A COMMON REFERENCE-BASED INDIRECT COMPARISON META-ANALYSIS OF ESLICARB AZEPINE VERSUS LACOSAMIDE AS ADD ON TREATMENTS FOR FOCAL EPILEPSY

PROTOCOL

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The review will be guided by the following protocol describing research questions, review methods, and plan for data extraction and synthesis.
INTRODUCTION
Epilepsy is one of the most common neurologic disorders with an age-adjusted prevalence in developed countries of 4 to 8 per 1,000 population (Hauser et al., 1991; Hesdorffer et al., 1998). Despite the plethora of antiepileptic drugs (AEDs) currently available, 30% of patients with epilepsy continue having seizures (Kwan et al., 2011). In patients where monotherapy fails to controls seizure, an add-on treatment may therefore be required. Nevertheless, polytherapy often results in a number of adverse effects and interactions with other drugs. Consequently, several efforts have been done to identify novel AEDs with higher efficacy and better tolerability and with favorable pharmacokinetics profiles.

Eslicarbazepine acetate is a novel add-on treatment for patients with focal epilepsy which can be administered once daily because of its long half-life. Its molecular structure is similar with carbamazepine and oxcarbazepine but unlike them it does not inhibit most cytochrome P450 enzymes (CYP450) having therefore a low potential for pharmacodynamics interactions with other drugs (Almeida et al., 2007). Eslicarbazepine is the main active component of ESL and its clearance is dependent on renal function (Almeida et al., 2007). ESL acts by blocking voltage-gated sodium channels (Almeida et al., 2007).

Lacosamide is another novel add-on AED for adults with focal epilepsy (Chung et al., 2010) with a maximum licensed dose of 400 mg/day. It is a functionalized amino acid with linear kinetics and a half-life of 13 hours, so that it can be administered twice daily (Doty et al., 2007). Lacosamide is eliminated by renal clearance, does not interact with the hepatic P450 enzymes, and therefore has no known pharmacodynamics interactions with other drugs (Doty et al., 2007). Unlike traditional sodium channel blockers, LCM enhances the inactivation of slow sodium channels, hence selectively preventing the propagation of pathological currents and stabilizing the neural network (Doty et al., 2007).

Although ESL and LCM have different molecular structures, they share some characteristics: 1. modulate sodium currents (although at different sites and with different mechanisms); 2. have no or negligible interaction with the cytochrome P450 enzymes; 3. are eliminated by renal clearance; 4. have long half-life permitting administration once daily; 5. have clinical efficacy against focal epilepsy demonstrated in several randomised controlled trials (RCT).

Both therefore represent valid alternative as add-on treatment in patients with focal epilepsy experiencing seizures despite adequate monotherapy. However, to date no RCT has directly compared ESL with LCM as add-on treatments for focal epilepsy. Hence, from the available literature we have no information on efficacy and safety of these two drugs derived from head-to-head comparative trials. Until further data from direct head-to-head clinical trials comparing ESL with LCM as add-on antiepileptic treatment are available, other methods may be used to make comparisons between these AEDs.
Systematic reviews and meta-analyses of RCTs with similar design are useful, although limited, tools. Classical meta-analyses of RCTs focus on direct, pair-wise comparisons between two treatments (e.g. Treatment A versus treatment B). However, direct head-to-head comparisons are not available for all treatments, so that definite data on treatment effect cannot be 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 key assumption for this 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). Therefore, meta-analyses based on common reference-based indirect comparisons represent a useful tool where direct comparisons do not exist or are scarce.

An indirect-comparison meta-analysis has previously assessed the tolerability of these drugs (Zaccara et al., Seizure 2013;22:528-536), without nevertheless focusing on efficacy outcomes.

We therefore decided to undertake a meta-analysis of ESL compared with LCM as add-on AED in patients with focal epilepsy, indirectly estimating their efficacy through a common-reference based indirect comparison meta-analysis. Hence, the aim of this study is to provide further information on ESL and LCM used as add-on treatments in patients with focal epilepsy.

METHODS

Criteria for considering studies for this review
Randomized controlled trials (including registrative trials) comparing add-on ESL or LCM versus placebo in the treatment of focal epilepsy will be included in the meta-analysis. Briefly, we will include RCTs, blinded or unblinded, and exclude uncontrolled and non-randomised trials. Patients from any age group and diagnosed with focal epilepsy (simple focal, complex focal or secondary generalized tonic-clonic seizures) will be included.

We will consider all trials in which ESL or LCM has been used as add-on treatment in patients with focal epilepsy and compared with placebo. Trials will not be excluded on the basis of dose, duration of treatment, or length of follow-up.

Search methods
A comprehensive review of the will be performed to minimize publication bias. Following electronic databases and data sources will be searched using the search strategies reported in appendix:
1. MEDLINE, accessed through PubMed;
2. Cochrane Central Register of Controlled Trials (CENTRAL);
3. EMBASE;
4. ClinicalTrials.gov (available at: https://clinicaltrials.gov/);
5. handsearching of the references quoted in the identified trials;
6. contact with pharmaceutical companies (Eisai, UCB Pharma) to identify unpublished trials or data missing from articles;
7. contact with authors and known experts to identify any additional data.
There will be no language restrictions.

**Study selection**
Retrieved articles will be independently assessed for inclusion by two review authors (FB and EZ); any disagreement will be resolved through discussion.

**Methodological quality assessment**
Trials will be scrutinized, and the methodological quality of all included studies will be evaluated. Quality assessment will include the following aspects of methodology: study design, definition and clinical relevance of outcomes, type of control, method of allocation concealment, total study duration, completeness of follow-up, intention-to-treat analysis, data concerning adverse effects, risk of bias, and conflict of interests. The randomized trials will be judged on the reported method of allocation concealment and on the risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins and Green, 2011).

**Data extraction**
The following trial data will be extracted: main study author and age of publication; type of participants (children and/or adults); total number of participants for each treatment group; number of concomitant antiepileptic drugs; intervention details (starting and target dose, titration); length of treatment maintenance period; proportion of patients with 50% or greater reduction in seizure frequency (responders) in each group; proportion of patients achieving seizure freedom in each group; proportion of patients with treatment withdrawal for any reason in each group.

**Types of outcome measures**
We will choose dichotomous primary outcomes to have hard outcome measures of both treatment efficacy. Odds ratios (ORs) for binary outcomes will be chosen because they are associated with less heterogeneity in meta-analysis than risk differences or relative risks (Deeks, 2002). The following outcomes (reported in studies meeting the inclusion criteria) relevant to the efficacy of the intervention drug (ESL or LCM versus placebo) will be collected:
1. Proportion of patients with 50% or greater reduction in seizure frequency;
2. Proportion of patients achieving seizure freedom;
3. Proportion of patients with treatment withdrawal for any reason

**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. Analyses will be conducted using Revman 5.3 (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 add-on ESL versus placebo and add-on LCM versus placebo will be undertaken. Results from individual trials for each AED (ESL and LCM, each of them compared against placebo) will be pooled by using random effects, inverse variance, weighted meta-analysis (DerSimonian and Laird, 1986).

Each outcome will be analysed by calculating ORs 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 OR statistic and to combine ORs (Emerson, 1994).

**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, we will use the random effects model for the quantitative pooling in both direct and adjusted indirect comparisons (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 will be performed according to Higgins and Green, (2011). 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 were 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 compared add-on ESL with add-on LCM, an adjusted method of indirect comparison between ESL and LCM will be performed using the results of two meta-analyses (e.g. ESL versus placebo and LCM versus placebo).

**Statistical analysis**
To perform common reference-based indirect comparisons we will use the method suggested by Bucher (Bucher et al., 1997) and adopted in previous reviews (Otoul et al., 2005; Zaccara et al., 2006; Brigo et al., 2013): the indirect comparison of ESL and LCM will be adjusted by the results of their direct comparisons with placebo(common intervention).

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 ESL and LCM will be performed using the ORs derived from the conventional meta-analyses.
Comparison of each binary outcome measure 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 (i.e. ESL versus LCM) will be therefore calculated by the difference (diff) between the logs of the 2 ORs:

\[
\text{Diff} = \ln \text{OR}_{\text{ESL}} - \ln \text{OR}_{\text{LCM}};
\]

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

\[
((\ln \text{OR}_{\text{ESL}} - \ln \text{OR}_{\text{LCM}}) \pm (1.96 \times \text{SE (diff)}))
\]

where SE (diff) = (variance (ln OR \text{ESL}) + variance (ln OR \text{LCM}))^{1/2}. 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 add-on ESL than in the group receiving placebo. The same will be applied for add-on LCM. For the indirect comparisons, an OR > 1 indicates that the outcome is more likely with add-on ESL than with add-on LCM. A P value of 0.05 will be considered to be statistically significant.

**Subgroup analyses**

To take into account differences in efficacy due to different doses, in adjusted indirect comparisons we will compare ESL and LCM according to different doses: ESL 800 mg/day versus LCM 200 mg/day (minimum effective recommended daily dose) and ESL 1200 mg/day versus LCM 400 mg/day (highest effective recommended daily dose [Zaccara et al., 2013]).

**REFERENCES**


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


Appendix: search strategies used in the review.

**MEDLINE** (high-sensitivity strategy for the search of randomized controlled trials in PubMed [Robinson et al., 2002])

("Lacosamide" [Supplementary Concept] OR lacosamide) OR ("eslicarbazepine"

**EMBASE and CENTRAL**

((Eslicarbazepine OR Lacosamide) AND (Epilepsy) AND (random* AND control*))

**ClinicalTrials.gov**

((Eslicarbazepine OR Lacosamide) AND (Epilepsy))

References: