual patient data were provided

Four trials used adequate methods of concealment of randomization, one used minimization (Craig 1994) and three used sealed opaque envelopes (Heller 1995; de Silva 1996; Turnbull 1985). The method of concealment was not mentioned in the fifth trial. In one trial the main investigator conducting cognitive function testing was blind to the medication participants were receiving (Craig 1994) and the remainder were not blinded.

(2) Trials for which no individual patient data were available

One trial (Forsythe 1991) used quota allocation which was considered an inadequate method of concealment as the choice of allocation is usually left to the interviewer subject to 'quota controls'. The trial by Callaghan 1985 used an independent person to carry out the randomization, and telephone randomization was used by Shakir 1981. Both methods of concealment of allocation were considered adequate. The method of concealment was not mentioned in the three remaining trials.

One trial was double blinded (Thilothammal 1996), one was single blinded (Forsythe 1991) and the remaining trials were unblinded. For further details, *see* table of 'characteristics of included studies'.

Effects of interventions

Details regarding the number of individuals 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 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 can be found on the Cochrane Epilepsy Group website at http://www.epilepsy.cochrane.org/Files/phenval.pdf.

(1) Time to withdrawal of allocated treatment

- For this outcome, a HR greater than one indicates a clinical advantage for valproate.
- Time to withdrawal of allocated treatment and reason for withdrawal were available for 494 individuals from four trials

(74% of individuals from five trials providing individual patient data). Withdrawal data are currently not available for the fifth trial (Craig 1994). Sufficient IPD were available in the trial publications for a further 74 individuals from two trials (Forsythe 1991; Shakir 1981). Therefore a total of 568 individuals from six trials were potentially available for the analysis of this outcome. However, the IPD extracted from the Forsythe 1991 publication were not stratified by seizure type, thus could not be included in the meta-analysis stratified by seizure type.

- A sensitivity analysis was undertaken (i) including six trials not stratified by seizure type, and (ii) including five trials stratified by seizure type.
- The overall pooled HR for these analyses were (i) 1.10 (95% CI 0.80 to 1.51) and (ii) 1.10 (95% CI 0.79 to 1.54). Due to the similarity of these results, we will focus on the second analysis (stratified by seizure type) which includes 527 individuals from five trials.
- There was no evidence of statistical heterogeneity between trials (chi squared = 6.40, df = 4, p = 0.171).
- For people with generalized seizures (341), the pooled HR was 0.98 (95% CI 0.60 to 1.58) indicating no clear advantage for either drug. For people with partial onset seizures (186), the pooled HR was 1.23 (95% CI 0.77 to 1.98) suggesting a potentially important advantage for valproate. Overall, the pooled HR (adjusted for seizure type) was 1.10 (95% CI 0.79 to 1.54) suggesting a potential overall advantage for valproate.
- No interaction between treatment and seizure type (generalized versus partial onset) was found (chi squared = 0.47, df = 1, p = 0.50).

(2) Time to achieve 12 month remission

- For this outcome, a HR greater than one indicates a clinical advantage for phenytoin.
- Data for 514 individuals (77% of those providing IPD) from four trials were available for the analysis of this outcome. Individuals were only followed up for six months in the fifth trial (Ramsay 1992), therefore time to achieve 12 month remission could not be calculated.
- There was no evidence of statistical heterogeneity between trials (chi squared = 0.52, df = 3, p = 0.915).
- For people with generalized seizures (270), the pooled HR was 1.06 (95% CI 0.71 to 1.57) indicating no clear advantage for either drug. For people with partial onset seizures (244), the pooled HR was 1.02 (95% CI 0.68 to 1.54) indicating no clear advantage for either drug. Overall, the pooled HR (adjusted for seizure type) was 1.04 (95% CI 0.78 to 1.38) suggesting no clear clinical advantage for either drug.
- No interaction between treatment and seizure type was found (chi squared = 0.02, df = 1, p = 0.903).

