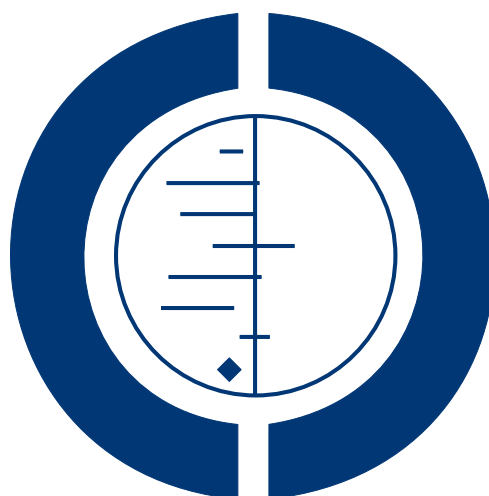


Antiepileptic drug monotherapy for epilepsy: a network meta-analysis (Protocol)

Nolan SJ, Sudell M, Weston J, Tudur Smith C, Marson AG



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[Intervention Protocol]

Antiepileptic drug monotherapy for epilepsy: a network meta-analysis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To review the time to withdrawal, remission and first seizure of 10 antiepileptic drugs (carbamazepine, phenytoin, valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide) currently used as monotherapy in children and adults with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types.

BACKGROUND

Description of the condition

Epilepsy is a common neurological condition in which recurrent, unprovoked seizures are caused by abnormal electrical discharges from the brain. Epilepsy is a disorder of many heterogeneous seizure types, with an estimated incidence of 33 to 57 per 100,000 person-years worldwide (Annegers 1999; Hirtz 2007; MacDonald 2000; Olafsson 2005; Sander 1996), accounting for approximately 1% of the global burden of disease (WHO 1994). The lifetime risk of epilepsy onset is estimated to be 1300 to 4000 per 100,000 person years (Hauser 1993; Juul-Jensen 1983), and the lifetime prevalence could be as large as 70 million people world-wide (Ngugi 2010). It is believed that with effective drug treatment, up to 70% of individuals with active epilepsy have the potential to become seizure free and go into long-term remission shortly after starting

drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), and that around 70% of individuals can achieve seizure freedom using a single antiepileptic drug in monotherapy (Cockerell 1995). The remaining 30% of individuals experience refractory or drug resistant seizures which often require treatment with combinations of antiepileptic drugs or alternative treatments such as epilepsy surgery (Kwan 2000).

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

Description of the intervention

For the treatment of partial and generalised onset seizures we will include in our evidence base the following 10 antiepileptic drugs,

which are currently licensed and used in clinical practice for use as monotherapy in at least one country (eMC 2014; FDA 2014):

- carbamazepine;
- phenytoin;
- valproate;
- phenobarbitone;
- oxcarbazepine;
- lamotrigine;
- gabapentin;
- topiramate;
- levetiracetam;
- zonisamide.

Carbamazepine, valproate, phenytoin and phenobarbitone are among the earliest traditional drugs licensed in the treatment of epileptic seizures. Carbamazepine and valproate have been commonly used as monotherapy for partial onset and generalised onset seizures for over 30 years (Shakir 1980), while phenytoin and phenobarbitone have been used in monotherapy for over 50 years (Gruber 1962).

These traditionally used drugs have all been recommended as first-line treatments due to their broad therapeutic anticonvulsant effect. However, the drugs are also associated with a number of adverse effects. Phenytoin and phenobarbitone are no longer considered as first-line agents in the United States and much of Europe due to worries over adverse events (Wallace 1997; Wilder 1995). Both drugs have been shown to be teratogenic (associated with malformations of an embryo or foetus) and are associated with low folic acid levels and megaloblastic anaemia; a blood disorder marked by the appearance of very large red blood cells (Carl 1992; Gladstone 1992; Meador 2008; Morrow 2006; Nulman 1997). PHT is particularly associated with “fetal hydantoin syndrome”, the name given to a group of birth defects associated with exposure to phenytoin (Scheinfeld 2003), and phenobarbitone has been associated with behavioural disturbances particularly in children (de Silva 1996; Trimble 1988). These agents are however still used as first-line drugs in low to middle-income countries (Ogunrin 2005; Pal 1998).

Carbamazepine and valproate are also associated with congenital abnormalities (Canger 1999; Gladstone 1992; Morrow 2006; Nulman 1997; Tomson 2011). A systematic review found valproate to have the highest incidence of congenital malformations of traditional first-line antiepileptic drugs (Meador 2008), particularly spina bifida as well as cardiac, craniofacial, skeletal and limb defects known as ‘valproate syndrome’ (Ornoy 2009). A recent study has shown an increased prevalence of neurodevelopmental disorders following prenatal valproate exposure (Bromley 2013). In the last 20 years, a second-generation of antiepileptic drugs including oxcarbazepine, lamotrigine, gabapentin, topiramate and most recently levetiracetam and zonisamide have been licensed as monotherapy following demonstrations of efficacy compared to the traditional antiepileptic drugs (Baulac 2012; Bill 1997; Brodie 1995; Brodie 1999; Brodie 2007; Chadwick 1998; Christe

1997; Dam 1989; Guerreiro 1997; Marson 2007a; Marson 2007b; Privitera 2003; Reunanen 1996; Rowan 2005; Steiner 1999; Trinka 2012). Comparative studies have also shown the newer antiepileptic drugs to be generally well tolerated as monotherapy in both adults and children and related to fewer adverse events, fewer serious adverse events, fewer teratogenic effects and fewer drug interactions with concomitant antiepileptic drugs and other concomitant medications than the traditional first-line antiepileptic drugs (French 2004; French 2007).

Current guidelines from the National Institute for Health and Care Excellence (NICE) for adults and children recommend carbamazepine or lamotrigine as first-line treatment for partial onset seizures and valproate for generalised onset seizures, on the condition that women and girls of childbearing are made aware of the potential teratogenic effects of the drug (NICE 2012).

How the intervention might work

Antiepileptic drugs suppress seizures by reducing neuronal excitability (disruption of the usual mechanisms of a neuron within the brain which may lead to an epileptic seizure). Different antiepileptic drugs have different mechanisms of action; therefore certain antiepileptic drugs are more effective at treating different seizure types. For example, there are reports of efficacy for valproate in generalised epilepsy syndromes such as juvenile myoclonic epilepsy and absence epilepsy (Bourgeois 1987; Delgado-Escueta 1984; Grünwald 1993; Jeavons 1977; Penry 1989), while carbamazepine on the other hand is reported to exacerbate some generalised seizure types such as myoclonic and absence seizures (Liporace 1994; Shields 1983; Snead 1985).

The majority of traditional antiepileptic drugs are thought to have multiple mechanisms of action such as through blocking ion channels, binding with neurotransmitter receptors or through inhibiting the metabolism or reuptake of neurotransmitters. However the precise mechanism of action is not known for all antiepileptic drugs, particularly valproate. It is thought that one of the mechanisms of action of phenytoin, valproate, carbamazepine, oxcarbazepine and lamotrigine is via blocking of sodium channels (Dichter 1996; Faigle 1990; Granger 1995; Grant 1992; Lees 1993; McLean 1986; Pinder 1977; Ragsdale 1991; Willow 1985), while phenobarbitone binds with gamma-aminobutyric acid (GABA) A receptors (Rho 1996). The similar anticonvulsant mechanisms of these drugs make them broad-spectrum treatments for many seizure types.

