Oxcarbazepine versus phenytoin monotherapy for epilepsy (Review)

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[Intervention Review]

Oxcarbazepine versus phenytoin monotherapy for epilepsy

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ABSTRACT

Background

Worldwide, phenytoin is a commonly used antiepileptic drug. Oxcarbazepine is one of the newer antiepileptic drugs and has similar chemical properties to its parent compound carbamazepine. For the new drugs such as oxcarbazepine, it is important to know how they compare with standard treatments.

Objectives

To review the best evidence comparing oxcarbazepine and phenytoin when used as monotherapy in patients with epilepsy.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (4 April 2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2008), and MEDLINE (1950 to March week 4, 2008). No language restrictions were imposed. We checked the reference lists of included studies for additional reports of relevant studies. We also contacted pharmaceutical companies to try and identify any unpublished studies.

Selection criteria

Randomized controlled trials in children or adults with epilepsy. Trials must have included a comparison of oxcarbazepine monotherapy with phenytoin monotherapy.

Data collection and analysis

This was an individual patient data review. Two review authors independently assessed trial quality and extracted data. Study authors were contacted for additional information.

Outcomes were (a) time on allocated treatment; (b) time to achieve 6, 12 and 24-month remission; (c) time to first seizure post randomization; (d) quality of life measures if available. Clinical heterogeneity was assessed by reviewing differences across trials in characteristics of randomized patients, dosing protocols and trial design. Data were analysed on an intention to treat basis. Stratified logrank tests were used to obtain study-specific and overall estimates of hazard ratios (with 95% confidence intervals), where a HR > 1 indicates that an event is more likely on phenytoin.

Main results

Individual patient data were available for 480 patients from two trials, representing 100% of the patients recruited into the two trials that met our inclusion criteria. By convention, for the outcomes time to withdrawal of allocated treatment and time to first seizure a hazards ratio (HR) > 1 indicates a clinical advantage for oxcarbazepine and for time to 6 and 12-month remission a HR > 1 indicates a clinical advantage for phenytoin. The main overall results (HR, 95% confidence interval (CI)) were: (i) time to withdrawal of allocated treatment 1.64 (1.09 to 2.47), (ii) time to 6-month remission 0.89 (0.66 to 1.22), (iii) time to 12-month remission 0.92 (0.62 to 1.37), (iv) time to first seizure 1.07 (0.83 to 1.39). The overall results indicate that oxcarbazepine is significantly better than phenytoin for time to treatment withdrawal, but suggest no overall difference between oxcarbazepine and phenytoin for other outcomes. Results stratified by seizure type indicate no significant advantage for either drug for patients with generalized onset seizures, but a potentially important advantage in time to withdrawal for oxcarbazepine for patients with partial onset seizures: HR 1.92 (95% CI 1.17 to 3.16). The age distribution of adults classified as having generalized epilepsy suggests a significant number of patients may have had their epilepsy misclassified.

Authors' conclusions

For patients with partial onset seizures oxcarbazepine is significantly less likely to be withdrawn, but current data do not allow a statement as to whether oxcarbazepine is equivalent, superior or inferior to phenytoin in terms of seizure control. Guidelines recommend carbamazepine as a first line treatment for patients with partial onset seizures and more evidence is needed regarding the comparative effects of oxcarbazepine and carbamazepine to further inform policy. For patients with generalized onset tonic-clonic seizures, valproate is considered the first line standard treatment and the results of this review do not inform current treatment policy. Misclassification of patients' epilepsy type may have confounded the results of this review.

PLAIN LANGUAGE SUMMARY

Oxcarbazepine versus phenytoin monotherapy for epilepsy

Oxcarbazepine is less likely to fail than phenytoin when used as monotherapy for partial onset seizures.

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Most seizures can be controlled by a single antiepileptic drug. The review of trials found that the new drug, oxcarbazepine, used as a single treatment, is more effective and tolerable than phenytoin, used as a single treatment, for patients with partial epilepsy.

BACKGROUND

Oxcarbazepine is one of the newer antiepileptic drugs and has similar chemical properties to its parent compound carbamazepine. It is licensed in a number of countries for use as both monotherapy and add-on (adjunctive) therapy. A review of oxcarbazepine as an add-on treatment in people with partial onset seizures has already been published (Castillo 2000) which provides reliable evidence that oxcarbazepine reduces seizure frequency compared to placebo when used as an add-on treatment.

The majority of people with epilepsy have their seizures controlled by a single drug (monotherapy) and therefore do not require add-on therapy (Cockerell 1995). There are an ever increasing number of antiepileptic drugs to choose from and both clinicians and people with epilepsy need reliable evidence upon which to base a choice among drugs. Such evidence will come from trials comparing one drug with another, rather than trials comparing drugs with placebo. For the new drugs such as oxcarbazepine, it is important to know how they compare with standard treatments. Our aim in this systematic review is to overview existing evidence for the comparative efficacy and tolerability of oxcarbazepine and phenytoin (one of the standard antiepileptic drugs) when used as monotherapy. Worldwide, phenytoin is a commonly used antiepileptic drug for patients with partial onset seizures and generalized onset tonic-clonic seizures. Although phenytoin is no longer considered as a first line treatment in Europe (Wallace 1997) it is more commonly used in the USA (Wilder 1995). Phenytoin is associated with long-term cosmetic changes including gum hypertrophy and acne (Mattson 1985). It also causes a rash (Tennis 1997) in five to ten

per cent of patients, which on rare occasions may be life threatening. It is also associated with congenital abnormalities (Gladstone 1992; Nulman 1997), where the risk is estimated to be two to three times that of the general population.

There are difficulties in undertaking a systematic review of epilepsy monotherapy trials as the important efficacy outcomes require analysis of time to event data (e.g. time to one year remission). Although methods have been developed to synthesise survival type data using summary information (Parmar 1998; Williamson 2002), it was unlikely that all trials have reported appropriate statistics; hence we have undertaken a review using individual patient data (IPD).

The use of individual patient data (IPD) also helps 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. An individual patient data approach will allow a thorough analysis of time to event data. This review is one in a series investigating individual monotherapy comparisons.

OBJECTIVES

To review the effects of oxcarbazepine compared to phenytoin when used as monotherapy in patients with epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

(1) Randomized controlled trials using either:
(a) an adequate method of allocation concealment (e.g. sealed opaque envelopes);
(b) a quasi method of randomization (e.g. allocation by date of birth).
(2) Studies may be double blind, single blind or unblinded.

Types of participants

Children or adults with epilepsy.

Types of interventions

Oxcarbazepine (OXC) or phenytoin (PHT) 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 inclusion in this review.
(1) Time on allocated treatment (retention time). This is a combined outcome reflecting both efficacy and tolerability as treatment may be withdrawn due to continued seizures, side effects or a combination of both. This is an outcome to which the patient makes a contribution, and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Commission 1998).
(2) Time to achieve 6, 12 and 24-month seizure free period (remission).
(3) Time to first seizure post randomization.
(4) Quality of life measures if available.