(3) Time to achieve six month remission

- For this outcome, a HR greater than one indicates a clinical advantage for phenytoin.
- Data for 639 individuals (96% of those providing IPD) from five trials were available for the analysis of this outcome.
- The most compatible analysis including only generalized tonic-clonic seizures produced the following results: for people with generalized seizures (395), the pooled HR was 0.80 (95% CI 0.59 to 1.08), suggesting a potentially important advantage for valproate. For people with partial onset seizures (244), the pooled HR was 1.02 (95% CI 0.73 to 1.43) indicating no clear advantage for either drug. Overall, the pooled HR (adjusted for seizure type) was 0.89 (95% CI 0.71 to 1.11) suggesting a potential overall advantage for valproate.
- A sensitivity analysis including generalized seizures of all types (only recorded in Ramsay 1992) produced the following results: for people with generalized seizures, the pooled HR was 0.84 (95% CI 0.62 to 1.14), suggesting a potentially important advantage for valproate. For people with partial onset seizures, the pooled HR was 1.02 (95% CI 0.73 to 1.43) indicating no clear advantage for either drug. Overall, the pooled HR (adjusted for seizure type) was 0.92 (95% CI 0.73 to 1.15), suggesting a potential overall advantage for valproate.
- By including only generalized tonic-clonic seizure types in the trial by Ramsay 1992, a slightly greater advantage for valproate emerges. As the overall results from both analyses are similar, we will focus on the most compatible analysis which includes only generalized tonic-clonic seizures in all trials.
- There was no evidence of statistical heterogeneity between trials (chi squared = 2.92, df = 4, p = 0.572).
- No interaction between treatment and seizure type was found (chi squared = 1.15, df = 1, p = 0.284).

(4) Time to first seizure post randomization

- For this outcome, a HR greater than one indicates a clinical advantage for valproate.
- Data for 639 individuals (96% of those providing IPD) from five trials were available for the analysis of this outcome.
- The most compatible analysis including only generalized tonic-clonic seizures produced the following results: for people with generalized seizures (395), the pooled HR was 1.03 (95% CI 0.77 to 1.39) indicating no clear advantage for either drug. For people with partial onset seizures (244), the pooled HR was 0.81 (95% CI 0.59 to 1.11) suggesting a potentially important advantage for phenytoin. Overall, the pooled HR (adjusted for seizure type) was 0.92 (95% CI 0.74 to 1.14) suggesting a potential overall advantage for phenytoin.
- A sensitivity analysis including generalized seizures of all types (only recorded in Ramsay 1992) produced the following results: for people with generalized seizures, the pooled HR was 1.05 (95% CI 0.79 to 1.40), indicating no clear advantage for either drug. For people with partial onset seizures, the pooled HR was 0.81(95% CI 0.59 to 1.10), suggesting a potentially important advantage for phenytoin. Overall, the pooled HR (adjusted for seizure type) was 0.93 (95% CI 0.75 to 1.15), suggesting a potential overall advantage for phenytoin.

- Due to the similarity in results from both analyses, we focussed on the most compatible analysis which includes only generalized tonic-clonic seizures in all trials.
- There was no evidence of statistical heterogeneity between trials (chi squared = 4.24, df = 4, p = 0.375).
- No interaction between treatment and seizure type was found (chi squared = 1.25, df = 1, p = 0.264).

(5) Quality of life measures

Quality of life measures were not recorded in any trial; therefore, they could not be examined.

(6) Misclassification of seizure type

Evidence of an interaction between treatment and seizure type was not found in any analysis. This result is surprising given the strong clinical impression that valproate is more effective in generalized onset seizures while phenytoin is more effective in partial onset seizures. The impression that valproate is better for generalized seizures may derive from its effects on generalized seizures other than tonic-clonic, but as already outlined, we were unable to investigate these seizure types in this review. Misclassification of seizure type (whereby some people with generalized seizures have been mistakenly classed as having partial onset seizures, and vice-versa) is a well recognized problem in epilepsy and it may be that an interaction between treatment and seizure type has been masked because of this. Given clinical evidence that people with generalized onset seizures are unlikely to have an 'age at onset' greater than between 25 and 30 years (Malafosse 1994), we examined the distribution of age at onset for people with generalized seizures. This revealed that a substantial number of people classified as having generalized seizures had age at onset over 30 years (percentages were 100% (Craig 1994); 18% (Ramsay 1992); 45% (Turnbull 1985); 40% (Heller 1995); 0% (de Silva 1996 (paediatric study)); suggesting that a significant number of individuals may have been misclassified as having generalized onset seizures. Such a misclassification would tend to bias our results against finding an interaction between treatment and broad seizure types (partial versus generalized onset). This could explain why we have not found strong evidence to support the clinical impression that such an interaction exists and we elected to investigate this further.

We undertook the following two analyses to investigate misclassification further:

(i) we reclassified all individuals with generalized seizures and age at onset greater than 30 into an 'uncertain seizure type' group;

(ii) individuals with generalized seizures and age at onset greater than 30 were reclassified as having partial onset seizures.