Zonisamide is thought to have multiple mechanisms of action (Endoh 1994; Kawai 1994; Okada 1998; Sackellares 2004; Schauf 1987; Suzuki 1992; Zhu 1999), while the mechanism of actions of gabapentin and topiramate are not fully understood (Coulter 1993; Dichter 1996; Hill 1993; McClean 1995; McLean 1999; White 1997). Levetiracetam has a novel mode of action which is different from that of other antiepileptic drugs (Cho 2011); it is thought to exhibit its antiepileptic effect by binding to synaptic

vesicle protein 2A (encoded within the SV2A gene), influencing excitatory neurotransmitter release (Gillard 2006; Lynch 2004).

Why it is important to do this review

With evidence that up to 70% of individuals with active epilepsy have the potential to go into long term remission of seizures shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), the correct choice of first-line antiepileptic therapy for individuals with newly diagnosed seizures is of great importance. There are currently over 50 drugs available worldwide for the treatment of various seizure types (Epilepsy Foundation of America 2013), therefore it is important that the choice of antiepileptic drugs for an individual is made using the highest quality evidence regarding potential benefits and harms of various treatments. It is also important that effectiveness and tolerability of antiepileptic drugs appropriate to given seizure types are compared to one another. For the treatment of partial and generalised onset tonic clonic seizures we will include in our evidence base the following 10 antiepileptic drugs which are currently licensed and used in clinical practice for use as monotherapy in at least one country:

1. carbamazepine;
2. phenytoin;
3. valproate;
4. phenobarbitone;
5. oxcarbazepine;
6. lamotrigine;
7. gabapentin;
8. topiramate;
9. levetiracetam;
10. zonisamide.

We have published a series of Cochrane systematic reviews investigating pairwise monotherapy comparisons using individual participant data (Gamble 2009; Marson 2000; Nolan 2013a; Nolan 2013b; Nolan 2013c; Tudur Smith 2009; Tudur Smith 2010). Each Cochrane review and meta-analysis provides high quality evidence for each pair of drugs but does not inform a choice between the whole evidence base of appropriate drugs for decision makers, clinicians or individuals with epilepsy. Furthermore, direct evidence from randomised controlled trials (RCTs) is not available between some of the drugs in our evidence base (such as between oxcarbazepine and phenobarbitone); therefore it is not possible to make pairwise comparisons of treatment effects between all ten drugs. Pairwise comparisons between certain drugs are unlikely to be made in the future; for example as phenobarbitone is no longer considered to be a first-line treatment as monotherapy for epilepsy, it is unlikely that a RCT will be designed in the future to compare oxcarbazepine with phenobarbitone (Tudur Smith 2007). However, it is possible to estimate an indirect treatment effect size between OXC and phenobarbitone by using existing evidence comparing oxcarbazepine with phenytoin and phenytoin with phenobarbitone (Nolan 2013a; Nolan 2013b). By similar methodology,

an indirect pairwise comparison is possible for all ten drugs in our treatment network. Indirect comparisons are also valuable in the case that a limited amount of data is available to inform a direct comparison or in the case that evidence informing a direct comparison is of poor methodological quality. The power and precision of a treatment effect estimate can be increased by “borrowing strength” from the indirect evidence in the network of treatments (Bucher 1997). Eight of the antiepileptic drugs included in this review have been included in an IPD network meta-analysis of epilepsy monotherapy drugs (Tudur Smith 2007). We wish to update the information in this network meta-analysis with new evidence from studies published since 2007 and including evidence for two drugs which were licensed for use as monotherapy after 2007.

As noted in the series of Cochrane reviews investigating pairwise monotherapy comparisons, the important efficacy outcomes in epilepsy monotherapy trials often require analysis of time-to-event data (for example, time to first seizure after randomisation or time to withdrawal of allocated treatment). Although methods have been developed to synthesise time-to-event data using summary information (Parmar 1998; Williamson 2002), the appropriate statistics are not commonly reported in published epilepsy trials (Altman 1995; Nolan 2013).

Furthermore, although seizure data have been collected in most epilepsy monotherapy trials, we have seen little uniformity in the definition and reporting of outcomes. For example, trials may report time to 12 month remission but not time to first seizure or vice versa or some trials may define time to first seizure from the date of randomisation but others use date of achieving maintenance dose. Trial investigators have also adopted differing approaches to the analysis, particularly with respect to the censoring of time-to-event data. For these reasons, we performed the pairwise meta-analyses using IPD which helps to overcome these problems and is considered to be the ‘gold standard’ approach to synthesis of censored data (Parmar 1998). We will therefore also perform the network meta-analysis of epilepsy monotherapy drugs as an IPD analysis.

OBJECTIVES

To review the time to withdrawal, remission and first seizure of 10 antiepileptic drugs (carbamazepine, phenytoin, valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide) currently used as monotherapy in children and adults with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs using either:

- an adequate method of allocation concealment (e.g. sealed opaque envelopes);
- a quasi method of randomisation (e.g. allocation by date of birth).

Studies may be double-blind, single-blind or unblinded. We will exclude studies of a monotherapy design; in other words participants are randomised to treatment with a single drug throughout the study period. We will also exclude studies with an add-on, polytherapy, transitional or withdrawal to monotherapy periods of any length.

We will include studies of parallel designs will be included. We will exclude studies of a cross-over design as we believe this design is inappropriate for measuring our primary time-to-event outcome 'time to withdrawal of allocated treatment' as a withdrawal of allocated treatment in the first treatment period would mean that the participant could not cross into the second treatment period, potentially leading to a large amount of incomplete outcome data and therefore a reduction in statistical power. Furthermore, the use of cross-over designs is no longer recommended in epilepsy due to concerns over study duration, large proportions of dropouts, unblinding of masked treatments as participants cross into the second period and potential carryover effects; a particular concern in studies of a monotherapy design which aim to assess the effect of a single treatment (Engel 2008; Wyllie 2006).

Types of participants

Children or adults with partial onset seizures (simple partial, complex partial, or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures (with or without other generalised seizure types). We will not include participants with other generalised seizure types alone (for example absence seizures alone without generalised tonic clonic seizures) as guidelines for the first-line treatment of other generalised seizure types are often different from the guidelines for generalised tonic-clonic seizures (NICE 2012), and due to documented evidence that certain drugs of interest in our review may exacerbate some generalised seizure types (How the interventions might work). We will also consider individuals with a new diagnosis of epilepsy, or who had had a relapse following antiepileptic monotherapy withdrawal.

We will exclude studies which consider antiepileptic drugs as treatment for conditions other than epilepsy.

Types of interventions

We will include the 10 antiepileptic drugs currently licensed and used as monotherapy in our network of treatments: carbamazepine, phenytoin, valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide. Included studies must make at least one pairwise comparison between at least 2 of the 10 antiepileptic drugs included in our network. For studies with three treatment arms or more, we will include treatment arms only of the 10 antiepileptic drugs included in our network; treatment arms of drugs not included in our network will be excluded from analysis. We will not make pairwise comparisons (direct or indirect) between any antiepileptic drugs not specified above. We will make pairwise comparisons (based on direct and/or indirect evidence) between all 10 drugs (Data synthesis).

Types of outcome measures

We will investigate the following outcomes in this review (Primary outcomes; Secondary outcomes). Reporting of these outcomes in the original trial report is not an eligibility requirement for inclusion in this review.

Primary outcomes

Time to withdrawal of allocated treatment (retention time). This is a combined outcome reflecting both efficacy and tolerability as treatment may be withdrawn due to continued seizures, adverse effects or a combination of both. This is an outcome to which the participant makes a contribution, and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Glauser 2006; ILAE Commission on Antiepileptic Drugs 1998)

Secondary outcomes

1. Time to achieve 12 month seizure-free period (remission) after randomisation
2. Time to achieve six month seizure-free period (remission) after randomisation
3. Time to first seizure post randomisation
4. Occurrence of adverse events (to be reported narratively) (Data synthesis)

Search methods for identification of studies

We will search the following databases with no language restrictions:

- the Cochrane Epilepsy Group Specialised Register using the search strategy outlined in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) using the search strategy outlined in Appendix 2;

- MEDLINE using the search strategy outlined in [Appendix 3](#);
- SCOPUS using the search strategy outlined in [Appendix 4](#);
- ClinicalTrials.gov (<http://clinicaltrials.gov/>) using the search terms '(Carbamazepine OR Phenytoin OR Valproic Acid OR Phenobarbital OR Oxcarbazepine OR Lamotrigine OR Gabapentin OR Topiramate OR Levetiracetam OR Zonisamide) AND epilepsy';
- (the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialssearch/>), using the search terms '(Carbamazepine OR Phenytoin OR Valproic Acid OR Phenobarbital OR Oxcarbazepine OR Lamotrigine OR Gabapentin OR Topiramate OR Levetiracetam OR Zonisamide) AND epilepsy'.

We will also review reference lists of retrieved studies to search for additional reports of relevant studies and review relevant conference proceedings and contact experts in the field for details of any ongoing or unpublished studies.

Data collection and analysis

Selection of studies

One author (SJM) will screen all titles and abstracts of all studies identified by the electronic searches as described in [Search methods for identification of reviews](#) according to the inclusion criteria specified above ([Types of studies](#); [Types of participants](#); [Types of interventions](#)). Subsequently, two authors (SJM and AGM) will independently assess full-text publications according to the same inclusion criteria specified above. We will resolve disagreements by discussion or by consulting a third author (CT) where necessary. We will record the reasons for exclusion of studies at both stages of study selection. We will contact trial authors for clarification if eligibility of a study is unclear from the published information.

Data extraction and management

For all studies meeting our inclusion criteria, two authors (SJM and AGM) will send a data request form to the first and/or corresponding author of the study or to the study sponsor where appropriate (referred to as data providers herein).

Our data request form will ask the data providers if the following information is available (tick yes or no).

- Trial methods:
 - method of generation of random list;
 - method of concealment of randomisation;
 - stratification factors;
 - blinding methods.
- Participant covariates:

- sex;
- age;
- seizure types;
- epilepsy status (newly diagnosed / relapsed seizures following drug withdrawal);
- time between first seizure and randomisation;
- number of seizures prior to randomisation (with dates);
- presence of neurological signs;
- electroencephalography (EEG) results;
- computed tomography (CT) or magnetic resonance imaging (MRI) results;
- aetiology of seizures (if known).
- Follow-up data:
 - treatment allocation;
 - date of randomisation;
 - dates of follow up;
 - dates of seizures post randomisation or seizure frequency data between follow-up visits;
 - dates of treatment withdrawal and reason(s) for treatment withdrawal;
 - starting dose of treatment;
 - dates of dose changes;
 - adverse events reported.

We will also request for any available, related documents such as case report forms, study protocols, clinical summaries from data providers.

In the event of no response to our IPD request, we will send a follow-up e-mail to the original data provider contacted. If we still receive no response for a particular study we will attempt to contact another study author or sponsor where appropriate. If a data provider is unable to make IPD available to us, we will request any aggregate data related to our outcome not reported in the publication.

If data cannot be obtained (no response to any requests or IPD is not available), two independent authors (SJM and MS) will assess whether any relevant and appropriate aggregate level data has been reported in the trial publication. We will resolve any disagreements on extracted aggregate data by discussion or by consulting a third author (CT) if necessary.

We will store all obtained data on a secure, dedicated network drive accessible only to the statisticians performing analysis (SJM, MS, CT). We will check all provided data for consistency and prepare them for analysis according to a pre-specified procedure prepared by one author (SJM) (available on request) and piloted by two authors (SJM and MS). For each trial where IPD are supplied, we will reproduce results from trial findings where possible and we will perform the following consistency checks:

- trial details cross-checked against any published report of the trial; original trial authors to be contacted if missing data, errors or inconsistencies are found;
- review of the chronological randomisation sequence by

checking the balance of prognostic factors, taking account of factors stratified for in randomisation procedure.

We will discuss any inconsistencies in the provided data with the corresponding data providers. If large or major inconsistencies are present which cannot be resolved by data providers, we will not include the data in any analyses. If minor inconsistencies are present, we will analyse the data and conduct sensitivity analyses to test the robustness of results ([Sensitivity analysis](#)).

For the analysis of time to withdrawal of allocated treatment as a time-to-event outcome, we define an 'event' as either the withdrawal of the allocated treatment due to poor seizure control or adverse events or both. Non-compliance with the treatment regimen or the addition of another antiepileptic drug will also be classed as 'events'. The outcome will be censored if treatment was withdrawn because the individual achieved a period of remission, if a participant withdrew from allocated treatment for reasons not related to the treatment (such as loss to follow-up) or if the individual was still on allocated treatment at the end of follow-up. Two authors (SJN and AG) will independently review reasons for treatment withdrawal for classification as events or censored observations, and we will resolve any disagreements by mutual discussion or by involving a third author (CT).

If seizure data are provided or recorded in terms of the number of seizures recorded between clinic visits rather than specific dates of seizures, to enable time-to-event outcomes to be calculated, we will apply linear interpolation to approximate the dates on which seizures occurred. For example, if four seizures were recorded between two visits which occurred on March 1st and May 1st (an interval of 61 days), then date of first seizure would be approximately March 13th. This will allow an estimate of the time to six-month and 12-month remission and the time to first seizure to be computed.

We will calculate time to six-month and 12-month remission from the date of randomisation to the date (or estimated date) the individual had first been free of seizures for six or 12 months respectively. If the person had one or more seizures in the titration period, a six-month or 12-month seizure-free period could also occur between the estimated date of the last seizure in the titration period and the estimated date of the first seizure in the maintenance period

We will calculate time to first seizure from the date of randomisation to the date that their first seizure was estimated to have occurred. If seizure data are missing for a particular visit, these outcomes will be censored at the previous visit. These outcomes will also be censored if the individual died or if follow-up ceased prior to the occurrence of the event of interest.