Search methods for identification of studies

We searched the Epilepsy Group's Specialized Register (4 April 2008, using the search terms 'oxcarbazepine AND phenytoin'). 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:

Electronic databases

We searched the following databases. There were no language restrictions.
(1) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* Issue 1, 2008) was searched using the strategy outlined in Appendix 1.
(2) MEDLINE (Ovid) (1950 to March week 4, 2008) was searched using the strategy outlined in Appendix 2.

References from published studies

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

Efforts to identify unpublished studies

We contacted Novartis (manufacturers of oxcarbazepine) and Parke-Davis (manufacturers of phenytoin). We also contacted the original investigators of relevant trials.

Data collection and analysis

Trial assessment and data collection

Two of the review authors (MM and AGM) independently assessed all identified trials for inclusion.
The following data were requested for all trials meeting our inclusion criteria.
(1) Trial methods:

(a) method of generation of random list;
(b) method of concealment of randomization;
(c) stratification factors;
(d) blinding methods.
(2) Patient covariates:
(a) sex;
(b) age;
(c) seizure types;
(d) time between first seizure and randomization;
(e) number of seizures prior to randomization (with dates);
(f) presence of neurological signs;
(g) EEG results;
(h) CT / MRI results.
(3) Follow-up data:
(a) treatment allocation;
(b) date of randomization;
(c) dates of follow up;
(d) dates of seizures post randomization or seizure frequency data between follow-up visits;
(e) dates of treatment withdrawal and reasons for treatment withdrawal;
(f) dose;
(g) dates of dose changes.

Data checking

For each trial where IPD were supplied we performed the following:
(a) range and consistency checks - missing data, errors and inconsistencies were followed up with a nominated individual;
(b) trial details were cross checked against any published report of the trial;
(c) review of the chronological randomization sequence. The balance of prognostic factors were checked, taking account of factors stratified for in randomization procedure.
Where inconsistencies were found, we contacted the original investigators and explored the reasons.

Data manipulation

For both included trials (Bill 1997; Guerreiro 1997) seizure data were provided in terms of the mean number of seizures recorded per week in the titration period (first eight weeks) and the maintenance period (following 48 weeks) rather than specific dates of seizures. To enable time to event outcomes to be calculated, linear interpolation was applied to approximate the days on which seizures occurred. For example, if the mean number of seizures per week in the titration period was 0 and in the maintenance period was 0.02115 and the patient started treatment on 28/09/93 and ended treatment on 19/10/94 (interval of 387 days), then the date of first seizure would be approximately 165.5 days after the start of the maintenance period and thus 221.5 days after the start of treatment. This allowed an estimate of the time to 6 and 12-month remission and the time to first seizure to be computed. We calculated time to 6 and 12-month remission from the date of randomization to the estimated date the individual had been free of seizures for 6 or 12 months respectively. If the patient had one or more seizures in the titration period, a 6 or 12-month seizure-free period could also occur between the estimated date of the last seizure in the titration period and the estimated date of the first seizure in the maintenance period. Time to first seizure was calculated from the date of randomization to the date that their first seizure was estimated to have occurred. If the mean number of seizures per week data were missing for the titration period (first eight weeks), the estimated time of the first seizure could not be calculated. Eight patients in total (five in Bill 1997 and three in Guerreiro 1997) had missing seizure data for the titration period (All eight also had missing seizure data for the maintenance period). The number of days on trial medication ranged between one and 36 days for these eight patients. They were excluded from analyses of time to first seizure, time to 6-month remission and time to 12-month remission, but included in the analysis of time to withdrawal. If the mean 'number of seizures per week' data were missing for the maintenance period (but not for the titration period), the values for 6 and 12-month remission would be censored at the end of the titration period (effectively excluding them from the analysis). These outcomes were also censored if the individual died or follow up ceased prior to the occurrence of the event of interest.
For both trials (Bill 1997; Guerreiro 1997) the date of and reason for the treatment withdrawal were provided directly. Two of the review authors (MM & PRW) extracted detail about the reason for the treatment withdrawal from study case report forms (when necessary e.g. for death and protocol violation(s)). A third review author (AGM) checked the decisions. For the analysis of time to withdrawal of allocated treatment, an event was defined to be withdrawal of allocated treatment due to an adverse experience by the patient, unsatisfactory therapeutic effect, concomitant illness, patient non-compliance, or abnormal laboratory values. The outcome was censored if treatment was withdrawn because of protocol violation(s), loss to follow up or administrative problems, or if the individual was still on allocated treatment at the end of follow up. For one patient a protocol violation was further specified as non-compliance and this was classified as an event. Two deaths were recorded. One was classified as a censored value, because the cause of death was unrelated to the treatment or the condition. The other death was classified as an event: the patient died after experiencing an episode of status epilepticus, but had been non-compliant and discontinued treatment before they died.

Data analysis

(1) The analysis was carried out on an intention to treat basis and included all randomized patients, analysed in the treatment group to which they were allocated, irrespective of which treatment they actually received.
(2) The included trials were double blind. After completion of the maintenance period, some patients continued to be followed up, however the blind was broken and these patients took 'open label' treatment. The primary analyses included data from this

open label period. The analysis was repeated, including only data from the double blind period (eight week titration period plus the 48-week maintenance period).
(3) Clinical heterogeneity was assessed by reviewing differences across trials in characteristics of randomized patients, dosing protocols and trial design.
(4) With 'time to event' outcomes (time to treatment withdrawal, time to period remission, time to first seizure), logrank tests (stratified by trial to preserve the within trial randomization) were used to obtain study-specific and overall estimates of hazard ratios (with 95% confidence intervals). We used the information provided by the stratified logrank tests to investigate the main effect of drug and to assess evidence of heterogeneity in drug effect between trials (EBCTCG 1990).
(5) Results are expressed as a hazard ratio (HR) and 95% confidence interval, and by convention a HR > 1 indicates that an event is more likely on phenytoin. Hence, for time to withdrawal of allocated treatment or time to first seizure a HR > 1 indicates a clinical advantage for oxcarbazepine (e.g. HR = 1.2 would suggest a 20% increase in risk of withdrawal from phenytoin compared to oxcarbazepine) and for time to 6 and 12-month remission a HR > 1 indicates a clinical advantage for phenytoin.
(6) We used the original seizure classifications that were adopted in the published reports of trials (main seizure type at baseline). Partial seizures (simple or complex) and partial secondarily generalized seizures were classified as partial epilepsy. Primarily generalized seizures were classified as generalized epilepsy. Data from individual studies were used in a stratified analysis to examine the potential impact of seizure type on the results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
We identified a total of two trials in which participants have been randomized to oxcarbazepine or phenytoin as potentially eligible for this systematic review. Both trials were included in this review (Bill 1997; Guerreiro 1997). IPD were available for both trials which recruited a total of 480 patients. Computerized data were provided directly for both trials. One trial recruited adults only (Bill 1997) and one trial recruited children and adolescents only (Guerreiro 1997). Both trials recruited patients with newly diagnosed and previously untreated epilepsy. Both trials recruited patients with partial onset seizures (simple/complex partial or secondary generalized tonic-clonic) and patients with generalized tonic-clonic seizures without partial onset. In the trial including adults only (Bill 1997) 61% of patients were male (57% males in the OXC group and 64% in the PHT group). In the trial including children and adolescents (Guerreiro 1997) 50% of patients were male (47% males in the OXC group and 52% in the PHT group). During the eight week titration period, treatment was started with daily doses of:

- 300mg OXC or 100mg PHT (Bill 1997) and then increased bi-weekly (every two weeks) based on clinical response (for adults);
- 150 mg OXC or 50mg PHT (Guerreiro 1997) and then increased gradually based on clinical response (for children and adolescents).