The results for each outcome are summarized in Table 4 (due to space limitations in this table, the term 'partial' is used to denote partial onset seizures). For the outcome time to first seizure, removing individuals from the generalized seizure group thought to have been misclassified, results in a more obvious interaction between treatment and seizure type. The direction of effect for the 'uncertain seizure type' subgroup is similar to that of the partial onset subgroup. Valproate appears even more effective in generalized onset seizures when compared to the original analysis. For time to withdrawal of allocated treatment, reclassifying individuals does not provide stronger evidence of an interaction. In addition, results for the 'uncertain seizure type' subgroup are substantially different from estimates for partial and generalized onset seizure groups. The results for time to six or 12 month remission are very similar regardless of whether individuals have been reclassified or not.

Re-defining seizure type on the basis of age of onset provides evidence for an interaction between treatment and seizure type for the outcome time to first seizure only. In a review comparing carbamazepine and valproate monotherapy for epilepsy (Marson 2000), a similar investigation of seizure type misclassification was undertaken. For the outcome time to 12 month remission, re-defining seizure type on the basis of age of onset provided evidence for an interaction between seizure type and treatment for that outcome. In that review however, a significant interaction between age at onset and treatment was also found for time to first seizure. There were therefore two potential explanations for the interaction found when people were reclassified according to age of onset. Firstly, misclassification had obscured the interaction between treatment and seizure type in the primary analyses, but reclassifying individuals according to age of onset has reduced the bias caused by misclassification. Alternatively, age at onset was acting as an independent predictor of outcome, and the misclassification analysis using age of onset forced the results to reflect this. For the review presented here comparing phenytoin and valproate, there was insufficient evidence to suggest an interaction between age at onset and treatment (http://www.epilepsy.cochrane.org/Documents/phenval.pdf). As a result, the hypothesis that age at onset is an independent predictor of outcome proposed in the carbamazepine versus valproate review has not been confirmed here.

DISCUSSION

We have gratefully received individual patient data (IPD) from the authors of five trials (669 individuals) which included a comparison of phenytoin with valproate for the treatment of epilepsy. Although 11 trials were identified as eligible, 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.

An important limitation is that, of the five trials providing full IPD, only one trial (Ramsay 1992) collected data on generalized seizure types other than generalized tonic-clonic seizures. Hence, the results for seizure outcomes (time to remission and first seizure), apply only to generalized tonic-clonic seizures, despite the fact that individuals may have been experiencing other generalized seizure types. This problem must be addressed in future trials.

We have failed to demonstrate a statistically significant effect in favour of either valproate 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, particularly when results for generalized and partial onset seizure subgroups are examined.

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 phenytoin and valproate, the confidence intervals are too wide to confirm equivalence.

Examining the subgroup analyses for trends shows inconsistent results. For the global outcome time to treatment withdrawal, estimates indicate a potentially important advantage for valproate for partial onset seizures with no clear advantage for either drug for generalized tonic-clonic seizures, which goes against current practice and belief. Trends for the purer efficacy outcomes are more in keeping with current practice. For time to six month remission, estimates favour valproate for generalized tonic-clonic seizures, with no clear trend for partial onset seizures. For time to 12 month remission there are no clear trends. For time to first seizure, there is a trend in favour of phenytoin for partial onset seizures, with no clear trend for generalized tonic-clonic seizures.

Despite a strong prior clinical impression that valproate is more effective in generalized seizures while phenytoin is more effective in partial onset seizures, we have failed to detect a significant interaction between treatment and seizure type for any outcome to support current practice. It must however be understood that the confidence intervals around estimates are wide, and these results do not exclude the possibility of important differences existing.

So why have we failed to find an interaction between drug and seizure type? It may well be that an interaction does not exist. Alternatively, it may be that an interaction does exist but we have failed to detect it. We suggest the following reasons why this might have occurred.

(1) Our meta-analysis may not have the statistical power needed to detect an interaction.

(2) Generalized tonic-clonic seizures were the only generalized seizure type contributing to the main analyses. It may be that there is no difference between phenytoin and valproate for control of this seizure type, but important differences could exist for absence and myoclonus seizure types. However, were this the case, we might have expected to see a treatment-seizure type interaction for the outcome time to treatment withdrawal if treatment were being withdrawn or a further drug added to combat other seizure types.

(3) Due to the strong clinical impression that valproate is the treatment of choice for people with myoclonus and absence seizures, physicians may have been reluctant to randomize individuals with epilepsy syndromes particularly responsive to valproate into these studies (eg. juvenile myoclonic epilepsy). This seems unlikely given that recruitment for those studies recruiting individuals with generalized tonic-clonic seizures took place some time before such beliefs became widely held in the UK.

(4) The results of the original studies and hence this meta-analysis may have been confounded by classification bias, ie. individuals with partial onset seizures may have been misclassified as having generalized seizures and vice versa. There is good evidence from a similar review comparing carbamazepine and valproate that misclassification is indeed an important issue in epilepsy trials (Marson 2000). The most striking indication that misclassification may be a problem for the current review is the classification of subjects in Craig 1994. In this study, over half of the recruited individuals were classified as having a generalized epilepsy, which seems unlikely, given that the individuals were newly diagnosed and over the age of 65. It is also interesting to note that Ramsay 1992 report the only trial in this review that attempted to recruit only people with generalized tonic-clonic seizures. This trial recruited too few individuals to have the power to detect a difference between phenytoin and valproate. For a subgroup of individuals with definite EEG changes to support a diagnosis of an idiopathic generalized epilepsy, there appeared to be a greater (but not significant) advantage for valproate. This could again be interpreted as supporting the potential for misclassification confounding an interaction between treatment and seizure type. We were unable to test for the effects of EEG changes on the interaction between treatment and seizure type due to EEG data not being collected for all studies, and even where it was, it was not done in a uniform way. It is worth pointing out that these studies were initiated before the publication of the International League Against Epilepsy Classification of Epileptic Syndromes in 1989 (Commission 1989). However, they did use the International League Against Epilepsy Classification of Epileptic Seizures that was published in 1981(Commission 1981), which does allow individuals to be classified as those with partial onset or generalized seizures. The age of onset distribution of people classified as having generalized seizures indicates misclassification is likely to have occurred. However, our results based on reclassifying a group of potentially misclassified individuals indicate that classification bias is only a potentially important confounder of the results of this study for the outcome time to first seizure. The issue of misclassification must be addressed in future trials.

Finally, it should be mentioned that the preparation of valproate used in the included studies may have influenced the results. The trials conducted in the UK (Craig 1994; de Silva 1996; Heller 1995; Turnbull 1985) all used sodium valproate (Epilim). Ramsay 1992 used valproic acid (Depakene) which is thought to cause more gastrointestinal side effects than preparations containing ei-

ther a mixture of sodium valproate and valproic acid, or preparations containing sodium valproate alone. There is however no evidence from randomized controlled trials to support this, but there are some data from observational studies (Brasfield 1999; Cranor 1997; Wilder 1983a). Given that this meta-analysis and a similar meta-analysis comparing valproate and carbamazepine (Marson 2000) have failed to find convincing evidence of differences in effect between different drugs, it seems unlikely that differing preparations of the same drug are likely to have a major effect.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review do not provide hard evidence to overthrow or support the current practice of using valproate for people with generalized onset tonic-clonic seizures and phenytoin for people with partial onset seizures.

Implications for research

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

If future studies are to detect whether particular antiepileptic drugs are to be preferred for certain epilepsy syndromes they will need to be designed and powered accordingly. One approach would be to conduct trials that recruit only individuals with specific epilepsy syndromes. However, an approach more likely to reflect and inform clinical practice, as well as being statistically more powerful would be to recruit heterogeneous populations for whom epilepsy syndromes have been adequately defined, with testing for interaction between treatment and epilepsy syndrome. In view of potential problems of misclassification, syndromes will have to be well defined, adequate checking mechanisms will be required to ensure that classifications are accurate, and a system to recognize uncertainty is necessary for subjects about whom this exists.

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

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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**:639–44.

Craig 1994 *{published data only}*
Craig I, Tallis R. Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study. *Epilepsia* 1994;**35**(2): 381–90.

Czapinski 1997 *{unpublished 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 BGR, 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 RDC, Crawford P, Chadwick DW, 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**:44–50.

Ramsay 1992 ***{published data only}***
Ramsay RE, Wilder BJ, Murphy JV, Holmes GL, Uthman B, Slater J, et al.Efficacy and safety of valproic acid versus phenytoin as sole therapy for newly diagnosed primary generalized tonic-clonic seizures. *Journal of Epilepsy* 1992;**5** (1):55–60.

Rastogi 1991 ***{published data only}***
Rastogi P, Mehrotra TN, Agarwala RK, Singh VS. Comparison of sodium valproate and phenytoin as single drug treatment in generalised and partial epilepsy. *Journal of the Association of Physicians of India* 1991;**39**(8):606–7.

Shakir 1981 ***{published data only}***
Shakir RA, Johnson RH, Lambie DG, Melville ID, Nanda RN. Comparison of sodium valproate and phenytoin as single drug treatment in epilepsy. *Epilepsia* 1981;**22**:27–33.

