COMMON REFERENCE-BASED INDIRECT COMPARISON META-
ANALYSIS OF NEW ANTIEPILEPTIC DRUGS AS ADD-ON TREATMENT
IN DRUG-RESISTANT PARTIAL EPILEPSY

PROTOCOL

Francesco Brigo, Giulia Turri, Luigi Giuseppe Bongiovanni

Department of Neurological, Neuropsychological, Morphological and Movement Sciences. Section of Clinical Neurology. University of Verona, Italy.

FINAL VERSION
CONTENTS

Section 1: Introduction
Section 2: Objectives
Section 3: Methods
3.1 Criteria for considering studies for this review
3.2 Search methods for identifications of studies
3.3 Data collection and analysis
3.4 Quality assessment
3.5 Statistical analysis
Section 4: Final report
References
Appendices:
A. Search strategies
B. Study selection and extraction form
C. PRISMA Flow diagram
D. PRISMA Checklist
SECTION 1: INTRODUCTION

Epilepsy is defined as the occurrence of at least two unprovoked epileptic seizures (International League Against Epilepsy, 1989). It is one of the most common neurologic disorders: in Western countries the incidence in adults is 50/100,000 per year (Hauser et al., 1998) with a prevalence of 5/1000 to 10/1000 (Goodridge et al., 1983; McDonald et al., 2000).

Despite the plethora of antiepileptic drugs (AEDs) developed since the introduction of phenobarbital in 1912, 30% of epilepsy patients continue having seizures (Kwan and Brodie, 2000). This group of patients requires a more aggressive treatment, since monotherapy, the first choice scheme, fails to control seizures. Nevertheless, polytherapy often results in a number of unwanted effects, including neurologic disturbances (somnolence, ataxia, dizziness), psychiatric and behavioral symptoms, and metabolic alteration (osteoporosis, inducement or inhibition of hepatic enzymes, etc.). The need for better tolerated AEDs is even more urgent in this group of patients.

In recent years several new antiepileptic drugs (AEDs), known as second- and third-generation AEDs, have been added to the clinical armamentarium for the treatment of partial epilepsy (Perucca et al., 2007; Fattore and Perucca, 2011; Brodie and Kwan, 2012). In randomized controlled trials (RCTs) each of these AEDs has been demonstrated to be superior to placebo when used as add-on therapy for drug-resistant partial epilepsy. However, these RCTs did not perform direct head-to-head comparisons between different AEDs, so that comparative data on which clinicians can support their decisions is still lacking.

Classical meta-analyses of RCTs focus on the pair-wise comparison between two treatments (e.g. treatment A versus treatment B), with each included trial providing information for the direct comparison between the two treatments. However, for some treatment (as for AEDs used as add-on treatment for drug-resistant partial epilepsy) direct head-to-head comparisons are not available, and consequently the treatment effect cannot be directly estimated. However, it is possible to estimate the indirect effect of treatment A versus treatment B using evidence from trials comparing treatment A with treatment C, and trials comparing treatment B with treatment C (Tudur Smith et al., 2007).

The common comparator (treatment C) may also be a placebo. The key assumption for the indirect comparison is that of exchangeability of the treatment effect across all included trials (ICWG, 2009).

The validity of indirect comparisons based on a common comparator (also known as “adjusted indirect comparison”, Song et al., 2003, or “common reference-based indirect comparison”, ICWG, 2009) depends upon the internal validity and similarity of the included trials (Song et al., 2003). Meta-analyses based on common reference-based indirect comparisons may therefore represent a useful tool where direct comparisons do not exist () such as in RCTs comparing newer AEDs with placebo for the treatment of drug-resistant partial epilepsy.

Two previous systematic reviews indirectly compared the effect of add-on LEV (Otoul et al., 2005) and add-on retigabine (Maryn-St James et al., 2012) with other new AEDs used as adjunctive therapy for drug-resistant partial epilepsy. However, these reviews performed only a few indirect comparisons and focused only on some AEDs, therefore providing only a partial fragment of the whole picture.

We therefore decided to undertake a systematic review with a common reference-based indirect comparison of RCTs that compared efficacy and acceptability of second- and third-generation AEDs against placebo in the treatment of adults with drug-resistant partial epilepsy. Our aim is to comprehensively synthesise data from the literature to provide a clinically useful summary that can guide treatment decisions. The present review represents the first attempt to indirectly compare each new AED with all other second- and third-generation AEDs.
This protocol will describe the methods and processes used with the level of detail and transparency required to report systematic reviews as described in the PRISMA guidance (http://www.prisma-statement.org/) (Liberati et al., 2009).

SECTION 2: OBJECTIVES

To compare individual new AEDs used as add-on treatment for adults with drug-resistant partial epilepsy in terms of:

1. Efficacy (expressed as dichotomous outcome), defined as fifty per cent or greater reduction in seizure frequency: proportion of participants with at least 50% reduction in seizure frequency at the end of the study compared to the pre-randomization baseline period.

2. Acceptability of treatment, defined as the proportion of patients who left the study early by any cause (withdrawal rate). The withdrawal rate is a global measure reflecting both efficacy and tolerability. In trials of short duration, the withdrawal rate mainly reflects discontinuations for side effects rather than a lack of efficacy on seizure frequency (Marson et al., 2001).

SECTION 3: METHODS

A systematic review involves the systematic and transparent identification, selection, extraction and synthesis of studies relevant to the research question. In this systematic review an approach is being adopted which will facilitate the investigation of indirect comparisons if feasible and required. The first stage of the systematic review is to define the criteria for considering studies.

3.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

To be included in the present review studies must meet all of the following inclusion criteria:
- Be a study of new AED as an adjuvant therapy, compared to placebo;
- Be a randomized, double-blind, placebo-controlled, add-on trial, or cross-over trial in which data from the first treatment period could be treated as a parallel study;
- Have recruited patients with drug-resistant partial epilepsy (i.e., simple partial, complex partial, and/or secondarily generalised tonic-clonic seizures not controlled by at least 2 or more other AEDs);
- Have a maintenance treatment period of 8 weeks or longer, with a prospective baseline of minimum 4 weeks.

Studies published as abstracts or conference presentations will be included in the analysis if reporting all of the above items.

Types of studies
Double-blind (patient and clinician) RCTS comparing one new AED with placebo used as oral add-on therapy in the treatment of partial drug-refractory epilepsy will be included. Quasi-randomized trials (such as those allocating by using alternate days of the week) will be excluded. Parallel and crossover RCTs will be considered for inclusion. For trials which have a crossover design only results from the first treatment period will be considered to avoid some possible carryover effect.
RCTs with a baseline period of at least 4 weeks and with a treatment period of 8 weeks or longer will be included. We will exclude all other study designs, including RCTs with “responder enriched” design, cohort studies, case-control studies, outcomes research, case studies, case series and expert opinion.

**Types of participants**
Adult patients of any gender with a primary diagnosis of drug-resistant partial epilepsy. Partial epilepsy includes simple partial, complex partial, and/or secondarily generalized tonic-clonic seizures (ILAE, 1989). Drug-resistant epilepsy is considered as an epilepsy not controlled by at least 2 or more other AEDs.
The study population of interest is adults aged over 18. Studies will be eligible for inclusion if the study population is fully adult (all participants aged over 18 years) or partially adult (some of the population are aged under 18). Separate analyses will be conducted to explore differences resulting from mixed populations as follows: (a) all included studies and (b) those studies recruiting samples which include populations aged under 18 years of age. There is no upper age limit; however studies where age is capped at 65 will not be excluded for that reason.
Studies reporting any baseline seizure rate will be included.
To be eligible for inclusion, study participants must have failed to respond to previous AEDs. The specific drugs and the number of previous treatments are not important to this review, although data on this aspect will be collected if provided.

**Types of interventions**
(1) Active treatment group receiving a second- or third-generation AED in addition to conventional antiepileptic drug treatment.
(2) Control group receiving matched placebo (used as a comparator) in addition to conventional antiepileptic drug treatment.

**AEDs**
RCTs directly comparing one of the following AED used as add-on treatment for drug-resistant partial epilepsy with placebo will be considered for inclusion (AEDs listed in alphabetical order):

- Eslicarbazepine acetate
- Felbamate
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Losigamone
- Oxcarbazepine
- Pregabalin
- Remacemide
- Retigabine
- Stiripentol
- Tiagabine
- Topiramate
- Zonisamide

These drugs must be adjuvant to other treatments. Study participants must be receiving at least one other AED. The type or dose of the other drugs is not a criterion for exclusion.
The exclusion of older AEDs is justified by the fact that, unlike these drugs, new AEDs 1. have much more favorable pharmacokinetic properties (i.e. less or no enzyme-induction or inhibition profile) responsible for minimal or no drug-drug interactions with concomitant AEDs; 2. have been primarily conceived and assessed as add-on treatments for drug-resistant partial epilepsy. The decision of including only new AEDs (drugs added to the clinical armamentarium in the last two decades) was taken also to minimize the possibility of an increase in placebo response rate over the years (so-called "placebo drift") (Guekht et al., 2010), thus ensuring adjusted indirect comparisons with a homogeneous placebo. In fact, the validity of the adjusted indirect comparison depends on the assumption that the two sets of placebo controlled trials are sufficiently similar for moderators of relative treatment effect (Song et al., 2009).

**Types of outcome measures**

We chose dichotomous primary outcomes mainly for clinical reasons. We will use both the number of patients who responded and the number of patients who dropped out to have hard outcome measures of both treatment efficacy and acceptability. The use of odds ratios for binary outcomes was chosen because it is associated with less heterogeneity in meta-analysis than is the use of risk differences or relative risks (Deeks, 2002). The following outcomes (reported in studies meeting the inclusion criteria) relevant to the efficacy and acceptability of the intervention drug (versus placebo) will be collected:

1. **Overall efficacy of antiepileptic treatment**
   Overall efficacy will be measured as the proportion of participants with at least 50% reduction in seizure frequency at the end of the study compared to the pre-randomization baseline period (responder rate).

2. **Acceptability of treatment**
   Treatment discontinuation (acceptability) is defined as the proportion of patients who left the study early for any reason (side effects, lack of effect on seizures, protocol violations, etc.), out of the total number of patients randomly assigned to each treatment arm (withdrawal rate).

The outcomes will be collected for drug-resistant partial epilepsy of all types.

**3.2 Search methods for identification of studies**

**Electronic searches**

The literature search will be conducted in a range of relevant databases to identify studies reporting on the drugs of interest.

We will search the following databases:

- Cochrane Epilepsy Group Specialised Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) *(The Cochrane Library)*;
- MEDLINE;

For each database a specific search strategy have been developed (appendix A). No language restrictions will be imposed.

**Searching other resources**

Experts in the field will be contacted for information about any unpublished or ongoing studies. Reference lists of retrieved studies will be searched for additional reports of relevant studies. We will also undertake searches for grey literature and conference abstracts.

**3.3 Data collection and analysis**
Selection of studies
Two review authors will independently screen all the titles and abstracts of publications identified by the searches to assess their eligibility. Publications that do not meet the criteria at this stage will be excluded. Following screening, the full texts of eligible citations will be assessed for inclusion. The review authors will reach consensus on the selection of trials and the final list of studies. We will discuss any disagreements and resolve them, where possible. If we cannot reach consensus, we will consult a third reviewer.
The number of studies identified by the search and excluded at various stages will be recorded and reported in a PRISMA study flow diagram (appendix C).

Data extraction and management
Two review authors will independently extract the following characteristics of each included trial from the published reports, where possible. We will use data extraction forms and any disagreements will be resolved by mutual agreement. We will record the rawest form of the data, when possible. In the case of missing or incomplete data, we will contact the principal investigators of included trials and require additional information.
A structured data extraction form has been designed and will be used to ensure consistency of appraisal for each study (appendix B).
Information extracted will include:

Study characteristics
(a) First author
(b) Publication year
(c) Journal

Participant characteristics
(a) Age
(b) Sex
(c) Epileptic seizure type and epilepsy syndrome
(d) Number of seizures or seizure frequency prior to randomization (if available)
(e) Number and types of AEDs previously taken (if available)
(f) Concomitant AEDs (if available)

Trial characteristics
(a) Single centre / multicentre
(b) Country / Countries
(c) Trial design (i.e. parallel or cross-over)
(d) Inclusion and exclusion criteria
(e) Criteria used to diagnose epilepsy
(f) Number of partial-onset seizures per month used in inclusion criteria
(g) Definition of drug-resistant epilepsy adopted in the study
(h) Trial design (i.e. RCT, parallel group or cross-over)
(i) Method of randomization
(j) Number of patients randomized
(k) Number of patients in each intervention group
(l) Duration of the different phases of the trial (baseline, titration, maintenance and optional open-label extension (if any))

Active treatment and control
(a) Intervention given to controls
(b) AED given to active treatment group
(c) Dosage of active AED
(d) Duration of treatment period

Follow-up data
(a) Duration of follow-up
(b) Reasons for incomplete outcome data
(c) Drop-out or loss to follow-up rates
(d) Methods of analysis (e.g. intention-to-treat, per protocol, worst-case or best-case scenario analysis)

Outcomes
For each outcome following data will be extracted:
(1) Fifty per cent or greater reduction in seizure frequency: proportion of participants with at least 50% reduction in seizure frequency at the end of the study (numerator)/number of participants at pre-randomization baseline period (denominator).
(2) Number of participants that drop out or withdraw due to side effects, lack of efficacy or other reasons (numerator)/number of participants in pre-randomization baseline period (denominator).

3.4 QUALITY ASSESSMENT
Trial quality (internal validity) will be independently assessed by two review authors in accordance with the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) (Higgins and Green, 2011).
The Cochrane risk of bias tool consists of seven items, providing a framework for assessing the whole trial with explicit and transparent criteria.
Risk of bias will be assessed as low risk of bias, high risk of bias, or uncertain risk of bias. Following characteristics will be evaluated.
(1) Random sequence generation (selection bias).
(2) Allocation concealment (selection bias).
(3) Blinding of participants, personnel (performance bias).
(4) Blinding of outcome assessment (detection bias).
(5) Incomplete outcome data.
(6) Selective reporting (reporting bias).
(7) Other bias (including outcome reporting bias).
Two of the items (random sequence generation and allocation concealment) assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions; the third and fourth item (blinding) assesses the influence of performance and detection bias on the study results and the fifth the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The sixth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes (this item requires a comparison of published data with trial protocols, when such are available). The final item refers to other sources of bias that are relevant in certain circumstances, such as, for example, sponsorship bias. Each domain includes one or more specific entries in a ‘Risk of bias’ table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. Inadequate concealment undermines the principle of randomization, because participants may then be allocated to a treatment according to prognostic variables rather than by pure chance. Particular attention will be therefore payed to the adequacy of the random allocation concealment and double
blinding. Studies will be given a quality rating of A (adequate), B (unclear), and C (inadequate) according to these two items. Studies which will score A or B on these criteria constitute the final list of included studies. Where inadequate details of allocation concealment and other characteristics of trials are provided, the trial authors will be contacted in order to obtain further information.

3.5 **STATISTICAL ANALYSIS**

We will use statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins and Green, 2011) to measure treatment effect.

For each outcome, an intention-to-treat primary analysis will be made in order to include all patients in the treatment group to which they were allocated, irrespective of the treatment they actually received, hence including also drop-outs. The analysis will use intent-to-treat (ITT) data of all randomized patients recorded during the entire treatment period, including both titration and evaluation phases.

Analyses will be conducted using Revman 5 (conventional meta-analysis for each AED), Excel and R 2.15.1 (common reference-based indirect comparison meta-analysis).

**Conventional meta-analysis per AED**

A conventional meta-analysis of comparisons between each AED and placebo will be undertaken. Results from individual trials for each AED will be pooled by using random effects, inverse variance, weighted meta-analysis (DerSimonian and Laird, 1986).

Each outcome will be analysed by calculating odds ratios (OR) for each trial with the uncertainty being expressed using 95% CIs. For each outcome a weighted treatment effect across trials will be calculated. Mantel-Haenszel method will be used to estimate the odds ratio statistic and to combine ORs (Emerson, 1994).

Results of the conventional meta-analysis will be presented in forest plots.

**Random effects model**

Pair-wise meta-analyses will be performed by synthesizing studies that compare the same interventions using a random effects model (DerSimonian and Laird, 1986) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins and Green, 2011). Adjusted indirect comparison using the fixed effect model tend to underestimate standard errors of pooled estimates (Glenny et al., 2005; ICWG, 2009). Thus, the random effects model will be used for the quantitative pooling in both the direct and the adjusted indirect comparison (DerSimonian and Laird, 1986).

**Assessment of heterogeneity**

Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. Homogeneity among trial results will be evaluated using a standard Chi-squared test and the hypothesis of homogeneity will be rejected if the P value is less than 0.10.

Assessment of statistical heterogeneity will be supplemented using the I-squared ($I^2$) statistic which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al., 2003). The interpretation of $I^2$ for heterogeneity is as follows (Higgins and Green, 2011):

- 0% to 40%, may not be important;
• 30% to 60%, represents moderate heterogeneity;
• 50% to 90%, represents substantial heterogeneity;
• 75% to 100%, represents considerable heterogeneity.

We will assess and discuss possible sources of heterogeneity narratively.

Suitability of indirect comparisons
The suitability of indirect comparisons will be investigated considering whether studies are suitably similar by adopting the framework for assessing exchangeability assumption proposed by ICWG (ICWG, 2009).

Common reference-based indirect comparisons by combining meta-analyses of AEDs

Comparison method
We will conduct a common reference-based indirect comparison meta-analysis, which is a method of synthesizing information from trials addressing the same question but involving different interventions. For a given comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. In other terms, for the direct comparisons, comparison of the result of group A with the result of group B within a RCT give an estimate of the efficacy of intervention A versus B. However, indirect evidence is provided when studies that compare A versus C and B versus C are analyzed jointly.

Because none of the included trials directly compare an active AED with active comparators, an adjusted method of indirect comparison between each new AED will be performed using the results of two meta-analyses (e.g. antiepileptic A versus placebo and antiepileptic B versus placebo).

Statistical analysis
To perform common reference-based indirect comparisons we will use the method suggested by Bucher (Bucher et al., 1997). By means of this method, the indirect comparison of intervention A and B will be adjusted by the results of their direct comparisons with a common intervention C (placebo).

This adjusted method aims to overcome the potential problem of different prognostic characteristics between study participants among trials, and it is valid if the relative efficacy of interventions is consistent across different trials. In order for this indirect comparison to be valid, the overall characteristics of the trials included in the meta-analyses should not differ systematically.

The comparison between each AED and other AEDs will be performed using the ORs derived from the meta-analyses. Comparison of each binary outcome measure (response rate and withdrawal rate) will be performed using the log of OR and its variance derived from the meta-analyses (Bucher et al., 1997). The logs of the OR of each meta-analysis are asymptotically normally distributed and statistically independent. The estimate of the treatment effect (e.g. AED A versus AED B) will be therefore calculated by the difference (diff) between the logs of the 2 ORs:

\[
\text{Diff} = \ln \text{OR}_{\text{treatment A}} - \ln \text{OR}_{\text{treatment B}}
\]

The 95% confidence interval of this estimated effect will be derived from the standard error of the difference:

\[
[\ln \text{OR}_{\text{treatment A}} - \ln \text{OR}_{\text{treatment B}}] \pm (1.96 \times \text{SE (diff)})
\]
where \( SE(\text{diff}) = \sqrt{\text{variance}(\ln \ OR_{\text{treatment A}}) + \text{variance}(\ln \ OR_{\text{treatment B}})} \). Back transformation will be then performed to give the OR and its 95% CIs for the indirect comparisons.

By convention, ORs > 1 indicate that the outcome is more likely in the group receiving treatment A than in the group receiving placebo. The same will be applied for the treatment B. For the indirect comparisons, an OR > 1 indicates that the outcome is more likely with treatment A than with treatment B. A P value of 0.05 will be considered to be statistically significant.

**Subgroup analyses**

**Age of participants**
Separate analyses will be conducted to explore differences resulting from mixed populations as follows: (a) all included studies and (b) those studies recruiting samples which include populations aged under 18 years of age.

**Comparability of dosages**
The common reference-based indirect comparison meta-analysis will be undertaken comparing all dosages combined: when a trial included more than one dose of AED, the data for the different doses will be combined to estimate an overall effect for AED comparison. However, in order to avoid comparing trials using one AED at the upper limit of its therapeutic range with other studies using another agent at the lower limit of its therapeutic range (or even below therapeutic range) we will perform a subgroup analysis including in the adjusted indirect comparisons only RCTs in which AEDs were tested at dosage equal or superior to the World Health Organization Defined Daily Dose (DDD) (available at www.WHOCC.no/atc_ddd_index/?code=NO3A (World Health Organization, 2010). We decided to adopt DDD because in the literature there is no clear definition about equivalence of dosages among new-generation AEDs. DDD will be therefore employed to detect inequalities in dosing that could affect comparative efficacy, and will be used in the subgroup analysis by defining within the therapeutic dose only those studies that used comparable dosages equal or superior to the DDD.

**SECTION 4: FINAL REPORT**
The content of final report will be detailed according to the PRISMA reporting guidelines (http://www.prisma-statement.org/) (Liberati et al., 2009).
Two systematic reviews (one concerning only second-generation and one focusing on third-generation AEDs, i.e. Eslicarbazepine acetate, lacosamide, losigamone, remacemide and retigabine) will be submitted for publication separately. A final report reporting comparisons among both second- and third-generation AEDs will be also submitted for publication separately. Conventional meta-analysis for each AED can also be submitted for publication separately.
REFERENCES


Tudur Smith C, Marson AG, Chadwick DW, Williamson PR. Multiple treatment comparisons in epilepsy monotherapy trials. Trials. 2007 Nov 5;8:34.
APPENDICES
APPENDIX A: SEARCH STRATEGIES

MEDLINE search strategy


Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format

| #1 | randomized controlled trial [pt] |
| #2 | controlled clinical trial [pt] |
| #3 | randomized [tiab] |
| #4 | placebo [tiab] |
| #5 | drug therapy [sh] |
| #6 | randomly [tiab] |
| #7 | trial [tiab] |
| #8 | groups [tiab] |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #10 | animals [mh] NOT humans [mh] |
| #11 | #9 NOT #10 |
| #12 | antiepileptic drug.tw¹ |
| #13 | exp epilepsy/ OR epilep$.tw. |
| #14 | exp seizures/ OR seizure$.tw. |
| #15 | convolution$.tw. |
| #16 | 13 OR 14 OR 15 |
| #17 | 12 AND 16 |
| #18 | 11 AND 18 |

PubMed search syntax

¹#12 International non-proprietary name of the AED (e.g. Levetiracetam, Zonisamide, Pregabalin)
[pt] denotes a Publication Type term;
[tiab] denotes a word in the title or abstract;
[sh] denotes a subheading;
[mh] denotes a Medical Subject Heading (MeSH) term (‘exploded’);
[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not ‘exploded’);
[ti] denotes a word in the title;
[$] indicates truncation;
**CENTRAL SEARCH STRATEGY**

<table>
<thead>
<tr>
<th>#</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>antiepileptic drug&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>#2</td>
<td>MeSH descriptor Epilepsy explode all trees</td>
</tr>
<tr>
<td>#3</td>
<td>MeSH descriptor Seizures explode all trees</td>
</tr>
<tr>
<td>#4</td>
<td>epilep* or seizure* or convulsion*</td>
</tr>
<tr>
<td>#5</td>
<td>(#2 OR #3 OR #4)</td>
</tr>
<tr>
<td>#6</td>
<td>(#1 AND #5)</td>
</tr>
</tbody>
</table>

<sup>1</sup> #12 International non-proprietary name of the AED (e.g. Levetiracetam, Zonisamide, Pregabalin)
APPENDIX B: STUDY SELECTION AND EXTRACTION FORM

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study eligibility**

<table>
<thead>
<tr>
<th>RCT</th>
<th>Relevant participants</th>
<th>Relevant interventions</th>
<th>Relevant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No* / Unclear</td>
</tr>
</tbody>
</table>

Do not proceed if any of the above answers are ‘No’. If study to be included in ‘Excluded studies’ section of the review, record below the information to be inserted into ‘Table of excluded studies’.

**References to trial**

Check other references identified in searches. If there are further references to this trial link the papers now & list below.

<table>
<thead>
<tr>
<th>Code each paper</th>
<th>Author(s)</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The paper listed above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Further papers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Participants and trial characteristics**

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Further details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of participants</td>
<td></td>
</tr>
<tr>
<td>Sex of participants</td>
<td></td>
</tr>
<tr>
<td>Epileptic seizure type and epileptic syndrome</td>
<td></td>
</tr>
<tr>
<td>Number of seizures or seizure frequency prior to randomization (if available)</td>
<td></td>
</tr>
<tr>
<td>Number and types of AEDs previously taken (if available)</td>
<td></td>
</tr>
<tr>
<td>Concomitant AEDs (if available)</td>
<td></td>
</tr>
<tr>
<td>Trial characteristics</td>
<td>Further details</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Single centre / multicentre</td>
<td></td>
</tr>
<tr>
<td>Country / Countries</td>
<td></td>
</tr>
<tr>
<td>Parallel / cross-over design</td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Criteria used to diagnose epilepsy</td>
<td></td>
</tr>
<tr>
<td>Number of partial-onset seizures per month used in inclusion criteria (if data available)</td>
<td></td>
</tr>
<tr>
<td>Definition of drug-resistant epilepsy</td>
<td></td>
</tr>
<tr>
<td>How many people were randomised?</td>
<td></td>
</tr>
<tr>
<td>Number of participants in each intervention group</td>
<td></td>
</tr>
<tr>
<td>Number of participants who received intended treatment</td>
<td></td>
</tr>
<tr>
<td>Duration of the different phases of the trial</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active treatment and control</th>
<th>Further details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention given to controls</td>
<td></td>
</tr>
<tr>
<td>AED given to active treatment group</td>
<td></td>
</tr>
<tr>
<td>Dosage of active AED</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment period</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up data</th>
<th>Further details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up</td>
<td></td>
</tr>
<tr>
<td>Reasons for incomplete outcome data</td>
<td></td>
</tr>
<tr>
<td>Drop-outs or loss to follow-up rates</td>
<td></td>
</tr>
<tr>
<td>Methods of analysis (e.g. intention-to-treat, per protocol, etc.)</td>
<td></td>
</tr>
</tbody>
</table>
# Methodological quality

## Allocation of intervention

<table>
<thead>
<tr>
<th>State here method used to generate allocation and reasons for grading</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adequate (Random)</td>
</tr>
<tr>
<td></td>
<td>Inadequate (e.g. alternate)</td>
</tr>
<tr>
<td></td>
<td>Unclear</td>
</tr>
</tbody>
</table>

## Concealment of allocation

Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding

<table>
<thead>
<tr>
<th>State here method used to conceal allocation and reasons for grading</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td></td>
<td>Inadequate</td>
</tr>
<tr>
<td></td>
<td>Unclear</td>
</tr>
</tbody>
</table>

## Blinding

| Person responsible for participants care | Yes / No |
| Participant                             | Yes / No |
| Outcome assessor                        | Yes / No |
| Other (please specify)                  | Yes / No |

## Intention-to-treat

An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

| All participants entering trial | |
| 15% or fewer excluded | |
| More than 15% excluded | |
| Not analysed as ‘intention-to-treat’ | |
| Unclear | |

Were withdrawals described?  
Yes  
No  
not clear

Discuss if appropriate
## Data extraction

<table>
<thead>
<tr>
<th>Outcomes relevant to the review</th>
<th>Reported in paper</th>
</tr>
</thead>
</table>
| **Outcome 1**  
Fifty per cent or greater reduction in seizure frequency (responder rate). | Yes / No |
| **Outcome 2**  
Number of participants that drop out or withdraw due to side effects, lack of efficacy or other reasons (withdrawal rate) | Yes / No |

### For Dichotomous data

| Code of paper | Outcome 1: Responder rate | Intervention group (n)  
n = number of participants, not number of events | Control group (n)  
n = number of participants, not number of events |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### For Dichotomous data

| Code of paper | Intervention group (n)  
n = number of participants, not number of events | Control group (n)  
n = number of participants, not number of events |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### References to other trials

Did this report include any references to **published reports** of potentially eligible trials not already identified for this review?  

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal / Conference</th>
<th>Year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Did this report include any references to **unpublished data** from potentially eligible trials not already identified for this review? If yes, give list contact name and details
APPENDIX C: PRISMA FLOW DIAGRAM
Available at:
http://www.prisma-statement.org/2.1.4-%20PRISMA%20Flow%20Diagram.pdf

APPENDIX D: PRISMA CHECKLIST
Available at:
http://www.prisma-statement.org/2.1.2-%20PRISMA%20Checklist.pdf