No fixed titration schedule was used except that after eight weeks patients were to be on a t.i.d. (three times per day) regimen of OXC or PHT with daily doses of 450 to 2400 mg and 150 to 800 mg, respectively. The daily dose range and t.i.d. regimen were to be continued during the subsequent 48-week maintenance period. However; adjustment of the daily dose according to clinical response was possible during this period. The median daily doses actually taken (with lower and upper quartiles) for OXC was 900 mg (900; 1200) for Bill 1997 and 600 mg (450; 900) for Guerreiro 1997. The median daily dose (with lower and upper quartiles) for PHT was 300 mg (300; 300) for Bill 1997 and 200 mg (150; 300) for Guerreiro 1997.
Data were available for the following patient characteristics (percentage patients with data available): time between first seizure and randomization (100%); seizure types (99.2%); age (99.8%); sex (100%); number of seizures prior to randomization (100%); EEG results (97.7%); CT scan results (79.2%).
The two trials were similar in design and the main potential source of heterogeneity is that one trial recruited children whilst the other recruited adults (*see* table 'Characteristics of included studies').

Risk of bias in included studies

Randomization, blinding and allocation concealment
For both included trials (Bill 1997; Guerreiro 1997) randomization numbers were sequentially assigned across centres within each country. A computer-generated randomization scheme was used to provide balanced blocks of patient numbers for each of the two treatment groups within each centre. A block size of six was used, but participating centres were not informed of the block size (Pohlmann 2005).
Allocation concealment was achieved as follows: sequentially numbered packages were prepared which were identical and containing identical tablets (Pohlmann 2005). Recruiting clinicians were asked to allocate each patient the package with the lowest number available at the centre (Pohlmann 2005). Both trials were double blinded by using divisible tablets with identical appearance.
Loss to and exclusions from follow up
In both included trials, patients were not followed up after the randomized treatment had been withdrawn. For most of these patients, the treatment withdrawal was an event for the time to treat-

ment failure analysis. However these patients had to be censored at the time of treatment withdrawal for the seizure outcomes, which contravenes the principle of intention to treat.

Of the 287 patients who were randomized in Bill 1997 (143 to oxcarbazepine and 144 to phenytoin), 117 patients (56 (39.2%) in the oxcarbazepine group and 61 (42.2%) in the phenytoin group) discontinued prematurely from the trial (5 and 16 respectively for tolerability reasons). Of these patients, 37 (18 on oxcarbazepine and 19 on phenytoin) discontinued during the eight week titration period. An additional 80 patients (38 on oxcarbazepine and 42 on phenytoin) discontinued during the 48-week maintenance period. The numbers for premature discontinuation in the titration period differ from the numbers reported in the publication (49 patients - 25 on oxcarbazepine and 24 on phenytoin). The differences were followed up with the trial statistician who proposed a possible explanation: it is likely that the raw premature discontinuation data (0 or 1) as collected in the CRF (clinical record file) was provided for this Cochrane review, but for the time to premature discontinuation analyses in the publication a derived premature discontinuation variable based on the "time under assessment" was created. If certain patients had empty records in the maintenance period, the created variable will indicate a premature discontinuation at the end of the titration period, although in the CRF they were coded as discontinuing during the maintenance period. If this was the case, it is possible that we find fewer patients who discontinued during the titration period, compared to the publication. (Note that the trial statistician who proposed this explanation was not the original trial statistician and could only explain how they handled data at the time of the trial (in the 1990s). The data used for the publication were not accessible at the time of our query).

Of the 193 patients who were randomized in Guerreiro 1997 (97 to oxcarbazepine and 96 to phenytoin), 58 patients (24 (24.7%) in the oxcarbazepine group and 34 (35.4%) in the phenytoin group) discontinued prematurely from the trial (2 and 14 respectively for tolerability reasons). Of these patients, 27 (13 on oxcarbazepine and 14 on phenytoin) discontinued during the eight week titration period. These numbers differ from the numbers reported in the publication (31 patients - 15 on oxcarbazepine and 16 on phenytoin). The differences were followed up with the trial statistician who proposed a possible explanation (*see* the previous paragraph). An additional 31 patients (11 on oxcarbazepine and 20 on phenytoin) discontinued during the 48-week maintenance period.

See Table 1 for a breakdown of reasons for premature discontinuation according to trial and treatment.

Classification of patients

To be included in the trials (Bill 1997; Guerreiro 1997) patients had to have a minimum of two seizures, separated by at least 48 hours, in the six months before entering the study. In both trials the baseline assessment included a medical and seizure history, physical examination, laboratory evaluations, electrocardiogram (ECG), electroencephalogram (EEG) and an optional cranial computed tomography (CT) scan to rule out any progressive neurological disorder such as a brain tumour. Seizures were classified according to the 1981 International Classification of seizure types (ILAE 1981; Bill 1997; Guerreiro 1997) and the 1989 classification of epilepsies and epileptic syndromes (ILAE 1989; Guerreiro 1997). In Bill 1997, 104 of the 287 patients randomized were classified as having generalized onset seizures, 48 of whom were over the age of 25 years at randomization. Given that generalized onset seizures present primarily in childhood and adolescence, it is likely that many of the latter patients were misclassified. Hence the generalized onset seizure sub-group is likely to represent a combination of patients with generalized onset and patients with partial onset seizures.

Effects of interventions

Details regarding the number of patients contributing to each analysis are given in Table 2 and Table 3. Four patients had missing data for the main seizure type at baseline (one in Bill 1997 and three in Guerreiro 1997) and therefore their epilepsy type could not be derived. These four patients are excluded from subgroup analyses according to seizure types. All results are summarized in Metaview (*see* summary of analysis below). For the Metaview plots produced in this review, the 'Peto OR (IPD)' label is equivalent to 'HR'. The survival curve plots can be found under 'Additional Figures' (Figure 1; Figure 2; Figure 3; Figure 4; Figure 5; Figure 6; Figure 7; Figure 8).

Figure 1. Time to withdrawal

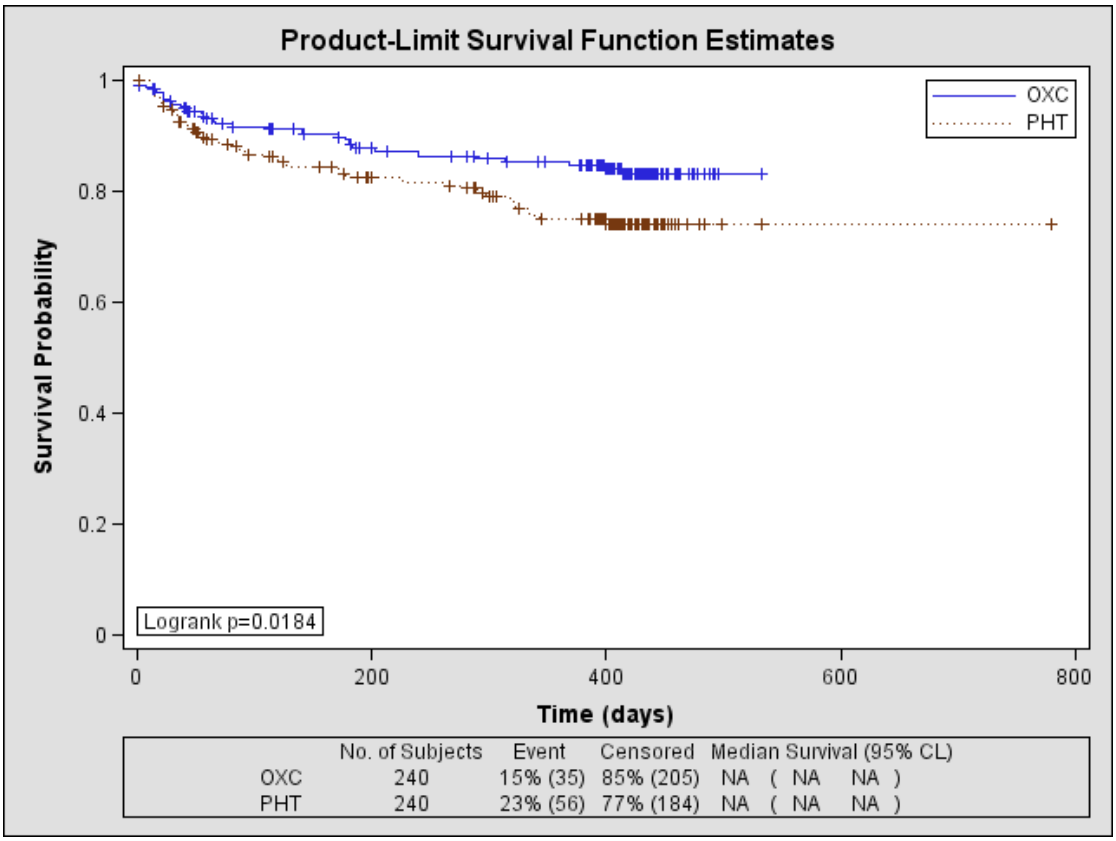


Figure 2. Time to withdrawal - stratified by epilepsy type

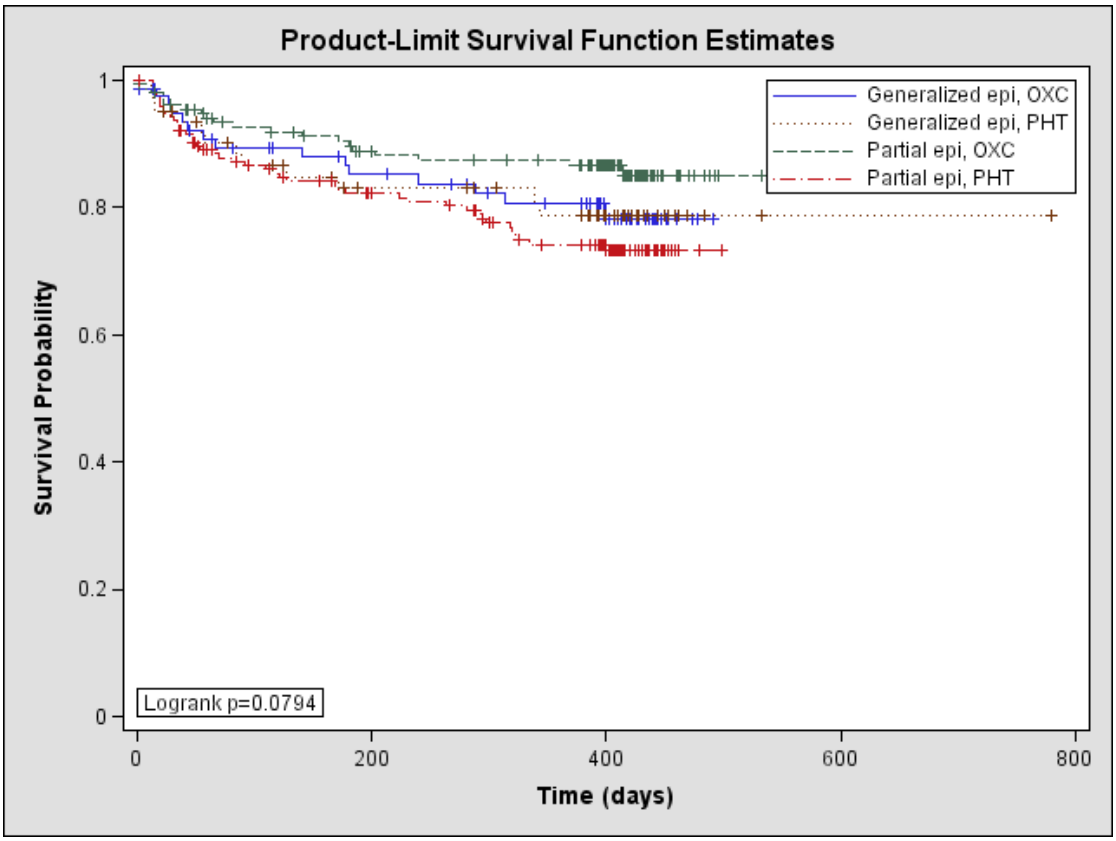


Figure 3. Time to 6 month remission