Thilothammal 1996 ***{published data only}***
Thilothammal N, Banu K, Ratnam RS. Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. *Indian Pediatrics* 1996;**33**: 549–55.

Turnbull 1985 ***{published data only}***
Turnbull DM, Howel D, Rawlins MD, Chadwick DW. Which drug for the adult epileptic patient: phenytoin or valproate?. *British Medical Journal* 1985;**290**:815–9.

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.

Shakir 1980 ***{published data only}***
Shakir RA. Sodium valproate, phenytoin and carbamazepine as sole anticonvulsants. *Royal Society of Medicine International Congress and Symposium No.30* 1980:7–16.

Tallis 1994 ***{published data only}***
* Tallis R, Easter D. Multicenter comparative trial of Valproate and Phenytoin. *Epilepsia* 1994;**35**(Suppl 7):62.

Wilder 1983 ***{published data only}***
Wilder BJ, Ramsay RE, Murphy JV, et al.Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;**33**:1474–6.

References to studies awaiting assessment

Misra 2006 ***{published data only}***
Misra UK, Kalita J, Patel R. Sodium valproate versus phenytoin in status epilepticus: a pilot study. *Neurology* 2006;**67**(2):340–2.

Additional references

Bodensteiner 1988
Bodensteiner JB, Bronsworth RD, Knapik JR, et al.Interobserver variability in the ILAE classification of seizures in childhood. *Epilepsia* 1988;**29**(2):123–8.

Bourgeois 1987
Bourgeois B, Beaumanoir A, Blajev B, Cruz ND, Despland PA, Egli M, et al.Monotherapy with valproate in primary generalized epilepsies. *Epilepsia* 1987;**28**(Suppl 2):S8–11.

Brasfield 1999
Brasfield KH. Pilot study of divalproex sodium valproate versus valproic acid: drug acquisition costs versus all related costs. *Current Therapeutic Research* 1999;**60**(3):138–44.

Chadwick 1994
Chadwick DW. Valproate in the treatment of partial epilepsies. *Epilepsia* 1994;**35**(5):S96–8.

Commission 1981
Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;**22**(4):489–501.

Commission 1989
Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**(4):389–99.

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.

Cranor 1997
Cranor CW, Sawyer WT, Carson SW, Early JJ. Clinical and economic impact of replacing divalproex sodium with valproic acid. *American Journal of Health-System Pharmacy* 1997;**54**:1716–22.

Delgado-Escueta 1984
Delgado-Escueta AV, Enrile-Bascal F. Juvenile myoclonic epilepsy of Janz. *Neurology* 1984;**34**(3):285–94.

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

Higgins 2005
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. *Cochrane Database of Systematic Reviews* 2005, Issue 2.

Jeavons 1977
Jeavons PM. Choice of drug therapy in epilepsy. *Practitioner* 1977;**219**:542–56.

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. *Epilepsia* 1994;**35**(5):1026–8.

Malafosse 1994
Malafosse A, Genton P, Hirsch E, Marescaux C, Broglin D, Bernasconi R. *Idiopathic Generalised Epilepsies: Clinical, Experimental and Genetic*. Eastleigh: John Libbey and Company, 1994. [: 0861964365]

Marson 2000
Marson AG, Williamson PR, Hutton JL, Clough HE, Chadwick DW, on behalf of the epilepsy monotherapy trialists. Carbamazepine versus valproate monotherapy for epilepsy. *Cochrane Database of Systematic Reviews* 2000, Issue 3.[Art. No.: CD001030. DOI: 10.1002/14651858.CD001030]

Ottman 1993
Ottman R, Lee JH, Hauser WA, et al.Reliability of seizure classification using a semi structured interview. *Neurology* 1993;**43**(12):2526–30.

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

Penry 1989
Penry JK, Dean JC, Riela AR. Juvenile myoclonic epilepsy: long term response to therapy. *Epilepsia* 1989;**30 suppl 4**:S19–23.

Troupin 1975
Troupin AS, Ojemann LM. Paradoxical intoxication - a complication of anticonvulsant administration. *Epilepsia* 1975;**16**:753–8.

Vallarta 1974
Vallarta JM, Bell DB, Reichert A. Progressive encephalopathy due to chronic hydantoin intoxication. *American Journal of Diseases of Children* 1974;**128**:27–34.

Wilder 1983a
Wilder BJ, Karas BJ, Penry JK, Asconape J. Gastrointestinal tolerance of divalproex sodium. *Neurology* 1983;**33**:808–11.