Assessment of risk of bias in included studies

Two independent authors (SJN, JW) will assess risk of bias in all included trials using the Cochrane Collaboration's tool for assess-

ing risk of bias ([Higgins 2011](#)). The following methodological criteria are assessed according to this tool:

- selection bias (sequence generation and allocation concealment);
- performance bias (blinding of participants and personnel);
- detection bias (blinding of outcome assessment);
- attrition bias (incomplete outcome data);
- reporting bias (selective outcome reporting).

We will resolve any disagreements by discussion. In theory, a review using IPD should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated. Any selective reporting bias detected could be assessed with the Outcome Reporting Bias in Trials (ORBIT) classification system ([Kirkham 2010](#)). As specified in [Data extraction and management](#), we will ask the data providers to provide trial methods such as randomisation and blinding methods, and we will discuss any missing data and/or inconsistencies with them.

We will conduct sensitivity analyses by excluding any study judged to be at high risk of bias for any methodological aspect ([Sensitivity analysis](#)).

Measures of treatment effect

We will summarise all time-to-event outcomes using the hazard ratio (HR) as the measure of treatment effect. We will calculate outcomes from IPD provided where possible or extract them from published studies. We will not attempt to analyse or synthesise adverse event data; a large range of different adverse events are thought to be associated with the 10 different drugs and such data is generally collected and presented in different ways across studies. For these reasons, we believe a synthesis of adverse event data would present only selective information while a narrative description of adverse event data from IPD or extracted from published studies will be the most informative way of presenting this data.

Unit of analysis issues

We do not anticipate any unit of analysis issues. For inclusion in the review, the unit of allocation must be individual and studies of a repeated measures (longitudinal) nature or of a cross-over design are not eligible for inclusion

Dealing with missing data

For all included studies, we will conduct an assessment of the proportion of missing outcome, demographic and covariate data and make a judgement regarding the extent and nature of missing data (e.g. missing at random, missing not at random). We will attempt to contact all study authors in order to request relevant data; we will include any information regarding missing data in such requests ([Data extraction and management](#)). If further information regarding missing data cannot be provided and we judge that an

important proportion of data (particularly outcome data) is missing, we will conduct sensitivity analyses to investigate the potential impact of the missing data (for example best case scenario or worst case scenario analyses, assuming those with missing outcome data all have a favourable/unfavourable outcome, respectively).

Assessment of heterogeneity

We will use a fixed-effect model for all pairwise and network meta-analyses in the first instance ([Data synthesis](#)). For each pairwise comparison, we will assess the presence of heterogeneity statistically using the Q test (P value < 0.10 for significance) and the I² statistic with the following interpretation ([Higgins 2003](#)).

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will also assess the presence of heterogeneity by visually inspecting forest plots, particularly in terms of the magnitude and direction of effects. If considerable heterogeneity is found to be present, we will perform network meta-analysis with random effects and inspect trial and participant characteristics for sources of heterogeneity.

Assessment of reporting biases

Two authors (SJN and JW) will undertake a full risk of bias check for each eligible study, including risk of reporting biases. In theory, a review using IPD should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated. We will assess potential selective reporting bias using the ORBIT classification system ([Kirkham 2010](#)). As specified in [Data extraction and management](#), we will ask the data providers for trial methods such as randomisation and blinding methods, and we will discuss any missing data and inconsistencies with them.

Data synthesis

We will present all direct evidence visually via a treatment network diagram of the 10 antiepileptic treatments. This treatment diagram will have a maximum of direct 45 pairwise comparisons

We will take an intention-to-treat approach to analysis; in other words, participants will be analysed in the group to which they were randomised in an individual trial, irrespective of which treatment they actually received. Therefore, for time-to-event outcomes, 'time to six month remission', 'time to 12 month remission' and 'time to first seizure post randomisation' participants will not be censored if treatment was withdrawn. For the primary outcome, time to withdrawal of allocated treatment, we will consider withdrawals due to lack of efficacy (i.e. recurrent seizures), poor tolerability (i.e. adverse events) or a combination of both poor efficacy and tolerability. Other withdrawals such as losses to follow

up, non-treatment related deaths, administrative trial reasons etc. will be censored at the time of withdrawal.

For all time-to-event outcomes, we will investigate the relationship between the time-to-event and treatment effect of the anti-epileptic drugs. We will use Cox proportional hazards regression models will be used to obtain study-specific estimates of log(HR) or treatment effect and associated standard errors. The model assumes that ratio of hazards (risks) between the two treatment groups is constant over time (i.e. hazards are proportional). This proportional hazards assumption of the Cox regression model will be tested for each outcome of each study by testing the statistical significance of a time-varying covariate in the model for each study. If a violation of this assumption is detected, we will perform sensitivity analyses via interval censored (piecewise) Cox models. To preserve the within-trial randomisation, we will stratify Cox regression models by trial.

A key assumption made in network meta-analysis is that treatment effect is "exchangeable" across all included trials; in other words, the indirect comparison made between two treatments is a feasible comparison to make (known as the transitivity assumption) and that the indirect evidence is consistent with the direct evidence where a comparison exists (known as the consistency assumption). Transitivity requires that all treatments are "jointly randomisable"; in other words, all 10 antiepileptic drugs could feasibly be randomised in the same trial and those which are not treatment arms in any given trial are "missing at random" ([Lu 2006](#)). This assumption can not be formally tested statistically; transitivity must be judged by careful consideration of trial settings and characteristics, treatment mechanisms and participant demographics to investigate if any differences would be expected to modify relative treatment effects. The consistency assumption can be evaluated statistically via the Bucher Method ([Bucher 1997](#)), which applies a z-test to the difference between the direct treatment effect estimate and the indirect estimate for each loop of evidence. Given the simplicity of this test, the influence of the precision of the treatment effect estimate on the result of this test and the complexity introduced by multi-arm trials and therefore association between treatment effects estimated from arms of the same trial, we will use a conservative significance threshold of 10% (P value < 0.1) to judge the presence of heterogeneity. We will also evaluate the presence of inconsistency statistically by comparing the fit of the consistency model (the primary analysis model) to the inconsistency model (the primary model adjusted for inconsistency factors) ([Higgins 2012](#); [Lu 2006](#)).

We will perform all analyses using statistical software packages SAS (version 9.2) (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.), Stata software version 11.2 ([StataCorp 2009](#)), or R version 2.13 ([CRAN 2011](#)). At the time of writing, a data access system is under development to enable secure access to de-identified pharmaceutical data from clinical trials (ClinicalStudyDataRequest.com) (<https://>

clinicalstudydatarequest.com/Default.aspx). It is currently unclear which format participant data held within this secure data access system will in and therefore which statistical package(s) we will be able to use for analysis. We anticipate this will become clear by the time of analysis in the review.

For the 10 antiepileptic drugs included in the treatment network, we are able to make 45 possible pairwise comparisons for both partial and generalised onset seizures. For clinical interest and relevance, we will present HR estimates for each antiepileptic drug in the network compared to the current recommended first-line treatments (carbamazepine or lamotrigine for partial onset seizures and valproate for generalised onset seizures) in the main results of this review via forest plots, and we will present the results for all 45 pairwise comparisons by seizure type as an 'Additional table' for each outcome.

Subgroup analysis and investigation of heterogeneity

There are strong clinical beliefs that certain antiepileptic drugs are more effective in certain seizure types than others, for example carbamazepine is more effective in partial onset seizures and valproate is more effective in generalised onset seizures (Marson 2000), suggesting that there is a treatment by seizure type (partial or generalised) interaction; if such an interaction exists then the key assumption of an exchangeable treatment effect across all included trials would be violated. To account for this, we will conduct all analyses separately by epilepsy type (partial onset or generalised onset) according to the classification of main seizure type at baseline. Partial seizures (simple or complex) and partial secondarily generalised seizures are classified as partial epilepsy. Primarily generalised seizures are classified as generalised epilepsy. We will then judge exchangeability of treatment effect separately by analyses of seizure type. If sufficient demographic participant level data is made available to us, we will also consider stratified or subgroup analyses according to participant covariates specified in [Data extraction and management](#) as potential magnifiers of treatment effect and as potential sources of heterogeneity and/or inconsistency. Specifically, in addition to differences between seizure types, we would also like to explore differences in age of seizure onset (paediatric onset, adult onset, elderly onset), seizure frequency before randomisation (time since first ever seizure and/or num-

ber of seizures before randomisation) and aetiology of seizures (if known according to pre-treatment investigations such as EEG, CT and/or MRI scan).

Sensitivity analysis

As discussed above ([Data extraction and management](#)), we will discuss any inconsistencies in provided data with the corresponding data providers. If large or major inconsistencies are present which cannot be resolved by data providers, we will not include the data in any analyses. If minor inconsistencies are present, we will include the data in analyses and pursue sensitivity analyses to test the robustness of results included in this data. The exact sensitivity analyses we would perform would depend on the inconsistency present.

Given that misclassification of seizure type is a recognised problem in epilepsy (whereby some individuals with generalised seizures have been mistakenly classed as having partial onset seizures and vice versa) and such misclassification did impact upon the results of a review in our series of pairwise reviews for monotherapy in epilepsy comparing phenytoin and sodium valproate in which nearly 50% of participants analysed may have had their seizure type misclassified (Nolan 2013b), we intend to investigate the potential impact of misclassification on results in a sensitivity analysis. Given clinical evidence that individuals with generalised onset seizures are unlikely to have an 'age of onset' greater than 25 to 30 years (Malafosse 1994), we will examine the distribution of age at onset for individuals with generalised seizures. We intend to undertake two sensitivity analyses to investigate misclassification:

- re-classification of all individuals with generalised seizure types and age at onset greater than 30 into an 'unclassified seizure type' group;
- re-classification of all individuals with generalised seizures and age of onset greater than 30 as having partial onset seizures.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy for the Cochrane Epilepsy Groups Specialised Register

#1 MeSH DESCRIPTOR Carbamazepine Explode All WITH AD AE AG AA AN AI BL CF CS CH CL CT DU EC HI IM IP ME PK PD PO RE ST SD TU TO UR

#2 Carbamazepine OR CBZ OR SPD417 OR Apo-Carbamazepine OR Atretol OR Biston OR Calepsin OR Carbagen OR Carbamazepin OR Carbatrol OR Carbazepine OR Carbelan OR Epitol OR Equetro OR Finlepsin OR Karbamazepin OR Lexin OR Neurotol OR Novo-Carbamaz OR Nu-Carbamazepine OR Sirtal OR Stazepin OR Stazepine OR Taro-Carbamazepine OR Tegretal OR Tegretol OR Telesmin OR Teril OR Timonil

#3 #1 OR #2

#4 MeSH DESCRIPTOR Phenytoin Explode All WITH AD AE AG AA AN AI BL CF CS CH CL CT DU EC HI IM IP ME PK PD PO RE ST SD TU TO UR

#5 Dihydantoin OR Diphenylhydantoin OR Diphenylhydantoine OR Diphenylhydatanoin OR Fenitoina OR Phenytoine OR Phenytoinum OR Aleviatin OR Antisacer OR Auranile OR Causoin OR Citrullamon OR Citrulliamon OR Comital OR Comitoina OR Convul OR Danten OR Dantinal OR Dantoinal OR Dantoine OR Denyl OR Di-Hydan OR Di-Lan OR Di-Phetine OR Didan OR Difenilhidantoina OR Difenin OR Difetoin OR Difhydan OR Dihycon OR Dilabid OR Dilantin OR Dilantine OR Dillantin OR Dintoin OR Dintoina OR Diphantoin OR Diphedal OR Diphedan OR Diphenat OR Diphenin OR Diphenine OR Dipheninum OR Diphentoin OR Diphentyn OR Diphenylan OR Ditoinate OR Ekko OR Elepsindon OR Enkelfel OR Epamin OR Epanutin OR Epasmir OR Epdantoin OR Epdantoine OR Epelin OR Epifenyl OR Epihydan OR Epilan OR Epilantin OR Epinat OR Epised OR Eptal OR Eptoin OR Fenantoin OR Fenidantoin OR Fentoin OR Fenylepsin OR Fenytoin OR Fenytoine OR Gerot-epilan-D OR Hidan OR Hidantal OR Hidantilo OR Hidantina OR Hidantomin OR Hindatal OR Hydantal OR Hydantin OR Hydantoin OR Hydantoinal OR Hydantol OR Ictalis OR Idantoil OR Idantoin OR Iphenylhydantoin OR Kessodanten OR Labopal OR Lehydan OR Lepitoin OR Lepsin OR Mesantoin OR Minetoin OR Neos-Hidantoina OR Neosidantoina OR Novantoina OR Novophenytoin OR Om-hidantoina OR Om-Hydantoine OR Oxylan OR Phanantin OR Phantatine OR Phenatine OR Phenatoine OR Phenhydan OR Phenhydanin OR Phenitoin OR Phentoin OR Phentytoin OR Phenytek OR Phenytex OR Ritmenal OR Saceril OR Sanepil OR Silantin OR Sinergina OR Sodanthon OR Sodantoin OR Sodanton OR Solantin OR Solantoin OR Solantyl OR Sylantoic OR Tacosal OR Thilophenyl OR TOIN OR Zentrinal OR Zentropil OR PHT

#6 #4 OR #5

#7 MeSH DESCRIPTOR Valproic Acid Explode All WITH AD AE AG AA AN AI BL CF CS CH CL CT DU EC HI IM IP ME PK PD PO RE ST SD TU TO UR

#8 Avugane OR Baceca OR Convulex OR Delepsine OR Depacon OR Depakene OR Depakine OR Depakote OR Deproic OR Epitect OR Epilex OR Epilim OR Episenta OR Epival OR Ergenyl OR Mylproin OR Orfiril OR Orlept OR Selenica OR Stavzor OR Valcote OR Valparin OR Valpro OR Valproate OR Valproic OR VPA

#9 #7 OR #8

#10 MeSH DESCRIPTOR Phenobarbital Explode All WITH AD AE AG AA AN AI BL CF CS CH CL CT DU EC HI IM IP ME PK PD PO RE ST SD TU TO UR

#11 Fenobarbital OR Phenobarbital OR Phenobarbitone OR “Phenobarbituric Acid” OR Phenylethylbarbiturate OR “Phenylethylbarbituric Acid” OR Phenylethylmalonylurea OR Adonal OR Aephenal OR Agrypna OR Amylofene OR Aphenylbarbit OR Aphenyletten OR Barbenyl OR Barbinal OR Barbiphen OR Barbiphenyl OR Barbipil OR Barbita OR Barbivis OR Barbonal OR Barbophen OR Bardorm OR Bartol OR Bialminal OR Blu-Phen OR Cabronal OR Calmetten OR Calminal OR Cardenal OR Chinoïn OR Codibarbita OR Coronaletta OR Cratecil OR Damoral OR Dezibarbitur OR Dormina OR Dormiral OR Dormital OR Doscalun OR Duneryl OR Ensobarb OR Ensodorm OR Epanal OR Epidorm OR Epilol OR Episodal OR Epsylone OR Eskabarb OR Etilfen OR Euneryl OR Fenbital OR Fenemal OR Fenosed OR Fenylettae OR Gardenal OR Gardepanyl OR Glysoletten OR Haplopan OR Haplos OR Helional OR Hennoletten OR Henotal OR Hypnaletten OR Hypnette OR Hypno-Tablinetten OR Hypnogen OR Hypnolone OR Hypnoltol OR Hysteps OR Lefebar OR Leonal OR Lephebar OR Lepinal OR Lepinaletten OR Linasen OR Liquital OR Lixophen OR Lubergal OR Lubrokal OR Lumen OR Lumesettes OR Lumesyn OR Luminal OR Lumofridetten OR Luphenil OR Luramin OR Molinal OR Neurobarb OR Nirvonal OR Noptil OR Nova-Pheno OR Nunol OR Parkotal OR Pharmetten OR Phen-Bar OR Phenamal OR Phenemal OR Phenemalum OR Phenobal OR Phenobarbyl OR Phenoluric OR Phenolurio OR Phenomet OR Phenonyl OR Phenoturic OR Phenyletten OR Phenylal OR Phob OR Polcominal OR Prominal OR Promptonal OR Seda-Tablinen OR Sedabar OR Sedicat OR Sedizorin OR Sedlyn OR Sedofen OR Sedonal OR Sedonettes OR Sevenal OR Sinoratox OR Solfoton OR Solu-Barb OR Sombutol OR Somnolens OR Somnoletten OR Somnosan OR Somonal OR Spasepilin OR Starifen OR Starilettae OR Stental OR Talpheno OR Teolaxin OR Teoloxin OR Thenobarbital OR Theoloxin OR Triabarb OR Tridezibarbitur OR Triphenatol OR Versomnal OR Zadoletten OR Zadonal OR PB

#12 #10 OR #11

#13 Oxcarbazepine

#14 “GP 47680” OR OCBZ OR Oxcarbamazepine OR Actinium OR Barzepin OR Carbox OR Deprectal OR Lonazet OR Oxalepsy OR Oxetol OR Oxpın OR Oxrate OR Oxtellar OR Oxypine OR Pharozepine OR Prolepsi OR Timox OR Trexapın OR Trileptal OR Trileptin OR OXC

#15 #13 OR #14

#16 Lamotrigine

#17 “GW 273293” OR Lamotrigina OR Lamotriginum OR Lamictal OR Lamotrine OR Lamitrin OR Lamictin OR Lamogine OR Lamitor OR LTG

#18 #16 OR #17

#19 Gabapentin

#20 Gabapentine OR Gabapentino OR Gabapentinum OR Gabapetin OR Aclonium OR Fanatrex OR Gabarone OR Neogab OR Gralise OR Neurontin OR Novo-Gabapentin OR Nupentin OR GBP

#21 #19 OR #20

#22 Topiramate

#23 Tipiramate OR Topiramatum OR “Topiramic acid” OR Topamax OR TPM

#24 #22 OR #23

#25 Levetiracetam

#26 Levetiracetamum OR Levetiracetam OR Keppra OR LEV

#27 #25 OR #26

#28 Zonisamide

#29 Zonisamida OR Zonisamidum OR Zonegran OR Exceglan OR Excegram OR Excegran OR ZNS

#30 #28 OR #29

#31 #3 OR #6 OR #9 OR #12 OR #15 OR #18 OR #21 OR #24 OR #27 OR #30

#32 (adjunct* or “add-on” or “add on”) NOT monotherap*

#33 #31 NOT #32

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Carbamazepine] explode all trees

#2 Carbamezepine or CBZ or SPD417 or Apo-Carbamazepine or Atretol or Biston or Calepsin or Carbagen or Carbamazepin or Carbatrol or Carbazepine or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotol or Novo-Carbamaz or Nu-Carbamazepine or Sirtal or Stazepin or Stazepine or Taro-Carbamazepine or Tegretal or Tegretol or Telesmin or Teril or Timonil
#3 #1 or #2

#4 MeSH descriptor: [Phenytoin] explode all trees

#5 Dihydantoin or Diphenylhydantoin or Diphenylhydantoine or Diphenylhydatanoin or Fenitoina or Phenytoine or Phenytoinum or Aleviatin or Antisacer or Auranile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoinal or Dantoine or Denyl or Di-Hydan or Di-Lan or Di-Phetine or Didan or Difenilhidantoina or Difenin or Difetoin or Difhydan or Dihycon or Dilabid or Dilantin or Dilantine or Dillantin or Dintoin or Dintoina or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin or Diphenine or Dipheninum or Diphentoin or Diphentyn or Diphenylan or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin or Epdantoine or Epelin or Epifenyl or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fentoin or Fenylepsin or Fenytoin or Fenytoine or Gerot-epilan-D or Hidan or Hidantal or Hidantilo or Hidantina or Hidantomon or Hindatal or Hydantal or Hydantin or Hydantoin or Hydantoinal or Hydantol or Ictalis or Idantoil or Idantoin or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or Neos-Hidantoina or Neosidantoina or Novantoina or Novophenytoin or Om-hidantoina or Om-Hydantoine or Oxylan or Phanantin or Phanatine or Phenatine or Phenatoine or Phenhydan or Phenhydanin or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytek or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodantoin or Sodanton or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentrional or Zentropil or PHT
#6 #4 or #5

#7 MeSH descriptor: [Valproic Acid] explode all trees

#8 Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valcote or Valparin or Valpro or Valproate or Valproic or VPA

#9 #7 or #8

#10 MeSH descriptor: [Phenobarbital] explode all trees

#11 Fenobarbital or Phenobarbitol or Phenobarbitone or “Phenobarbituric Acid” or Phenylethylbarbiturate or “Phenylethylbarbituric Acid” or Phenylethylmalonylurea or Adonal or Aephenal or Agrypna or Amylofene or Aphenylbarbit or Aphenyletten or Barbenyl or Barbinal or Barbiphen or Barbiphenyl or Barbipil or Barbita or Barbivis or Barbonal or Barbophen or Bardorm or Bartol or Bialminal or Blu-Phen or Cabronal or Calmetten or Calminal or Cardenal or Chinoïn or Codibarbita or Coronaletta or Cratecil or Damoral or Dezibarbitur or Dormina or Dormiral or Dormital or Doscalun or Duneryl or Ensobarb or Ensodorm or Epanal or Epidorm or Epilol or Episedal or Epsylone or Eskabarb or Etilfen or Euneryl or Fenbital or Fenemal or Fenosed or Fenylettae or Gardenal or Gardepanyl or Glysoletten or Haplopan or Haplos or Helional or Hennoletten or Henotal or Hypnaletten or Hypnette or Hypno-Tablinetten or Hypnogen or Hypnolone or Hypnoltol or Hysteps or Lefebar or Leonal or Lephebar or Lepinal or Lepinaletten or Linasen or Liquital or Lixophen or Lubergal or Lubrokal or Lumen or Lumesettes or Lumesyn or Luminal or Lumofridetten or Luphenil or Luramin or Molinal or Neurobarb or Nirvonal or Noptil or Nova-Pheno or Nunol or Parkotal or Pharmetten or Phen-Bar or Phenamal or Phenemal or Phenemalum or Phenobarb or Phenobarbyl or Phenoluric or Phenolurio or Phenomet or Phenonyl or Phenoturic or Phenyletten or Phenyral or Phob or Polcominal or Prominal or Promptonal or Seda-Tablinen or Sedabar or Sedicat or Sedizorin or Sedlyn or Sedofen or Sedonal or Sedonettes or Sevenal or Sinoratox or Solfoton or Solu-Barb or Sombutol or Somnolens or Somnoletten or Somnosan or Somonal or Spasepilin or Starifen or Starilettae or Stental or Talpheno or Teolaxin or Teoloxin or Thenobarbital or Theoloxin or Triabarb or Tridezibarbitur or Triphenatol or Versomnal or Zadoletten or Zadonal or PB

#12 #10 or #11

#13 Oxcarbazepine or “GP 47680” or OCBZ or Oxcarbamazepine or Actinium or Barzepin or Carbox or Deprectal or Lonazet or Oxalepsy or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepine or Prolepsi or Timox or Trexapin or Trileptal or Trileptin or OXC

#14 Lamotrigine or “GW 273293” or Lamotrigina or Lamotriginum or Lamictal or Lamotrine or Lamitrin or Lamictin or Lamogine or Lamitor or LTG

#15 Gabapentin or Gabapentine or Gabapentino or Gabapentinum or Gabapetin or Aclonium or Fanatrex or Gabarone or Neogab or Gralise or Neurontin or Novo-Gabapentin or Nupentin or GBP

#16 Topiramate or Tipiramate or Topiramatum or “Topiramic acid” or Topamax or TPM

#17 Levetiracetam or Levetiracetamum or Levitiracetam or Keppra or LEV

- #18 Zonisamide or Zonisamida or Zonisamidum or Zonegran or Excegran or Excegram or Excegran or ZNS
- #19 #3 or #6 or #9 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)
- #21 MeSH descriptor: [Epilepsy] explode all trees
- #22 MeSH descriptor: [Seizures] explode all trees
- #23 (#20 or #21 or #22) in Trials
- #24 #19 and #23
- #25 (adjunct* or “add-on” or “add on” or adjuvant* or combination* or polytherap*) not monotherap*:ti (Word variations have been searched)
- #26 #24 not #25

Appendix 3. MEDLINE search strategy

1. exp Carbamazepine/
2. (Carbamezepine or CBZ or SPD417 or Apo-Carbamazepine or Atretol or Biston or Calepsin or Carbagen or Carbamazepen or Carbatrol or Carbazepine or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotol or Novo-Carbamaz or Nu-Carbamazepine or Sirtal or Stazepin or Stazepine or Taro-Carbamazepine or Tegretal or Tegretol or Telesmin or Teril or Timonil).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. 1 or 2
4. exp Phenytoin/
5. (Dihydantoin or Diphenylhydantoin or Diphenylhydantoine or Diphenylhydatanoin or Fenitoina or Phenytoine or Phenytoinum or Aleviatin or Antisacer or Auratile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoinal or Dantoine or Denyl or Di-Hydan or Di-Lan or Di-Phetine or Didan or Difenilhidantoina or Difenin or Difetoin or Difhydan or Dihycon or Dilabid or Dilantin or Dilantine or Dillantin or Dintoin or Dintoina or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin or Diphenine or Dipheninum or Diphentoin or Diphentyn or Diphenylan or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin or Epdantoine or Epelin or Epifeny or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fentoin or Fenylepsin or Fenytoin or Fenytoine or Gerot-epilan-D or Hidan or Hidantal or Hidantilo or Hidantina or Hidantomin or Hindatal or Hydantal or Hydantin or Hydantoin or Hydantoinal or Hydantol or Ictalis or Idantoil or Idantoin or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or Neos-Hidantoina or Neosidantoina or Novantoina or Novophenytoin or Omhidantoina or Om-Hydantoine or Oxylan or Phanantin or Phanatine or Phenatine or Phenatoine or Phenhydan or Phenhydanin or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytek or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodantoin or Sodanton or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentronal or Zentropil or PHT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. 4 or 5
7. exp Valproic Acid/
8. (Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valcote or Valparin or Valpro or Valproate or Valproic or VPA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. 7 or 8
10. exp Phenobarbital/
11. (Fenobarbital or Phenobarbitol or Phenobarbitone or “Phenobarbituric Acid” or Phenylethylbarbiturate or “Phenylethylbarbituric Acid” or Phenylethylmalonylurea or Adonal or Aephenal or Agrypinal or Amylofene or Aphenylbarbit or Aphenyletten or Barbenyl or Barbinal or Barbiphen or Barbiphenyl or Barbipil or Barbita or Barbivis or Barbonal or Barbophen or Bardorm or Bartol or Bialminal or Blu-Phen or Cabronal or Calmetten or Calminal or Cardenal or Chinoin or Codibarbita or Coronaletta or Cratecil or Damoral or Dezibarbitur or Dormina or Dormiral or Dormital or Doscalun or Duneryl or Ensobarb or Ensodorm or Epanal or Epidorm or Epilol or Episedal or Epsylone or Eskabarb or Etilfen or Euneryl or Fenbital or Fenemal or Fenosed or Fenylettae or Gardenal or Gardepanyl or Glysoletten or Haplopan or Haplos or Helional or Henoletten or Henotal or Hypnaletten or Hypnette or Hypno-Tablinetten or Hypnogen or Hypnolone or Hypnoltol or Hysteps or Lefebar or Leonal or Lephebar or Lepinal or Lepinaletten or

Linasen or Liquital or Lixophen or Lubergal or Lubrokal or Lumen or Lumesettes or Lumesyn or Luminal or Lumofridetten or Luphenil or Luramin or Molinal or Neurobarb or Nirvonol or Noptil or Nova-Pheno or Nunol or Parkotal or Pharmetten or Phen-Bar or Phenaemal or Phenemal or Phenemalum or Phenobal or Phenobarbyl or Phenoluric or Phenolurio or Phenomet or Phenonyl or Phenoturic or Phenyletten or Phenyral or Phob or Polcominal or Prominal or Promptonal or Seda-Tablinen or Sedabar or Sedicat or Sedizorin or Sedlyn or Sedofen or Sedonal or Sedonettes or Sevenal or Sinoratox or Solfoton or Solu-Barb or Sombutol or Somnolens or Somnoletten or Somnosan or Somonal or Spasepilin or Starifen or Starilettae or Stental or Talpheno or Teolaxin or Teoloxin or Thenobarbital or Theoloxin or Triararb or Tridezibarbitur or Triphenatol or Versomnal or Zadoletten or Zadonal or PB).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

12. 10 or 11

13. (Oxcarbazepine or "GP 47680" or OCBZ or Oxcarbamazepine or Actinium or Barzepin or Carbox or Deprectal or Lonazet or Oxalepsy or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepline or Prolepsi or Timox or Trexapin or Trileptal or Trileptin or OXC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

14. (Lamotrigine or "GW 273293" or Lamotrigina or Lamotriginum or Lamictal or Lamotrine or Lamitrin or Lamictin or Lamogine or Lamitor or LTG).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

15. (Gabapentin or Gabapentine or Gabapentino or Gabapentinum or Gabapetin or Aclonium or Fanatrex or Gabarone or Neogab or Gralise or Neurontin or Novo-Gabapentin or Nupentin or GBP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

16. (Topiramate or Tipiramate or Topiramatum or "Topiramic acid" or Topamax or TPM).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

17. (Levetiracetam or Levetiracetamum or Levitiracetam or Keppra or LEV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

18. (Zonisamide or Zonisamida or Zonisamidum or Zonegran or Excegran or Excegram or Excegran or ZNS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

19. 3 or 6 or 9 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. ((adjunct\$ or "add-on" or "add on" or adjuvant\$ or combination\$ or polytherap\$) not monotherap\$).ti.

21. 19 not 20

22. exp Epilepsy/

23. exp Seizures/

24. (epilep\$ or seizure\$ or convuls\$).tw.

25. 22 or 23 or 24

26. exp Pre-Eclampsia/ or exp Eclampsia/

27. 25 not 26

28. (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

29. clinical trials as topic.sh.

30. trial.ti.

31. 28 or 29 or 30

32. exp animals/ not humans.sh.

33. 31 not 32

34. 21 and 27 and 33

Appendix 4. SCOPUS search strategy

((TITLE (carbamazepine OR carbamezepine OR cbz OR spd417 OR apo-carbamazepine OR atretol OR biston OR calepsin OR carbagen OR carbamazepen OR carbatrol OR carbazepine OR carbelan OR epitol OR equetro OR finlepsin OR karbamazepin OR lexin OR neurotol OR novo-carbamaz OR nu-carbamazepine OR sirtal OR stazepin OR stazepine OR taro-carbamazepine OR tegretal OR tegretol OR telesmin OR teril OR timonil OR phenytoin OR dihydantoin OR diphenylhydantoin OR diphenylhydantoine OR diphenylhydatanoin OR fenitoina OR phenytoine OR phenytoinum OR aleviatin OR antisacer OR auranile OR causoin OR citrullamon OR citrulliamon OR comital OR comitoina OR convul OR danten OR dantinal OR dantoinal OR dantoine OR denyl OR di-hydan OR di-lan OR di-phetine OR didan OR difenilhidantoina OR difenin OR difetoin OR difhydan OR dihycon OR dilabid OR dilantin OR dilantine OR dillantint OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifeny OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantint OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR leptoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phenytoin OR phenytek OR phenytek OR ritmenal OR saceril OR sanepil OR silantin OR sinergina OR sodanthon OR sodantoin OR sodanton OR solantin OR solantoin OR solantyl OR sylantoic OR tacosal OR thilophenyl OR toin OR zentralon OR zentropil OR pht OR "Valproic Acid" OR avugane OR baceca OR convulex OR delepsine OR depacon OR depakene OR depakine OR depakote OR deproic OR epiject OR epilex OR epilim OR epilim OR episenta OR epival OR ergenyl OR mylproin OR orfiril OR orlept OR selenica OR stavzor OR valcote OR valparin OR valpro OR valproate OR valproic OR vpa OR phenobarbital OR fenobarbital OR phenobarbitol OR phenobarbitone OR "Phenobarbituric Acid" OR phenylethylbarbiturate OR "Phenylethylbarbituric Acid" OR phenylethylmalonylurea OR adonal OR aephenal OR agrypna OR amylofene OR aphenylbarbit OR aphenyletten OR barbenyl OR barbinal OR barbiphen OR barbiphenyl OR barbipil OR barbita OR barbivis OR barbonal OR barbophen OR bardorm OR bartol OR bialminal OR blu-phen OR cabronal OR calmetten OR calminal OR cardenal OR chinoin OR codibarbita OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dormital OR doscalun OR duneryl OR ensobarb OR ensodorm OR epanal OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenosed OR fenylettaa OR gardenal OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR henotal OR hypnaletten OR hypnette OR hypno-tablinetten OR hypnogen OR hypnolone OR hypnoltol OR hysteps OR lefebar OR leonal OR lephebar OR lepinal OR lepinaletten OR linasen OR liquital OR lixophen OR lubergal OR lubrokall OR lumen OR lumesettes OR lumesyn OR luminal OR lumofridetten OR luphenil OR luramin OR molinal OR neurobarb OR nirvonall OR noptil OR nova-pheno OR nunol OR parkotal OR pharmetten OR phenbar OR phenaemal OR phenemal OR phenemalum OR phenobal OR phenobarbyl OR phenoluric OR phenolurio OR phenomet OR phenonyl OR phenoturic OR phenyletten OR phenyral OR phob OR polcominal OR prominal OR promptonal OR sedatablinen OR sedabar OR sedicat OR sedizorin OR sedlyn OR sedofen OR sedonal OR sedonettes OR sevenal OR sinoratox OR solfoton OR solu-barb OR sombutol OR somnolens OR somnoletten OR somnosan OR somonal OR spasepilin OR starifen OR starilettaa OR stental OR talpheno OR teolaxin OR teoloxin OR thenobarbital OR theoloxin OR triarbarb OR tridezibarbitur OR triphenatol OR versomnal OR zadoletten OR zadonal OR pb OR oxcarbazepine OR "GP 47680" OR ocbz OR oxcarbamazepine OR actinium OR barzeppin OR carbox OR deprectal OR lonazet OR oxalepsy OR oxetol OR oxpin OR oxrate OR oxtellar OR oxypine OR pharozepine OR prolepsi OR timox OR trexapin OR tripleptal OR tripleptin OR oxc OR lamotrigine OR "GW 273293" OR lamotrigina OR lamotriginum OR lamictal OR lamotrine OR lamitrin OR lamictin OR lamogine OR lamitor OR lrg OR gabapentin OR gabapentine OR gabapentino OR gabapentinum OR gabapetin OR acloonium OR fanatrex OR gabarone OR neogab OR gralise OR neurontin OR novo-gabapentin OR nupentin OR gbp OR topiramate OR tipiramate OR topiramatum OR "Topiramic acid" OR topamax OR tpm OR levetiracetam OR levetiracetamum OR 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OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifenyl OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantin OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR lepitoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phentytoin OR phenytek OR phenytex OR ritmenal OR 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cluster OR "head to head") OR ABS(randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study) AND NOT INDEX(medl))) AND NOT (TITLE((adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*) AND NOT (monotherap* OR alone OR singl*)))

CONTRIBUTIONS OF AUTHORS

SJN wrote the protocol under the supervision of AGM and CT. MS and JW commented on drafts of the protocol

DECLARATIONS OF INTEREST

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SOURCES OF SUPPORT

Internal sources

- National Institute of Health Research, UK.

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External sources

- No sources of support supplied