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[Intervention Protocol]

Eslicarbazepine acetate monotherapy for epilepsy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and tolerability of eslicarbazepine acetate (ESL) monotherapy for focal onset seizures or generalised tonic-clonic epilepsy in children and adults.

BACKGROUND

Description of the condition

Epilepsy is one of the most common chronic neurological diseases characterised by recurrent unprovoked seizures that affects more than 50 million individuals worldwide (WHO 2018). The estimated incidence of epilepsy ranges from 40 to 70 per 100,000 per year in high-income countries, and it seems to be higher in low-income countries. The prevalence is around 4 to 10 per 1000 in most settings (de Boer 2008). Epilepsy not only has a considerable impact on individual health, psychosocial well-being, and economic status, but also on the family and the community. People with epilepsy tend to be stigmatised and have a lower quality of life than people with other chronic illnesses (de Boer 2008; Scott 2001). The majority of people with epilepsy have a good prognosis, but up to 30% of people continue to have seizures despite the availability of antiepileptic drugs (Perucca 2007). There is an unmet clinical need for new antiepileptic drugs that are effective and well-tolerated for use as monotherapy in the treatment of people with epilepsy.

Description of the intervention

Eslicarbazepine acetate (ESL) is a novel once-a-day antiepileptic drug that has been approved for add-on therapy and monotherapy for focal onset seizures with or without secondary generalisation in adults by the European Medicines Agency and the US Food and Drug Administration. Recently ESL was approved for add-on therapy in children and adolescents. However, it is not approved for monotherapy in generalised seizures. A systematic review reported that ESL was an effective drug as an add-on treatment for drug-resistant focal epilepsy (Chang 2017), and the most common side effects were dizziness, nausea, somnolence, vomiting and diplopia. It shares a similar structure with carbamazepine and oxcarbazepine but does not inhibit most cytochrome P450 enzymes (CYP450) and has a low potential for drug interaction (Almeida 2007). ESL is well absorbed (at least 90%) following ingestion, and is rapidly metabolised to its major active metabolite eslicarbazepine (S-licarbazepine) by hepatic first-pass hydrolysis. Peak plasma concentration of eslicarbazepine is reached two to three hours after administration. The effective half-life is 20 to 24 hours and its steady state in the plasma is achieved after four to five days. The pharmacokinetics of ESL are not affected by age, gender, food or moderate hepatic impairment, but its clearance is dependent on renal function (Almeida 2007; Galiana 2017; McCormack 2009).

How the intervention might work

ESL is thought to work by inhibiting voltage-gated sodium channels (VGSCs) (Almeida 2007). Eslicarbazepine, the main active metabolite of ESL, has a predominant selectivity of the inactive state of VGSC, which is the common feature of the rapidly firing neurons. ESL also reduces VGSC availability through enhancing slow inactivation of VGSCs selectively (Soares-da-Silva 2015).

Why it is important to do this review

In order to better inform clinicians and patients, we will review existing data regarding the effectiveness, efficacy and tolerability of ESL monotherapy in focal and generalised epilepsy in children and adults.

OBJECTIVES

To evaluate the efficacy and tolerability of eslicarbazepine acetate (ESL) monotherapy for focal onset seizures or generalised tonic-clonic epilepsy in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials
2. Double-blinded, single-blinded or unblinded trials
3. Placebo-controlled or actively controlled trials
4. Parallel-group or cross-over studies

Types of participants

1. Children or adults with focal onset seizures (simple focal, complex focal, or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures (with or without other generalised seizure types)
2. Children or adults treated with monotherapy

Types of interventions

Eslicarbazepine acetate (ESL) monotherapy versus placebo or another antiepileptic drug.

Types of outcome measures

Primary outcomes

1. Time to treatment withdrawal (retention time). Participants will achieve this outcome if allocated treatment is withdrawn for poor seizure control, adverse effects or non-compliance, or if additional add-on treatment is initiated. This is a combined outcome reflecting both efficacy and tolerability, and is recommended as the primary outcome measure by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE Commission 1998).

Secondary outcomes

1. Time to achieve six-month, 12-month remission (seizure-free period)
2. Time to first seizure post-randomisation
3. Validated quality of life measures
4. The proportion of individuals experiencing any adverse event and the proportion of individuals experiencing adverse effects requiring medication withdrawal
5. Cognitive outcomes

Search methods for identification of studies

Electronic searches

We will search the following databases.

1. Cochrane Register of Studies (CRS Web), using the search strategy shown in Appendix 1. CRS Web includes randomised or quasi-randomised, controlled trials from PubMed, EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central

Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy.

2. Medline (Ovid) 1946- using the search strategy shown in [Appendix 2](#).

We will not impose any language restrictions.

Searching other resources

We will review the reference lists of retrieved studies to search for additional reports of relevant studies. We will also contact the manufacturers of ESL and experts in the field for information about any unpublished or ongoing studies.

Data collection and analysis

Two review authors (Chang and Yu) will independently assess trials for inclusion. We will compare results and resolve any disagreements by discussion. If a disagreement is not resolved, a third review author (Hong) will be asked to arbitrate.

Selection of studies

The process for selecting studies for inclusion in the review will involve merging search results using reference management software and removing duplicates of the same report. We will examine titles and abstracts to remove obviously irrelevant reports. We will retrieve the full texts of these reports and examine studies for compliance with eligibility criteria. The review authors will agree on trials for inclusion before proceeding to data collection.

Data extraction and management

Two review authors (Chang and Yu) will independently extract the following information from included trials. We will resolve disagreements by discussion.

Trial design

1. Study design
2. Method of randomisation
3. Allocation concealment
4. Blinding

Demographic information

1. Age
2. Sex
3. Ethnicity
4. Types of seizure
5. Inclusion criteria
6. Exclusion criteria
7. Total number of participants recruited
8. Total number of participants randomised to each treatment group

Interventions and follow-up data

1. Dosage
2. Administration method
3. Primary outcome
4. Secondary outcomes
5. Adverse events
6. Follow-up data

7. Duration of follow-up period
8. Total number of participants followed up
9. Numbers of loss to follow-up
10. Reasons for treatment withdrawal

Assessment of risk of bias in included studies

We will assess the methodological quality of the included studies using the Cochrane 'Risk of bias' tool as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019](#)). Any disagreements will be evaluated by discussion between both review authors (Chang and Yu) if necessary.

Measures of treatment effect

Time-to-event data: we will present time-to-event outcomes (for example, time to withdrawal of allocated treatment) as hazard ratios (HRs) with 95% confidence interval (CI).

Continuous data (for example, validated quality of life measures): we will use the mean difference (MD) with 95% CI, or the standardised mean difference (SMD) with 95% CI when different scales are used.

Dichotomous data (for example, adverse effects): we will present dichotomous outcomes as risk ratios (RRs) with 95% CI.

Unit of analysis issues

For cross-over studies, we plan to use the first treatment period as a parallel group trial. For trials with more than two intervention groups, we will adjust the data by the methods stated in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019](#)).

Dealing with missing data

We will contact the manufacturers and original investigators for any missing data. If we do not receive a response, we will analyse the available data according to the intention-to-treat principle.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the distribution of important participant factors between trials (age, gender, seizure type, duration of epilepsy) and trial factors (randomisation concealment, blinding, losses to follow-up). We will assess statistical heterogeneity by using the Chi² test, where a P value lower than 0.1 indicates substantial heterogeneity. We will also use the I² statistic to quantify inconsistency across studies. A rough guide to the interpretation of the I² statistic is as follows ([Higgins 2019](#)).

1. 0% to 40%: might not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: considerable heterogeneity.

If statistical heterogeneity exists, we will explore potential causes. If statistical heterogeneity is below 30%, we will synthesise data using a fixed-effect model. If the substantial heterogeneity cannot readily be explained, we will adopt a random-effects model.

Assessment of reporting biases

We will try to avoid reporting biases by identifying unpublished data through comprehensive searches and the use of trial registries (Higgins 2019). In addition, we will explore the possibility of publication bias using funnel plots when there are at least 10 studies included in the meta-analysis. We will also evaluate selective outcome reporting biases through searching for study protocols and checking the methods section of the article.

Data synthesis

We will perform data synthesis and analysis using Review Manager software (Review Manager 2014).

For continuous data or dichotomous data, we will combine the results of the included studies using a fixed-effect model if we find no significant clinical or statistical heterogeneity, otherwise we may pool the data using a random-effects model. For time-to-event data, we will use the fixed-effect model for pooled analysis.

Subgroup analysis and investigation of heterogeneity

If we identify sufficient trials, we will perform subgroup analyses according to the different ages of participants (children younger than 17 years versus adults), different seizure types and different doses of ESL.

Sensitivity analysis

Where possible, we will perform sensitivity analyses to test the robustness of the meta-analysis by excluding trials at high or unclear risk of bias.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to interpret findings (Schünemann 2019). We will use GRADE profiler software (GRADEpro GDT), and import data from Review Manager 5 (Review Manager 2014), to create 'Summary of findings' tables for each comparison included in the review for the primary outcomes: time to treatment withdrawal (retention time).

The 'Summary of findings' table for each comparison will include information on overall certainty of the evidence from the trials and information of importance for healthcare decision making. The GRADE approach determines the certainty of evidence on the basis of an evaluation of a series criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, etc). We will use these to guide our conclusions.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1. CRS Web search strategy

1. Eslicarbazepin* or Zeb*nix or Exalief or Stedesa or "BIA 2-093" AND CENTRAL:TARGET
2. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET
3. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET
4. epilep* OR seizure* OR convuls* AND CENTRAL:TARGET
5. #2 OR #3 OR #4 AND CENTRAL:TARGET
6. #1 AND #5

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7. ((adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*)):TI AND CENTRAL:TARGET

8. #6 NOT #7

Appendix 2. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials ([Lefebvre 2011](#)).

1. (randomised controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
2. clinical trials as topic.sh.
3. trial.ti.
4. 1 or 2 or 3
5. exp animals/ not humans.sh.
6. 4 not 5
7. exp Epilepsy/
8. exp Seizures/
9. (epilep\$ or seizure\$ or convuls\$).tw.
10. 7 or 8 or 9
11. (Eslicarbazepin\$ or Zeb#nix or Exalief or Stedesa or BIA 2-093).tw.
12. 6 and 10 and 11
13. ((adjunct\$ or "add-on" or "add on" or adjuvant\$ or combination\$ or polytherap\$) not (monotherap\$ or alone or singl\$)).ti.
14. 12 not 13
15. remove duplicates from 14

CONTRIBUTIONS OF AUTHORS

Xian-Chao Chang, Xiao-dan Zhang and Dong-Xing Wang were responsible for writing the protocol.

Hu Yu and Wen-Ke Hong participated in providing clinical suggestions.

Yi Wang provided suggestions on statistics and methods.

DECLARATIONS OF INTEREST

Xian-Chao Chang: none known

Hu Yu: none known

Xiao-Dan Zhang: none known

Yi Wang: none known

Wen-Ke Hong: none known

Dong-Xing Wang: none known

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Internal sources

- No sources of support supplied

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- National Institute for Health Research (NIHR), UK.