* *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, SV: 64. 39% partial epilepsy. 55% male. Age range: 5 to 71 years. Duration of treatment (range in months): 3 to 48
Interventions	Monotherapy with PHT or SV. Mean daily dose achieved: PHT: 5.4 mg/kg; SV: 15.6 mg/kg
Outcomes	Seizure control: excellent (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

Craig 1994

Methods	Single-blind (for cognitive tests). Participants allocated using stratified minimization program
Participants	Number randomized: PHT:81, SV:85. 48% partial epilepsy. Age range: 61 to 95 years. Range of follow up (months) 1 to 20.
Interventions	Monotherapy with PHT or SV. Median daily dose achieved: PHT: 100 mg/day, SV: 200 mg/day
Outcomes	Psychological tests. Frequency of adverse effects. Summary of seizure control.
Notes	Trial report included a subset (n = 38) of participants. Full data set used in this review includes all 166 participants randomized in this trial

Risk of bias

Item	Authors' judgement	Description

Craig 1994 (*Continued*)

Allocation concealment?	Yes	A - Adequate

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; SV: 30. 100% partial epilepsy. Percentage male and range of follow up not mentioned. Age range: 18 to 40 years
Interventions	Monotherapy with PHT or SV. Dose achieved not stated.
Outcomes	Proportion achieving 24 month remission at 3 years. 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; SV: 49. 53% partial epilepsy. 50% male. Age range: 3 to 16 years. Range of follow up (months): 3 to 88
Interventions	Monotherapy with PHT or SV. Median daily dose achieved: PHT: 175 mg/day, SV: 600 mg/day
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12 month remission from all seizures. Adverse effects.
Notes	

Risk of bias

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

Forsythe 1991

Methods	Patients randomly allocated using quota allocation. Single-blinded (for cognitive tests)
Participants	Newly diagnosed. Number randomized: PHT: 20; SV: 21. No information on epilepsy type, sex or range of follow up. Age range: 5 to 14 years
Interventions	Monotherapy with PHT or SV. Mean dose: PHT: 6.1 mg/day, SV: 25.3 mg/day
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 on 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; SV: 61. 43% partial epilepsy. 50% male. Age range: 14 to 72 years. Range of follow up (months): 1 to 91
Interventions	Monotherapy with PHT or SV. Median daily dose achieved: PHT: 300 mg/day, SV: 800 mg/day
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12 month remission from all seizures. Adverse effects.
Notes	

Risk of bias

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

Ramsay 1992

Methods	Individuals assigned using randomization tables for each investigator (2:1 ratio for SV:PHT). Method of allocation concealment not stated. Unblinded
Participants	Newly diagnosed and previously untreated. Number randomized: PHT: 50, SV: 86. 0% partial epilepsy. 54% male. Age range: 3 to 64 years. Patients followed up for 6 months
Interventions	Monotherapy with PHT or SV. Dose achieved not stated.
Outcomes	Time to first GTC seizure. 6 month recurrence rates. Frequency of adverse events.
Notes	

Risk of bias

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

Rastogi 1991

Methods	Method of generation of random list and allocation concealment not stated. Unblinded
Participants	? newly diagnosed. Number randomized: PHT: 45, SV: 49. 29% partial epilepsy. 74% male. Age range: 8 to 52. No information on range of follow up
Interventions	Monotherapy with PHT or SV. Average daily dose achieved: PHT: 5.6 mg/kg/day, SV: 18.8 mg/kg/day
Outcomes	Reduction in frequency of seizures: excellent (100% reduction); good (75 to 99% reduction); fair (50 to 74% reduction); poor (< 50% reduction). Adverse effects.
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

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

Shakir 1981

Methods	Individuals allocated using telephone randomization. Unblinded
Participants	64% previously untreated, 36% continued to have seizures on previous drug therapies. Number randomized: PHT: 15, SV: 18. 58% partial epilepsy. 36% male. Age range: 7 to 55 years. Range of follow up (months): 9 to 48
Interventions	Monotherapy with PHT or SV. Dose achieved not stated.
Outcomes	Seizures during treatment. Adverse effects.
Notes	Outcomes chosen for this review were not reported. IPD not available, but could be constructed from the publication for the outcome 'time on allocated drug'

Risk of bias

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

Thilothammal 1996

Methods	Random list generated using computer generated random numbers. Method of concealment not mentioned. Double-blind
Participants	Previously untreated. Number randomized: PHT: 52, SV: 48. 0% partial epilepsy. 52% male. Age range: 4 to 12 years. Range of follow up (months): 22 to 36
Interventions	Monotherapy with PHT or SV. Dose achieved not stated.
Outcomes	Proportion with recurrence of seizures. Adverse effects.
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

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

Turnbull 1985

Methods	Method of generation of random list and allocation concealment not stated. Unblinded
Participants	Previously untreated. Number randomized: PHT: 70, SV: 70. 45% partial epilepsy. 52% male. Age range: 3 to 64 years. Range of follow up (months) 24 to 48
Interventions	Monotherapy with PHT or SV. Dose achieved not stated/available
Outcomes	Time to 2 year remission. Time to first seizure.
Notes	

Risk of bias

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

GTC: generalized tonic-clonic
IPD: individual patient data
PHT: phenytoin
SV: sodium valproate

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

Study	Reason for exclusion
Berg 1993	Reports the same trial as Forsythe 1991, but more relevant information given in the Forsythe publication
Shakir 1980	Reports the same trial as Shakir 1981. There are some differences between the results in the two publications. The reason why could not be established
Tallis 1994	Abstract only. Reports the same trial as Craig 1994.
Wilder 1983	Preliminary results of the trial reported in Ramsay 1992.

DATA AND ANALYSES

Comparison 1. Phenytoin versus sodium valproate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to withdrawal of allocated treatment	5	527	Peto Odds Ratio (95% CI)	1.10 [0.79, 1.54]
1.1 Generalized onset seizures (tonic-clonic only)	5	341	Peto Odds Ratio (95% CI)	0.98 [0.60, 1.58]
1.2 Partial onset seizures	4	186	Peto Odds Ratio (95% CI)	1.23 [0.77, 1.98]
2 Time to 12 month remission	4	514	Peto Odds Ratio (95% CI)	1.04 [0.78, 1.38]
2.1 Generalized onset seizures (tonic-clonic only)	4	270	Peto Odds Ratio (95% CI)	1.06 [0.71, 1.57]
2.2 Partial onset seizures	4	244	Peto Odds Ratio (95% CI)	1.02 [0.68, 1.54]
3 Time to six month remission	5	639	Peto Odds Ratio (95% CI)	0.89 [0.71, 1.11]
3.1 Generalized onset seizures (tonic-clonic only)	5	395	Peto Odds Ratio (95% CI)	0.80 [0.59, 1.08]
3.2 Partial onset seizures	4	244	Peto Odds Ratio (95% CI)	1.02 [0.73, 1.43]
4 Time to first seizure	5	639	Peto Odds Ratio (95% CI)	0.92 [0.74, 1.14]
4.1 Generalized onset seizures (tonic-clonic only)	5	395	Peto Odds Ratio (95% CI)	1.03 [0.77, 1.39]
4.2 Partial onset seizures	4	244	Peto Odds Ratio (95% CI)	0.81 [0.59, 1.11]

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	PHY SV 67% 53% . 12% 25% . 21% 22% . 10% 11%
Czapinski 1994	1.Proportion achieving 24 month remission at three years 2.Proportion excluded after randomization due to adverse effects or no efficacy	PHY SV 59% 64% . . 23% 23%
Forsythe 1991	1.Cognitive assessments. 2.Withdrawals from randomized drug.	Sodium valproate and phenytoin did not adversely affect memory PHY SV 30% 33%
Rastogi 1991	1.Reduction in frequency of seizures: Excellent (100% reduction) Good (75-99% reduction) Fair (50-74% reduction) Poor (<50% reduction) 2.Side effects	. PHY SV 51% 49% . 29% 35% . . 18% 10% . . 2% 6% . incomplete data
Shakir 1981	1.Seizures during treatment 2.Side effects	PHY SV 40% 17% 40% 44%

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

Thilothammal 1996	1.Recurrence of seizures 2.Side effects	PHY SV 27% 21% 63% 31%

Table 2. Number of individuals contributing to each analysis

Trial	Number randomized	Time to withdrawal of allocated treatment	Time to 12 month remission	Time to first seizure	Time to six month remission
Craig 1994	Total=166 PHT=81; SV=85	0 (information not available)	Total=147 PHT=71; SV=76	Total=147 PHT=71; SV=76	Total=147 PHT=71; SV=76
de Silva 1996	Total=103 PHT=54; SV=49	Total=100 PHT=53; SV=47	Total=103 PHT=54; SV=49	Total=103 PHT=54; Sv=49	Total=103 PHT=54; SV=49
Heller 1995	Total=124 PHT=63; SV=61	Total=118 PHT=61; SV=57	Total=124 PHT=63; SV=61	Total=124 PHT=63; SV=61	Total=124 PHT=63; SV=61
Ramsay 1992	Total=136 PHT=50; SV=86	Total=136 PHT=50; SV=86	0 (follow-up < 12 months)	Total=125 PHT=48; SV=77	Total=125 PHT=48; SV=77
Turnbull 1985	Total = 140 PHT= 70; SV=70	Total=140 PHT=70; SV=70	Total=140 PHT=70; SV=70	Total=140 PHT=70; SV=70	Total=140 PHT=70; SV=70
Shakir 1981	Total=33 PHT=15; SV=18	Total=33 PHT=15; SV=18	0 (information not available)	0 (information not available)	0 (information not available)