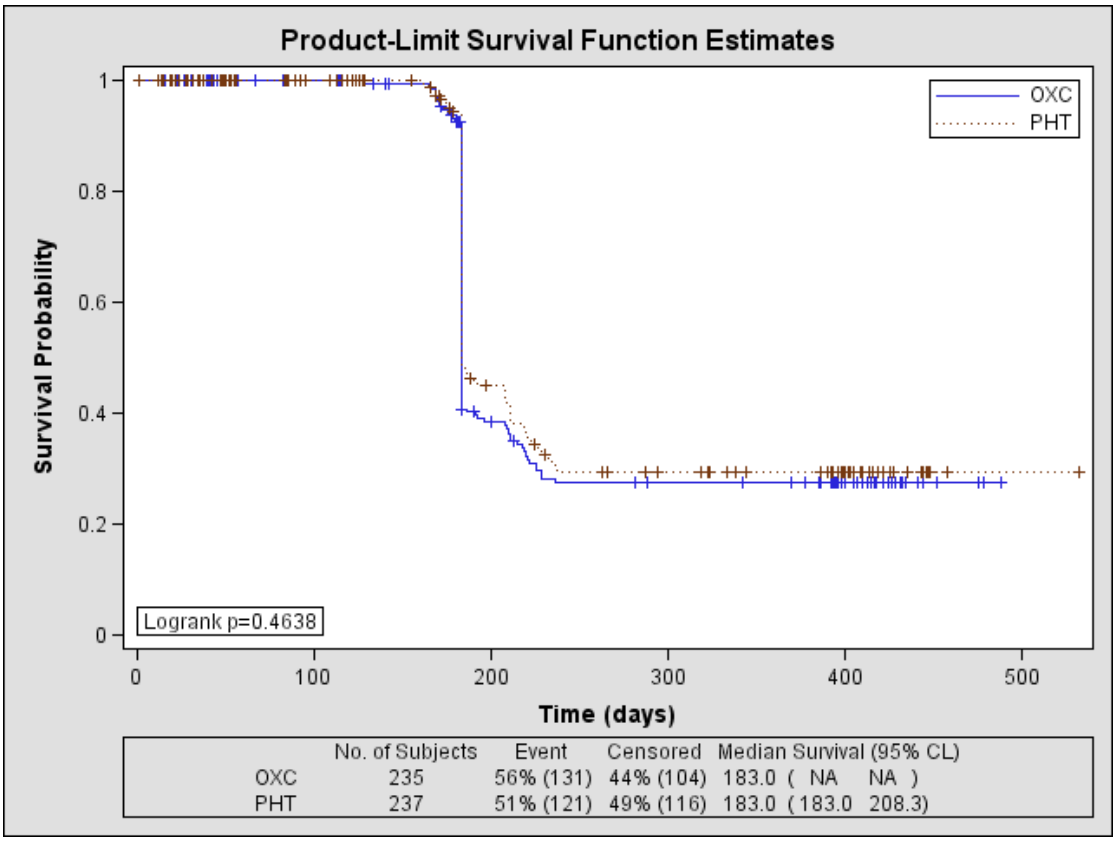


Figure 4. Time to 6 month remission - stratified by epilepsy type

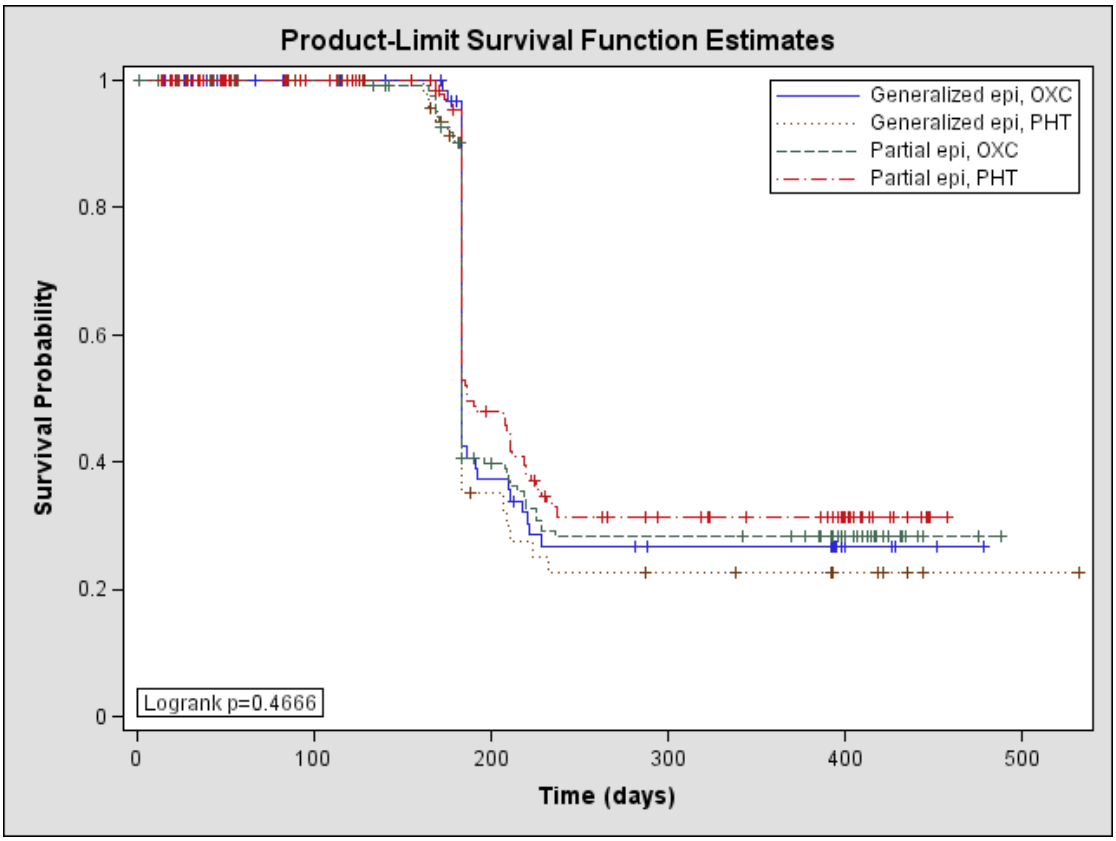


Figure 5. Time to 12 month remission

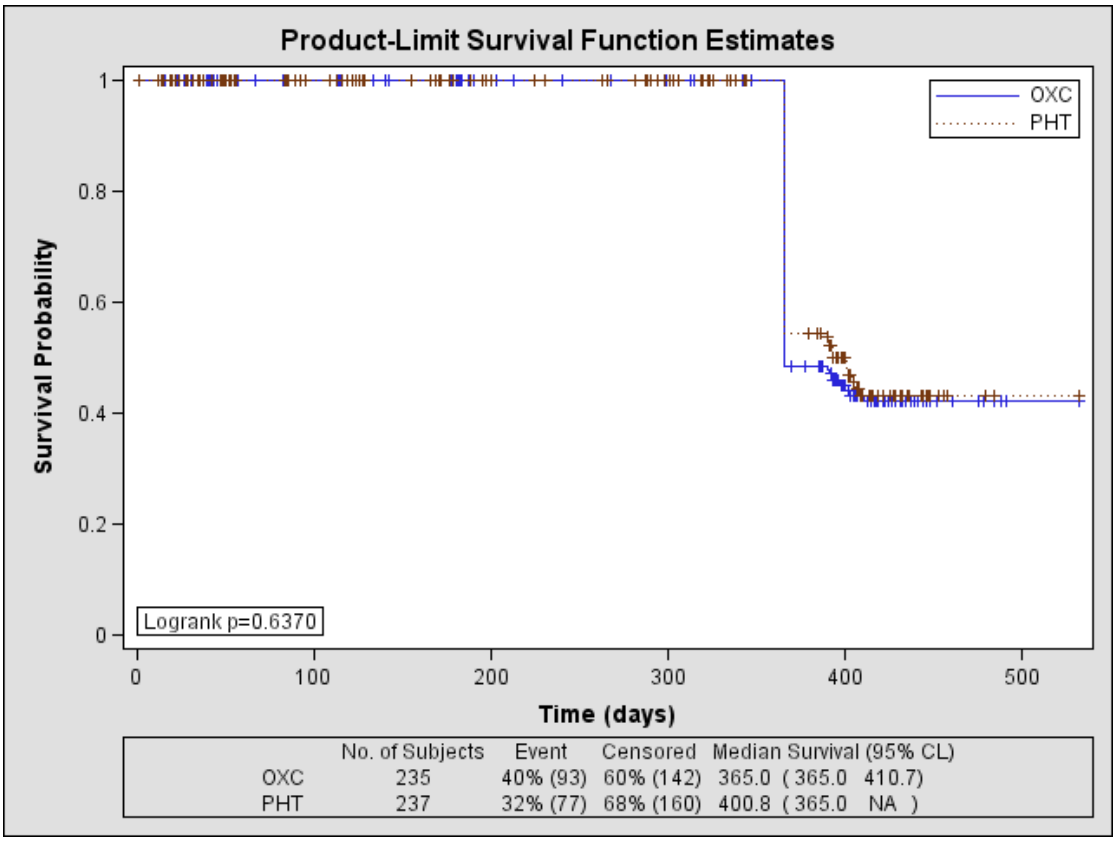


Figure 6. Time to 12 month remission - stratified by epilepsy type

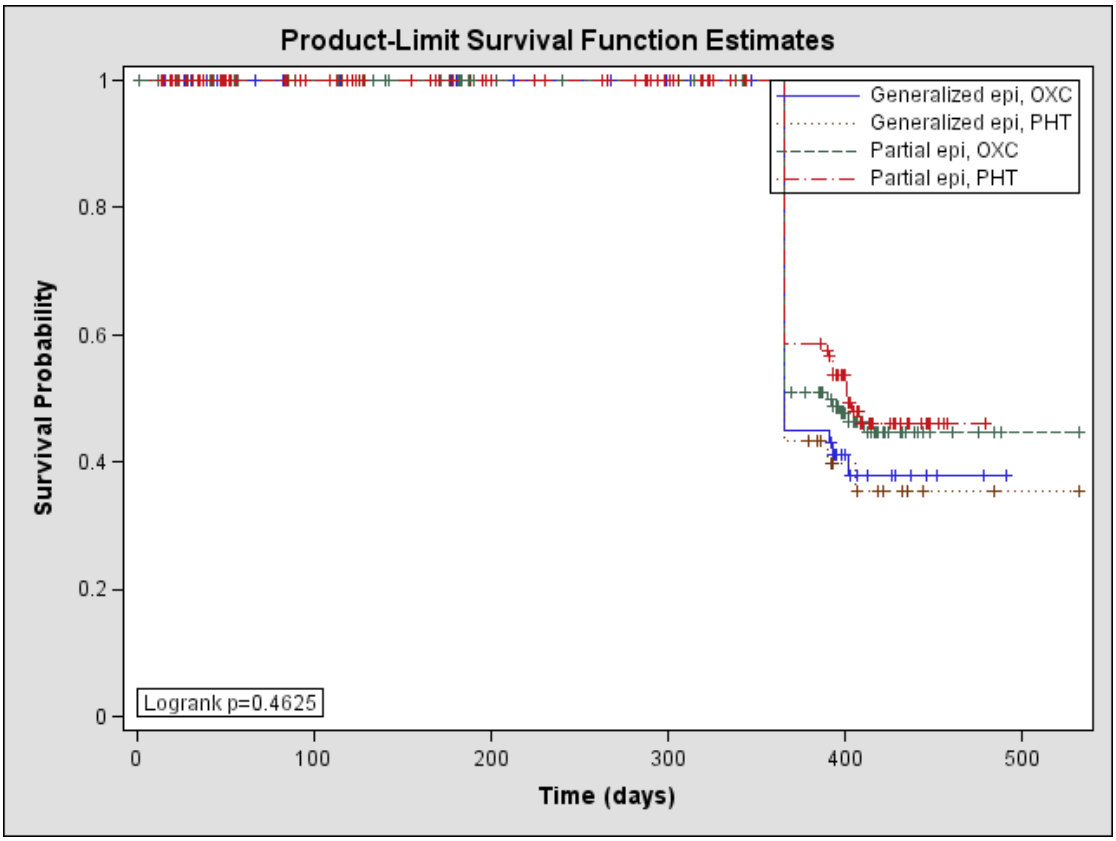


Figure 7. Time to first seizure

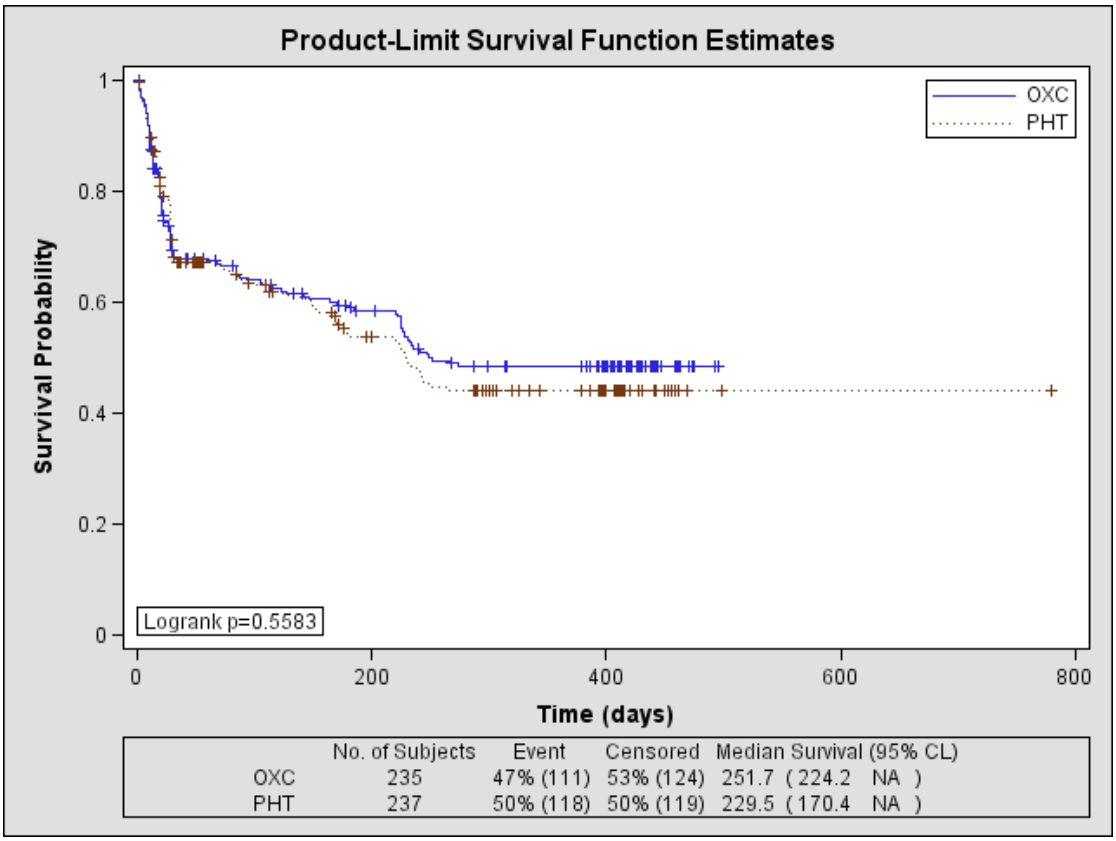
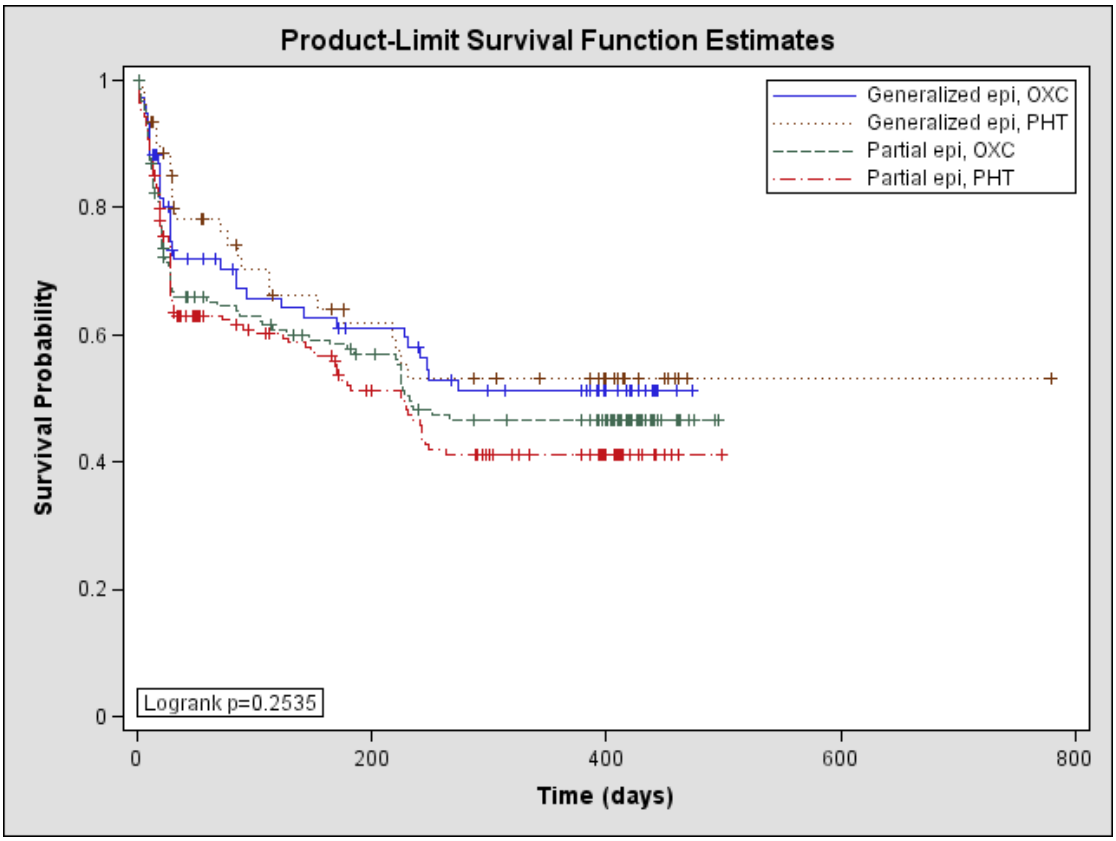


Figure 8. Time to first seizure - stratified by epilepsy type



(1) Time to withdrawal of allocated treatment

For this outcome, a HR > 1 indicates a clinical advantage of oxcarbazepine. Time to withdrawal of allocated treatment and reason for withdrawal were available for 480 patients from two trials (100% of patients from two trials providing IPD). There was no evidence of statistical heterogeneity between trials (chi squared = 0.24, df = 1, p = 0.62) and the percentage of variability in effect estimates (HR) that is due to heterogeneity rather than chance is zero (I^2 = 0%). The overall pooled HR and 95% confidence interval (CI) of 1.64 (1.09 to 2.47) suggests a clinical advantage of oxcarbazepine over phenytoin. Reasons for withdrawal are indicated in Table 1.

For four patients the type of seizures was not available (one in Bill 1997 and three in Guerreiro 1997) and therefore their epilepsy type could not be classified. Results stratified for epilepsy type give a summary HR of 1.03 (95% CI 0.48 to 2.20, I^2 = 52.9%) for generalized onset tonic-clonic seizures indicating no advantage for either drug, and 1.92 (95% CI 1.17 to 3.16, I^2 = 19%) for partial onset seizures indicating a clinically important advantage for oxcarbazepine. However the test for a statistical interaction for results stratified by seizure type was not significant and results for these subgroup analyses should be treated with caution.

When values greater than 392 days were censored in the above mentioned analyses (overall analysis and analysis stratified by epilepsy type), the HRs and 95% CIs were similar to the uncensored analyses and the conclusions were unchanged.

(2) Time to achieve six month remission

For this outcome, a HR > 1 indicates a clinical advantage for phenytoin. Data for 472 participants (98.3%) of those providing IPD) from two trials were available for the analysis of this outcome. This outcome could not be calculated for eight patients (three in Bill 1997 and five in Guerreiro 1997) due to missing data (no data for mean frequency of seizures in the maintenance period as well as in the titration period; number of days on trial medication ranged between one and 36 days for these eight patients). There was no evidence of statistical heterogeneity between trials (chi squared = 0.35, df = 1, p = 0.55) and the percentage of variability in effect estimates (HR) that is due to heterogeneity rather than chance is zero (I^2 = 0%). The overall pooled HR and 95% confidence interval (CI) of 0.89 (0.66 to 1.22) suggests no clear clinical advantage of either drug.

For four patients the type of seizures was not available (one in Bill 1997 and three in Guerreiro 1997) and therefore their epilepsy type could not be classified or included in this analysis. Results stratified for epilepsy type give a summary HR of 1.29 (95% CI 0.70 to 2.38) for generalized onset tonic-clonic seizures, indicating a non-significant trend in favour of phenytoin. The summary HR was 0.84 (95% CI 0.58 to 1.21) for partial onset seizures indicating a non-significant trend in favour of oxcarbazepine.

When values greater than 392 days were censored in the above mentioned analyses (overall analysis and analysis stratified by epilepsy type), the HRs and 95% CIs were identical to the uncensored analyses.

(3) Time to achieve 12-month remission

For this outcome, an HR > 1 indicates a clinical advantage for phenytoin. Data for 472 participants (98.3%) were available for the analysis of this outcome. This outcome could not be calculated for eight patients (three in Bill 1997 and five in Guerreiro 1997) due to missing data (no data for mean frequency of seizures in the maintenance period as well as in the titration period; number of days on trial medication ranged between one and 36 days for these eight patients). There was no evidence of statistical heterogeneity between trials (chi squared = 0.32, df = 1, p = 0.57) and the percentage of variability in effect estimates (HR) that is due to heterogeneity rather than chance is zero (I^2 = 0%). The overall pooled HR and 95% confidence interval (CI) of 0.92 (0.62 to 1.37) suggests no clear clinical advantage of either drug.

For four patients the type of seizures was not available (one in Bill 1997 and three in Guerreiro 1997) and therefore their epilepsy type could not be classified or included in this analysis. Results stratified for epilepsy type give a summary HR of 1.08 (95% CI 0.50 to 2.34) for generalized onset tonic-clonic seizures, and 0.93 (95% CI 0.58 to 1.50) for partial onset seizures. There is no clear indication of advantage for either drug. HRs and 95% CIs were similar to the uncensored analyses when values greater than 392 days were censored (for the overall analysis and the analysis stratified by epilepsy type) and the conclusions were unchanged.

(4) Time to achieve 24-month remission

It was not possible to calculate this outcome, since only one patient (Guerreiro 1997) was followed up for 24 months or longer.

(5) Time to first seizures post randomization

For this outcome, a HR > 1 indicates a clinical advantage for oxcarbazepine. Data for 472 participants (98.3% of those providing IPD) from two trials were available for the analysis of this outcome. This outcome could not be calculated for eight patients (five in Bill 1997 and three in Guerreiro 1997) due to missing data (no data for mean frequency of seizures in the maintenance period as well as the titration period; number of days on trial medication ranged between one and 36 days for these eight patients). There was no evidence of statistical heterogeneity between trials (chi squared = 0.30, df = 1, p = 0.58) and the percentage of variability in effect estimates (HR) that is due to heterogeneity rather than chance is zero (I^2 = 0%). The overall pooled HR and 95% confidence interval (CI) of 1.07 (0.83 to 1.39) suggests no clear clinical advantage of either drug.

For four patients the type of seizures was not available (one in Bill 1997 and three in Guerreiro 1997) and therefore their epilepsy type could not be classified or included in this analysis. Results stratified for epilepsy type give a summary HR of 0.90 (95% CI 0.54 to 1.51) for generalized onset tonic-clonic seizures, and 1.08 (0.80 to 1.47) for partial onset seizures. There is no clear indication of advantage for either drug.

When values greater than 392 days were censored in the above mentioned analyses (overall analysis and analysis stratified by epilepsy type), the HRs and 95% CIs were identical to the uncensored analyses.

(6) Quality of life measures

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

DISCUSSION

In this review we have included individual patient data from 480 patients from two trials in which participants were randomized to either oxcarbazepine or phenytoin. Both RCTs were of good methodological quality: they used adequate methods of randomization and adequate methods of allocation concealment, were double blind and loss to and exclusion from follow up were similar in the oxcarbazepine and phenytoin groups (except for more premature discontinuations due to tolerability reasons of patients on phenytoin compred to oxcarbazepine in Guerreiro 1997). *See* table 'Characteristics of included studies' and 'Additional tables' (Table 1: Table 2; Table 3). The main difference between the trials is that one recruited adults whilst the other recruited children. The overall results indicate that oxcarbazepine is significantly better than phenytoin for time to treatment withdrawal. Results stratified by seizure type indicate no significant advantage for either drug for patients with generalized onset seizures, but a potentially important advantage for oxcarbazepine for patients with partial onset seizures HR 1.92 (95% CI 1.17 to 3.16).

For the seizure outcomes which included time to 6 and 12-month remission from seizures and time to a first seizure after randomization, no significant differences were found in the overall or subgroup analyses. However there are consistent trends in all of the analyses indicating a potential advantage for oxcarbazepine for patients with partial onset seizures. Therefore the overall advantage for oxcarbazepine for time to treatment withdrawal presumably represents a combination of better tolerability and improved seizure control, the latter primarily in patients with partial onset seizures.

There are a number of limitations to this review which should be highlighted. Firstly, we did not have precise dates of seizures. We did have information regarding the mean number of seizures per

week in the titration (eight weeks) and maintenance phases (48 weeks) for both trials. Using this data we were able to interpolate the dates of seizures assuming a uniform distribution. Secondly, in both trials, patients were no longer followed up after the allocated treatment was withdrawn, and hence had to be censored at the time of treatment withdrawal for the analyses of seizure outcomes. Failure to follow patients up after the withdrawal of allocated treatment violates the principle of intention to treat and may bias analyses. This is because treatment may be withdrawn for differing reasons which may have lead to informative censoring. For these reasons the analyses of seizure outcomes require cautious interpretation, although no significant differences were found in any case. A further limitation of the trials is the relatively short follow-up period given that epilepsy is a chronic condition often requiring many years of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

For patients with partial onset seizures oxcarbazepine should be considered a first line treatment in preference to phenytoin. However, guidelines recommend carbamazepine as a first line treatment for patients with partial onset seizures and more evidence is needed regarding the comparative effects of oxcarbazepine and carbamazepine to further inform policy. Such evidence will come from an ongoing trial comparing oxcarbazepine and carbamazepine as well as other standard and new antiepileptic drugs (SANAD).

For patients with generalized onset tonic-clonic seizures, valproate is considered the first line standard treatment and the results of this review do not inform current treatment policy.

Implications for research

This review highlights the need for comparative antiepileptic drug monotherapy trials that measure longer term outcomes, as well as the need to continue to follow patients up after randomized treatment has been withdrawn in order to comply with the principle of intention to treat and to avoid the problems of informative censoring. The need for further trials of oxcarbazepine should be decided once the results of SANAD are published in early 2006.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bill 1997

Methods	Multicenter, parallel group trial. Randomization numbers sequentially assigned across centers/countries. A computer-generated randomization scheme provided balanced blocks (size 6) of patient numbers for each of the 2 treatment groups within each center. Double-blind. Written informed consent obtained from patients or parents/guardians. Approved by local ethics committees. Conducted 1991 to first quarter of 1995.
Participants	Patients aged between 16 and 65 years with newly diagnosed epilepsy with PS or GTCS. A minimum of 2 seizures, separated by at least 48 hours, within 6 months preceding trial entry. Centers in Argentina, Brazil, Mexico, South Africa. No previous AED, except emergency treatment of seizures for a maximum of 3 weeks prior to trial entry
Interventions	Monotherapy with oxcarbazepine or phenytoin. 8-week titration period started with 300mg OXC or 100mg PHT, increased bi-weekly, based on clinical response. After 8 weeks patients were to be on a t.i.d regimen with daily doses of 450-2400mg OXC or 150-800mg PHT. Continued during 48-week maintenance with adjustment according to clinical response
Outcomes	Efficacy: proportion of seizure-free patients who had at least 1 seizure assessment during the maintenance period. Tolerability: comparison of patients who prematurely discontinued because of adverse experiences. Clinical utility: comparing premature discontinuation.
Notes	

Risk of bias

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

Guerreiro 1997

Methods	Multicenter, parallel group trial. Randomization numbers sequentially assigned across centers/countries. A computer-generated randomization scheme provided balanced blocks (size 6) of patient numbers for each of the 2 treatment groups within each center. Double-blind. Written informed consent obtained from patients or parents/guardians. Approved by local ethics committees. Conducted 1991 to first quarter of 1995.
Participants	Patients aged 5 to 18 years with newly diagnosed epilepsy with PS or GTCS. A minimum of 2 seizures, separated by at least 48 h, within 6 months preceding trial entry. Centers in Argentina, Brazil. No previous AED, except emergency treatment of seizures for a maximum of 3 weeks prior to trial entry
Interventions	Monotherapy with oxcarbazepine or phenytoin. 8-week titration period started with 150mg OXC or 50mg PHT, increased bi-weekly, based on clinical response. After 8 weeks patients were to be on a t.i.d regimen with daily doses of 450-2400mg OXC or 150-800mg PHT. Continued during 48-week maintenance with adjustment according to clinical response
Outcomes	Efficacy: proportion of seizure-free patients who had at least 1 seizure assesment during the maintenance period. Tolerability: comparison of patients who prematurely discontinued because of adverse experiences. Clinical utility: comparing the rate of premature discontinuation
Notes	

Risk of bias

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

t.i.d.: three times per day
PS: partial onset seizures
GTCS: generalized onset tonic-clonic seizures

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

Study	Reason for exclusion
Christe 1997	Wrong drug comparison: oxcarbazepine versus sodium valproate