Table 3. Logrank analysis

Test for:	Statistic	Time to withdrawal of allocated treatment	Time to 12 month remission	Time to first seizure	Time to six month remission
Homogeneity (unstratified)	Chi square	(df=4) 6.40	(df=3) 0.52	(df=4) 4.24	(df=4) 2.92
	p-value	0.171	0.915	0.375	0.572
Interaction between treatment and epilepsy type	Chi square	(df=1) 0.47	(df=1) 0.02	(df=1) 1.25	(df=1) 1.15
	p-value	0.50	0.903	0.264	0.284
Overall effect	Chi square	(df=1) 0.31	(df=1) 0.07	(df=1) 0.57	(df=1) 1.07

Table 3. Logrank analysis (*Continued*)

	p-value	0.58	0.791	0.451	0.300
Hazard Ratio (95%CI)		1.10 (0.79-1.54)	1.04 (0.78-1.38)	0.92 (0.74-1.14)	0.89 (0.71-1.11)

Table 4. Seizure type misclassification; G:generalized, P:partial, O:overall, U:uncertain

	Time to withdrawal of allocated treatment	Time to 12 month remission	Time to first seizure	Time to 6 month remission
(i) original analysis . . test for interaction	0.98(0.60-1.58)G 1.23 (0.77-1.98)P 1.10(0.79-1.54)O . chi-square=0.47, df=1, p=0.50	1.06(0.71-1.57)G 1.02 (0.68-1.54)P 1.04(0.78-1.38)O . chi-square=0.02, df=1, p=0.90	1.03(0.77-1.39)G 0.81 (0.59-1.11)P 0.92(0.74-1.14)O . chi-square=1.25, df=1, p=0.26	0.80(0.59-1.08)G 1.02 (0.73-1.43)P 0.89(0.71-1.11)O . chi-square=1.15, df=1, p=0.28
(ii) generalized and age at onset>30 classified as uncertain . test for interaction	1.33(0.76-2.32)G 1.23 (0.77-1.98)P 0.42(0.16-1.09)U 1.11(0.79-1.55) O . . chi-square=4.60, df=2, p=0.10	0.94(0.59-1.49)G 1.02 (0.68-1.54)P 1.53(0.70-3.31)U 1.04(0.78-1.39) O . . chi-square=1.14, df=2, p=0.57	1.33(0.91-1.95)G 0.81 (0.59-1.11)P 0.72(0.45-1.14)U 0.92(0.74-1.14) O . . chi-square=5.31, df=2, p=0.07	0.79(0.54-1.14)G 1.02 (0.73-1.43)P 1.15(0.65-2.01)U 0.94(0.75-1.18) O . . chi-square=1.62, df=2, p=0.45
(iii) generalized and age at onset>30 reclassified as partial . test for interaction	1.33(0.76-2.32)G 0.98 (0.65-1.50)P 1.10(0.78-1.53)O . . . chi-square=0.70, df=1, p=0.40	0.94(0.59-1.49)G 1.06 (0.74-1.51)P 1.01(0.76-1.34)O . . . chi-square=0.16, df=1, p=0.69	1.33(0.91-1.95)G 0.81 (0.63-1.04)P 0.94(0.76-1.16)O . . . chi-square=4.60, df=1, p=0.03	0.79(0.54-1.14)G 1.00 (0.75-1.32)P 0.91(0.73-1.14)O . . . chi-square=1.03, df=1, p=0.31

WHAT'S NEW

Last assessed as up-to-date: 26 July 2007.

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

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 4, 2001

Date	Event	Description
23 September 2008	Amended	Converted to new review format.
27 July 2007	New search has been performed	We re-ran our searches on 27 July 2007; one new study has been identified and added to the 'studies awaiting assessment' section. It will be assessed for inclusion in the review at a later date

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 commented on each draft of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK.
- Walton Centre for Neurology and Neurosurgery, UK.

External sources

- Medical Research Council, UK.
- NHS R&D, UK.

NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans