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[Intervention Review]

Eslicarbazepine acetate add-on for drug-resistant focal epilepsy

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ABSTRACT

Background

This is an updated version of the Cochrane Review published in the Cochrane Library 2011, Issue 12.

The majority of people with epilepsy have a good prognosis, but up to 30% of people continue to have seizures despite several regimens of antiepileptic drugs. In this review, we summarized the current evidence regarding eslicarbazepine acetate (ESL) when used as an add-on treatment for drug-resistant focal epilepsy.

Objectives

To evaluate the efficacy and tolerability of ESL when used as an add-on treatment for people with drug-resistant focal epilepsy.

Search methods

The searches for the original review were run in November 2011. Subsequently, we searched the Cochrane Epilepsy Group Specialized Register (6 December 2016), the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 11) and MEDLINE (1946 to 6 December 2016). There were no language restrictions. We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies. We also contacted the manufacturers of ESL and experts in the field for information about any unpublished or ongoing studies.

Selection criteria

Randomized placebo controlled double-blind add-on trials of ESL in people with drug-resistant focal epilepsy.

Data collection and analysis

Two review authors independently selected trials for inclusion and extracted data. Outcomes investigated included 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal, adverse effects, and drug interactions. Primary analyses were by intention to treat (ITT). The dose-response relationship was evaluated in regression models.

Main results

We included five trials (1799 participants) rated at low risk of bias apart from a high risk of attrition bias; all studies were funded by BIAL. The overall risk ratio (RR) with 95% confidence interval (CI) for 50% or greater reduction in seizure frequency was 1.71 (95% CI 1.42 to 2.05). Dose regression analysis showed evidence that ESL reduced seizure frequency with an increase in efficacy with increasing doses of ESL. ESL was significantly associated with seizure freedom (RR 2.90, 95% CI 1.49 to 5.68). Participants were more likely to have ESL withdrawn for adverse effects (RR 2.66, 95% CI 1.42 to 4.96) but not for any reason (RR 1.19, 95% CI 0.86 to 1.64). The following adverse effects were significantly associated with ESL: dizziness (RR 2.81, 99% CI 1.86 to 4.27); nausea (RR 2.61, 99% CI 1.36 to 5.01); diplopia (RR 4.14, 99% CI

1.74 to 9.84); somnolence (RR 1.71, 99% CI 1.11 to 2.63) and vomiting (RR 3.30, 99% CI 1.34 to 8.13). Overall the quality of the evidence was rated as moderate due to a high discontinuation rate.

Authors' conclusions

ESL reduces seizure frequency when used as an add-on treatment for people with drug-resistant focal epilepsy. The trials included in this review were of short-term duration and focused on adults. One new trial has been included in this update, but the conclusions are unchanged.

PLAIN LANGUAGE SUMMARY

Eslicarbazepine acetate add-on for drug-resistant focal epilepsy

Review question

This review is an update of a review previously published in the Cochrane Library 2011, Issue 12. We reviewed the evidence on the efficacy and safety of eslicarbazepine acetate when used as an add-on treatment for medicine-resistant focal epilepsy.

Background

Eslicarbazepine acetate is an antiepileptic medicine that can be added (called an 'add-on' treatment) along with other medicines to treat people who are taking other antiepileptic medication but continue to have seizures. This drug may be beneficial for people who are taking other antiepileptic medicine but continue to have seizures (fits). This review looked at how well eslicarbazepine acetate worked when used as an add-on treatment and at some of the harms or side effects of the medicine.

Study characteristics

The evidence is current to December 2016. We included five clinical trials with 1799 participants aged 16 to 77 years. The included studies had different treatment periods of 12 to 14 weeks. All five trials were randomized controlled trials, which means that people were randomly divided into groups and compared.

Key results

This review found that eslicarbazepine acetate was effective when used in combination with other medicines to reduce the number of seizures in drug-resistant focal epilepsy. People who took eslicarbazepine acetate were more likely to have no seizures than people who took the placebo (a pretend tablet), but they were more likely to withdraw from eslicarbazepine acetate treatment because of side effects. Side effects associated with eslicarbazepine acetate were dizziness, nausea (feeling sick), somnolence (feeling sleepy), vomiting (being sick) and diplopia (having double vision).

Quality of evidence

Altogether the five trials used good methods, but information was missing from the trials for between 10% and 45% of people taking each medicine in each trial. This missing information may have introduced uncertainty into results so the evidence in this review is of moderate quality. More research is needed to look at the long-term effects of eslicarbazepine acetate and to explore how well it works in children with epilepsy.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Eslicarbazepine acetate add-on for drug-resistant focal epilepsy

Eslicarbazepine acetate add-on for drug-resistant focal epilepsy

Patient or population: people with drug-resistant focal epilepsy

Setting: outpatients

Intervention: eslicarbazepine acetate (ESL): all doses

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ESL				
≥ 50% reduction in seizure frequency Follow-up: up to 18 weeks	Study population 206 per 1000 359 per 1000 (299 to 429)		RR 1.71 (1.42 to 2.05)	1799 (5 RCTs)	⊕⊕⊕⊖ Moderate ^{1,2,3}	Results presented for ITT population. Best-case scenario (all participants with missing data on ESL assumed to be responders and all participants with missing data on placebo with missing data assumed to be non-responders) and worst-case scenario (opposite of best-case scenario) analyses conducted.
Freedom from seizures Follow-up: up to 18 weeks	Study population 18 per 1000 52 per 1000 (27 to 101)		RR 2.90 (1.49 to 5.68)	1799 (5 RCTs)	⊕⊕⊕⊖ Moderate ^{1,3}	-
Treatment withdrawal (any reason) Follow-up: up to 18 weeks	Study population 190 per 1000 246 per 1000 (202 to 301)		RR 1.29 (1.06 to 1.58)	1799 (5 RCTs)	⊕⊕⊕⊖ Moderate ^{1,4}	-
Treatment withdrawal (adverse effect) Follow-up: up to 18 weeks	Study population 44 per 1000 118 per 1000 (63 to 221)		RR 2.66 (1.42 to 4.96)	1799 (5 RCTs)	⊕⊕⊕⊖ Moderate ^{1,4}	-
Adverse effects Follow-up: up to 18 weeks	Study population		See comment	See comment	⊕⊕⊕⊕ Moderate ^{1,3}	Eslicarbazepine acetate was significantly associated with dizziness, nausea, somnolence, vomiting and diplopia.

See comment

See comment

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹ These studies were funded by BIAL - Portela & C^a, SA. There was no indication that the source of funding introduced bias

² Dose-response analysis indicated an increase in effect with increasing dose.

³ Downgraded once due to risk of bias: all five included studies judged to be at high risk of attrition bias due to large proportions of missing data. Best-case and worst-case scenario analyses were inconsistent with results of ITT analyses.

⁴ Downgraded once due to risk of bias: all five included studies judged to be at high risk of attrition bias due to large proportions of missing data.

BACKGROUND

This review is an updated of a previously published review in the Cochrane library 2011, Issue 12.

Description of the condition

Epilepsy is a common neurological condition. The incidence of epilepsy is estimated to be about 50 (range 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 5 to 10 per 1000 in most settings (Sander 2003).

The majority of people with epilepsy have a good prognosis but up to 30% of people continue to have seizures despite several regimens of antiepileptic drugs (AEDs) (Walker 1997).

People with refractory epilepsy often experience psychosocial, psychiatric and medical comorbidities, which are due to recurrent seizures, long-term drug effects and employment restrictions (Schuele 2008). The new drug eslicarbazepine acetate (ESL) may help to alleviate some of these problems by reducing seizure frequency.

Description of the intervention

Since the late-1990s, a large number of AEDs have been licensed worldwide. ESL is a novel, once-daily AED for the adjunctive treatment of drug-resistant epilepsy. 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). Eslicarbazepine is the main active component of ESL and its pharmacokinetics are not affected by age, gender, food or moderate hepatic impairment, but clearance of ESL is dependent on renal function (McCormack 2009; Mestre 2009).

How the intervention might work

The main mechanism of action of ESL is thought to be by blocking voltage-gated sodium channels (Almeida 2007).

Why it is important to do this review

ESL was launched onto the UK market in 2009 as an adjunctive therapy in adults with focal-onset seizures, with or without secondary generalization. In this review, we assessed the efficacy and tolerability of ESL when used as an add-on treatment in people with drug-resistant focal epilepsy.

OBJECTIVES

To evaluate the efficacy and tolerability of ESL when used as an add-on treatment for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials (RCTs) using an adequate method of concealment of randomization (e.g. sequential allocation of sealed packages of medication, sealed opaque envelopes, telephone allocation).

- Double-blind trials in which both participants and clinicians treating or assessing the outcome were blinded to the treatment allocated.
- Placebo controlled studies.
- Parallel group or cross-over studies.

Types of participants

People of any age with drug-resistant focal epilepsy (i.e. experiencing simple focal, complex focal or secondary generalized tonic-clonic seizures).

In this review, we defined drug resistance as continued seizures despite treatment with one or more AEDs.

Types of interventions

- Active treatment group received ESL in addition to an existing AED regimen at the time of randomization.
- Control group received a matched placebo in addition to an existing AED regimen at the time of randomization.

Types of outcome measures

Primary outcomes

- A 50% or greater reduction in seizure frequency

The proportion of people with a 50% or greater reduction in seizure frequency within the treatment period compared to the prerandomization baseline period.

This was chosen as the primary outcome because it is a commonly reported outcome and can be calculated for studies that did not report this outcome provided that baseline seizure data were recorded.

- Freedom from seizures

The proportion of participants with complete cessation of seizures from the time of randomization to the trial conclusion.

Secondary outcomes

- Treatment withdrawal

The proportion of participants withdrawn from treatment, for any reason, during the treatment period as a measure of global effectiveness. Treatment was likely to be withdrawn due to adverse effects, lack of efficacy, or a combination of both, and this is an outcome to which the individual makes a direct contribution. In trials of short duration, it was likely that adverse effects were the most common reason for withdrawal. We also assessed the proportion of people having treatment withdrawn because of adverse effects.

- Adverse effects

- Proportion of participants experiencing any of the following five adverse effects, which we considered to be common, important adverse effects of AEDs:
 - * ataxia;
 - * dizziness;
 - * fatigue;
 - * nausea;
 - * somnolence.
- Proportion of participants experiencing rash and the five most common adverse effects that were different from those listed above.
- Drug interactions

Any drug interactions reported in the included studies.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for RCTs and imposed no language restrictions. The searches for the original review were run in November 2011. Subsequent searches have been run on the dates shown below.

- The Cochrane Epilepsy Group Specialized Register (6 December 2016) using the strategy outlined in [Appendix 1](#).
- The Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 11, the Cochrane Library) using the strategy outlined in [Appendix 2](#).
- MEDLINE (Ovid) (1946 to 6 December 2016) using the strategy outlined in [Appendix 3](#).

Searching other resources

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

Data collection and analysis

Two review authors (XCC and HY) independently assessed trials for inclusion. We compared results and resolved any disagreements by discussion. If a disagreement was not resolved, a third review author arbitrated.

Selection of studies

The process for selecting studies for inclusion in the review involved merging search results using reference management software and removing duplicates of the same report. We examined titles and abstracts to remove obviously irrelevant reports. We retrieved the full texts of the remaining reports and examined studies for compliance with our eligibility criteria. The review authors agreed on trials for inclusion before proceeding to data collection.

Data extraction and management

The same two review authors extracted the following information from included trials. Disagreements were resolved by discussion. If a disagreement was not resolved, a third review author arbitrated.

- Methodology and trial design:
 - * method of randomization concealment;
 - * method of blinding;
 - * whether any participants were excluded from the reported analyses;
 - * duration of baseline period;
 - * duration of treatment period;
 - * dose(s) of ESL tested.
- Participant and demographic information:
 - * total number of participants allocated to each treatment group;
 - * age and sex;
 - * numbers with focal and generalized epilepsy;
 - * seizure types;
 - * number of background drugs;
 - * seizure frequency during the baseline period.
- Outcomes:
 - * number of participants experiencing each outcome (see [Types of outcome measures](#)) per randomized group.
- All trials found so far have been sponsored by BIAL (Portela & Ca, S.A.) who confirmed the following information ([Sperling 2015](#) was verified by Professor Sperling and Sunovion Pharmaceuticals Inc):
 - * method of randomization;
 - * total number of participants randomized to each group;
 - * number of participants in each group achieving a 50% or greater reduction in seizures;
 - * number of participants having treatment withdrawn postrandomization per treatment group;
 - * for those excluded, the reason for exclusion, whether any of those excluded completed the treatment phase, and whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Assessment of risk of bias in included studies

We evaluated methodological quality of the studies according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Measures of treatment effect

For dichotomous data, we determined the risk ratio (RR) and 95% confidence interval (CI).

Unit of analysis issues

For cross-over studies, we planned to use the first treatment period as a parallel group trial. For multiple dose trials, we planned to add analysis by dose.

Dealing with missing data

We contacted the manufacturers and original investigators of relevant trials to identify any additional published or unpublished data.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials (age, seizure type, duration of epilepsy, number of AEDs taken at the time

of randomization) and trial factors (randomization concealment, blinding, losses to follow-up). We assessed statistical heterogeneity by using the χ^2 test, where a P value lower than 0.1 indicated substantial heterogeneity. We also used the I^2 statistic to quantify inconsistency across studies. An approximate guide to the interpretation of the I^2 statistic was as follows (Higgins 2011):

- 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.

If statistical heterogeneity existed, we explored potential causes. If statistical heterogeneity was below 30%, we synthesized data using a fixed-effect model. If substantial heterogeneity could not readily be explained, we adopted a random-effects model.

Assessment of reporting biases

The possibility of publication bias was not explored using funnel plots because there was not a sufficient number of trials for the relevant comparisons.

Data synthesis

We performed data synthesis and analysis using Review Manager 5 (RevMan 2014). We calculated the RR. For the outcome measures of 50% reduction in seizure frequency and treatment withdrawal, we quoted 95% CIs. For individual adverse effects, we quoted 99% CIs to make an allowance for multiple testing (Bonferroni correction). Analyses included all participants in the treatment groups to which they were allocated (intention to treat (ITT)).

For the efficacy outcome (50% or greater reduction in seizure frequency), we undertook three analyses.

- Primary (ITT) analysis: participants not completing follow-up or with inadequate seizure data were assumed to be non-responders.
- Worst-case scenario analysis: participants not completing follow-up or with inadequate seizure data were assumed to be non-responders in the ESL group and responders in the placebo group.
- Best-case scenario analysis: participants not completing follow-up or with inadequate seizure data were assumed to be responders in the ESL group and non-responders in the placebo group.

Dose regression analysis: we also examined dose-response relationships for the primary outcome using logistic regression in the framework of generalized linear models (McCullagh 1989). Probabilities for the following were calculated for differing doses: the percentage of participants having a 50% response and the

difference in the percentage of participants responding to each dose compared to placebo. A binary variable was defined with value of 0 if the response was less than 50% and a value of 1 if otherwise.

Subgroup analysis and investigation of heterogeneity

We undertook a subgroup analysis according to different doses of ESL. Subgroup analysis according to age (children aged less than 17 years versus adults) was not possible because there were no relevant studies focused on children.

Sensitivity analysis

We intended to carry out sensitivity analyses if there were peculiarities between study quality, characteristics of participants, interventions and outcomes.

Summarizing and interpreting results

We used the GRADE approach to interpret findings (Schünemann 2011). We used GRADE Profiler software (GRADEpro 2004), and imported data from Review Manager 5 (RevMan 2014), to create 'Summary of findings' tables for each comparison included in the review for 50% or greater in seizure frequency, freedom from seizures, treatment withdrawal (any reason or adverse effects) and adverse effects.

The 'Summary of findings' table for each comparison included information on overall quality of the evidence from the trials and information of importance for healthcare decision making. The GRADE approach determined the quality of evidence on the basis of an evaluation of eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect and dose-response gradient). We used these to guide our conclusions and recommendations.

RESULTS

Description of studies

Full details of the individual studies are provided in the [Characteristics of included studies](#) table.

Results of the search

We carried out searches from the date of the previous search (November 2011) to 6 December 2016. In total, the search found 40 new records, 10 of which were duplicates and therefore removed. We excluded 19 of the remaining records due to irrelevance leaving 11 full-text articles to be assessed for eligibility. After this, we excluded ten studies (see [Figure 1](#) and [Characteristics of excluded studies](#) for reasons for exclusion). Therefore, we added one study (Sperling 2015), to the four studies already included in the previous version of this review (Ben-Menachem 2010; Elger 2007; Elger 2009; Gil-Nagel 2009).

Figure 1. Study flow diagram for update.

Included studies

Ben-Menachem and colleagues published a randomized double-blind placebo-controlled parallel group multi-centre (45 sites in 13 countries) study in 2010 with 395 participants aged between 18 and 69 years (Ben-Menachem 2010). The treatment arms included ESL 400 mg, 800 mg and 1200 mg once daily and a placebo arm. After a baseline period of eight weeks, participants were randomized to one of the four treatment arms for a treatment period of 14 weeks. A total of 115 participants dropped out of the study and two participants had no postbaseline data.

Elger and colleagues reported a multi-centre (19 sites in five countries) parallel group trial of 144 participants aged 18 to 65 years (Elger 2007). The treatment groups included an ESL once daily group, an ESL twice daily group and a placebo group. The daily doses of ESL were increased from 400 mg to 800 mg to 1200 mg at four-week intervals. The study consisted of a two-month retrospective baseline period, 12-week maintenance period and four-week tapering-off period. A total of 113 participants completed the study and one participant did not take any study medication. In this review, only the data in the once daily group and the placebo group were included in the analysis for clinical heterogeneity as the other studies have all used such a titration method of once daily.

Elger and colleagues published a multi-centre (40 sites in 11 countries) parallel group trial including 402 participants aged 18 to 76 years (Elger 2009). Participants were randomized into one of four treatment arms: ESL 400 mg (100 participants), 800 mg (98 participants) and 1200 mg (102 participants) once daily; while 102 participants were in the placebo group. The trial duration was 18 weeks including a two-week titration period, a 12-week

maintenance period and a four-week tapering-off period. A total of 72 participants discontinued the study and five participants lacked postbaseline efficacy data.

Gil-Nagel and colleagues described a multi-centre (39 sites in three countries) trial including 252 participants aged 17 to 77 years (Gil-Nagel 2009). Parallel groups included 85 participants taking ESL 800 mg once daily, 80 participants taking ESL 1200 mg once daily and 87 participants taking placebo. After a baseline assessment period of eight weeks, the trial was conducted over 18 weeks (including a two-week titration period, 12-week maintenance period and four-week tapering-off period). A total of seven participants had no postbaseline efficacy data and 58 participants dropped out of the study.

Sperling and colleagues described a multi-centre (173 sites in 19 countries) trial including 653 participants aged 16 to 71 years (Sperling 2015). Parallel groups included 216 participants taking ESL 800 mg once daily, 211 participants taking ESL 1200 mg once daily and 226 participants taking placebo. After a baseline assessment period of eight weeks, the trial was conducted over 14 weeks (including a two-week titration period, a 12-week maintenance period and a two-week tapering-off period). A total of 13 participants had no postbaseline efficacy data and 149 participants dropped out of the study.

Risk of bias in included studies

Detailed assessments of each risk item for each included study can be found in the 'Risk of bias' tables in the [Characteristics of included studies](#) table. A summary of the review authors' judgements is shown in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ben-Menachem 2010						
Elger 2007						
Elger 2009						
Gil-Nagel 2009						
Sperling 2015						

Allocation

For all five trials, we rated the methods by which allocation was concealed as low risk of bias, because four used sequentially numbered drug containers (Ben-Menachem 2010; Elger 2007; Elger 2009; Gil-Nagel 2009) and one used central randomization (Sperling 2015). For sequence generation, we rated the five studies at low risk of bias due to the use of a computer-generated randomization schedule.

Blinding

We rated all five trials at low risk of performance and detection bias because participants, personnel and outcome assessors were blinded.

Incomplete outcome data

All five trials reported missing data and performed an ITT analysis. However, the proportions of missing data were relatively high in all of the studies; ranging from 10% to 45% missing data per treatment

arm. In particular, in the four trials with an ESL 1200 mg dose arm, the proportion of missing data was high, ranging from 26% to 45%. Therefore we judged the risk of attrition bias to be high in all five studies and performed best-case scenario and worst case scenario analyses to examine the impact of the missing data (see Data synthesis).

Selective reporting

We rated all five studies at low risk of reporting bias as there was no suspicion of selective outcome reporting bias. All expected outcomes were reported in each of the publications.

Other potential sources of bias

All studies were at low risk of other potential sources of bias as there was no evidence of further bias in any of the included studies.

Effects of interventions

See: [Summary of findings for the main comparison](#)
Eslicarbazepine acetate add-on for drug-resistant focal epilepsy

Primary outcome

Intention-to-treat analysis: 50% or greater reduction in seizure frequency

An analysis pooling across doses (400 mg, 800 mg and 1200 mg once daily) showed no evidence of heterogeneity ($\text{Chi}^2 = 2.67$, degrees of freedom (df) = 4, $P = 0.61$; $I^2 = 0\%$). Those participants allocated to receive ESL were significantly more likely to achieve a 50% or greater reduction in seizure frequency (RR 1.71, 95% CI 1.42 to 2.05; [Analysis 1.1](#)). Subgroup analyses assessing the effects of individual doses showed that higher doses of ESL were associated with 50% or greater reductions in seizure frequency (400 mg/day: RR 1.22, 95% CI 0.80 to 1.85; 800 mg/day: RR 1.66, 95% CI 1.34 to 2.07; 1200 mg/day: RR 1.92, 95% CI 1.56 to 2.37; [Analysis 1.1](#)).

Best-case and worse-case scenarios: 50% or greater reduction in seizure frequency

The Chi^2 tests for heterogeneity for a response to ESL indicated no significant heterogeneity between trials (best-case: $\text{Chi}^2 = 5.19$, df = 4, $P = 0.27$; $I^2 = 23\%$; worst-case: $\text{Chi}^2 = 2.46$, df = 4, $P = 0.65$; $I^2 = 0\%$). For the best-case scenario, the overall RR was RR 2.93 (95% CI 2.47 to 3.49); [Analysis 1.2](#)) and for the worst-case scenario, it was 0.88 (95% CI 0.77 to 1.00; [Analysis 1.3](#)). These results were not consistent with the result of the ITT analysis, which may be due to the high dropout rate of the included studies.

Dose regression analysis for 50% or greater reduction in seizure frequency

Four trials studied the dose-response regression with aggregate data, as a result of the similar ways of titration ([Ben-Menachem 2010](#); [Elger 2009](#); [Gil-Nagel 2009](#); [Sperling 2015](#)). (As one trial tested different doses in each group and each dose period lasted only four weeks, the data from [Elger 2007](#) were not included in this analysis.) The results from the four studies indicated an increase in effect with increasing dose, with no clear plateau at the doses tested. The difference between ESL 400 mg and placebo was not significant. [Table 1](#) shows the estimated percentage of participants responding to each dose with 95% CIs. [Table 2](#) shows the percentage difference in participants responding to each dose compared to placebo with 95% CIs.

Freedom from seizures

An analysis pooling the data across doses (400 mg to 1200 mg once daily) showed no evidence of heterogeneity ($\text{Chi}^2 = 0.35$, df = 4, $P = 0.99$; $I^2 = 0\%$). Participants taking ESL were significantly more likely to achieve a seizure free state (RR 2.90, 95% CI 1.49 to 5.68; [Analysis 2.4](#)). Subgroup analysis showed that ESL 400 mg was not significantly associated with freedom from seizures (RR 1.03, 95% CI 0.21 to 5.02; [Analysis 2.1](#)), whereas higher doses of ESL were significantly associated with a seizure-free state (800 mg: RR 3.42, 95% CI 1.38 to 8.46; [Analysis 2.2](#); 1200 mg: RR 3.46, 95% CI 1.40 to 8.54; [Analysis 2.3](#)).

Secondary outcomes

Treatment withdrawal for any reason

Given that the test for overall heterogeneity among the included studies showed a statistical significance ($\text{Chi}^2 = 9.36$, df = 4, $P = 0.05$; $I^2 = 57\%$), the random-effects model was adopted. Although the cause of heterogeneity was not found, we found that with the increase of the participating countries and centre, the discontinuation rate also increased. Participants allocated ESL were not significantly more likely to have treatment withdrawn (RR 1.19, 95% CI 0.86 to 1.64; [Analysis 3.1](#)). The only dose associated with significant withdrawal for all reasons was 1200 mg once daily (RR 1.75, 95% CI 1.26 to 2.41; [Analysis 3.1](#)).

Treatment withdrawal for adverse effects

The random-effect model was also selected to analysis the data, due to significant heterogeneity ($\text{Chi}^2 = 7.73$, df = 4, $P = 0.10$; $I^2 = 48\%$) among the included studies. The overall RR across any dose was 2.66 (95% CI 1.42 to 4.96; [Analysis 3.2](#)). Subgroup analyses assessing treatment withdrawal with different doses of ESL suggested a higher withdrawal rate with higher doses (400 mg: RR 2.12, 95% CI 0.53 to 8.48; 800 mg: RR 2.52, 95% CI 1.47 to 4.35; 1200 mg: RR 4.66, 95% CI 2.68 to 8.09; [Analysis 3.2](#)). Therefore, there was moderate evidence to conclude that participants are more likely to discontinue ESL for adverse effects than with placebo.

Adverse effects

The following adverse effects were significantly associated with ESL: dizziness (RR 2.81, 99% CI 1.86 to 4.27; [Analysis 4.2](#)); nausea (RR 2.61, 99% CI 1.36 to 5.01; [Analysis 4.4](#)); somnolence (RR 1.71, 99% CI 1.11 to 2.63; [Analysis 4.5](#)); vomiting (RR 3.30, 99% CI 1.34 to 8.13; [Analysis 4.9](#)); and diplopia (RR 4.14, 99% CI 1.74 to 9.84; [Analysis 4.8](#)). Results for other adverse effects were: ataxia (RR 2.14, 99% CI 0.71 to 6.48; [Analysis 4.1](#)); fatigue (RR 1.39, 99% CI 0.58 to 3.31; [Analysis 4.3](#)); rash (RR 1.24, 99% CI 0.38 to 4.01; [Analysis 4.6](#)); and headache (RR 1.30, 99% CI 0.84 to 2.02; [Analysis 4.7](#)).

Drug interactions

The included studies did not assess related outcomes.

DISCUSSION

Summary of main results

The five trials included in this review recruited adults and were sponsored by BIAL. They used adequate methods of concealment of randomization and were double-blinded. The included studies had a high dropout rate.

The included studies tested ESL at doses of 400 mg, 800 mg and 1200 mg once daily. The results of this review show that ESL, when used as an add-on treatment, reduces seizure frequency in adults with drug-resistant focal epilepsy. In the analysis, pooling all doses of ESL, the RR for a 50% or greater reduction in seizure frequency was 1.71 (95% CI 1.42 to 2.05). There is a discrepancy between the results of the best-case scenario, worst-case scenario and ITT analyses, which is likely to be as a result of a higher discontinuation rate of included studies. There is a tendency that the discontinuation rate increases as the participating countries and subcentres increase. A dose-regression analysis showed

evidence of a dose effect, with no evidence of the plateauing of the effect for the doses tested.

For freedom from seizures, results show that ESL was significantly more likely to result in a complete seizure-free state than placebo in trials of relatively short duration. However, participants receiving ESL seemed more likely to discontinue ESL than placebo due to adverse effects. With respect to adverse effects, dizziness, nausea and diplopia were significantly more likely to occur in the ESL treated group, especially at higher doses.

Overall completeness and applicability of evidence

The trials included in this review focused on the use of ESL in adults with drug-resistant focal epilepsy, and the results cannot be generalized to add-on treatment for adults with generalized epilepsies or children. This review also does not tell us if ESL is effective in the long term and how ESL compares with other AEDs in the same scenario.

Quality of the evidence

The trials included in our review were of generally high quality with most of the outcomes reported. We were able to obtain further details of outcomes from trial sponsors. Each study was given a rating of low risk for selection bias, performance bias, detection bias and reporting bias. However, all five included trials were judged to be at high risk of attrition bias due to large proportions of missing data, ranging between 10% and 45% of data missing per arm of the trial. For efficacy outcome, 50% or greater reduction in seizure frequency, best-case and worst-case scenario analyses were inconsistent with results of ITT analyses. When the GRADE approach was used within a 'Summary of findings' table ([Summary of findings for the main comparison](#)), the quality of evidence overall was rated as moderate.

Potential biases in the review process

The main problems highlighted by our review are limitations on the lack of children in the current studies available. There were no major potential biases in the review process.

Agreements and disagreements with other studies or reviews

We found no other systematic reviews reporting the efficacy and safety of ESL when used as an add-on therapy for focal epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate quality evidence provided by this review demonstrates that both ESL 800 mg and 1200 mg taken once daily can significantly reduce seizure frequency in adults with treatment-resistant focal epilepsy, in the short term. For people entered into trials, approximately seven people needed to be treated with ESL for every additional person with a 50% or greater reduction in seizure frequency when compared to placebo. Dizziness, nausea, somnolence, vomiting and diplopia were significant adverse effects.

Implications for research

To further evaluate the place of ESL, more clinical trials are required addressing the following:

- long-term effects and adverse effects of add-on ESL;
- how ESL compares with other add-on treatments in drug-resistant focal epilepsy;
- role of ESL in children with refractory epilepsy;
- ESL as monotherapy for focal or generalized epilepsy.
- how ESL interacts with other AEDs, such as oxcarbazepine and carbamazepine.

ACKNOWLEDGEMENTS

We would like to acknowledge the Cochrane Epilepsy Group for their technical support. We also thank Graham Chan for her assistance in the search of relevant trials.

REFERENCES

References to studies included in this review

Ben-Menachem 2010 {published data only}

Ben-Menachem E, Gabbai AA, Hufnagel A, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. *Epilepsy Research* 2010;**89**:278-85.

Elger 2007 {published data only}

Elger C, Bialer M, Cramer JA, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine acetate: a double-blind, add-on, placebo-controlled exploratory trial in adult patients with partial-onset seizures. *Epilepsia* 2007;**48**:497-504.

Elger 2009 {published data only}

Elger C, Halasz P, Maia J, Almeida L, Soares-da-Silva P. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia* 2009;**50**:454-63.

Gil-Nagel 2009 {published data only}

Gil-Nagel A, Lopes-Lima J, Almeida L, Maia J, Soares-da-Silva P. Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures. *Acta Neurologica Scandinavica* 2009;**120**:281-7.

Sperling 2015 {published data only}

Sperling MR, Abou-Khalil B, Harvey J, Rogin JB, Biraben A, Galimberti CA, et al. Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: results of a phase III, double-blind, randomized, placebo-controlled trial. *Epilepsia* 2015; Vol. 53, issue 2:244-53.

References to studies excluded from this review

Aneja 2013 {published data only}

Aneja Satinder, Sharma Suvasini. Newer anti-epileptic drugs. *Indian Pediatrics* 2013;**50**:1033-40.

Cramer 2015 {published data only}

Cramer Joyce A, Velez Fulton F, Anastassopoulos Kathryn P, Bond T Christopher, Gilliam Frank G, Ryvlin Philippe, et al. Severity and burden of partial-onset seizures in a phase III trial of eslicarbazepine acetate. *Epilepsy & Behavior* 2015;**53**:149-53.

Ermolenko 2014 {published data only}

Ermolenko N A, Buchneva I A. [Exalief as a newer antiepileptic drug for adjunctive therapy of refractory partial-onset seizures]. *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova* 2014;**114**:129-34.

Grunze 2015 {published data only}

Grunze Heinz, Kotlik Eduardo, Costa Raquel, Nunes Teresa, Falcao Amilcar, Almeida Luis, et al. Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. *Journal of Affective Disorders* 2015;**174**:70-82.

Jacobson 2015 {published data only}

Jacobson M P, Pazdera L, Bhatia P, Grinnell T, Cheng H, Blum D. Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study. *BMC neurology* 2015;**15**:46.

Keating 2014 {published data only}

Keating Gillian M. Eslicarbazepine acetate: a review of its use as adjunctive therapy in refractory partial-onset seizures. *CNS Drugs* 2014;**28**:583-600.

Moreira 2012 {published data only}

Moreira J, TrinkAE, Mota F, Nunes T, Soares da Silva P. Design of a phase III, double-dummy, active-controlled, multi-national non-inferiority monotherapy trial of eslicarbazepine acetate versus controlled-release carbamazepine In adults with partial-onset seizures [abstract]. *Epilepsia* 2012;**53**:122, Abstract no: p415.

Sperling 2015a {published data only}

Sperling Michael R, Harvey Jay, Grinnell Todd, Cheng Hailong, Blum David, Study Team. Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a randomized historical-control phase III study based in North America. *Epilepsia* 2015;**56**:546-55.

Sperling 2016 {published data only}

Sperling Michael R, French Jacqueline, Jacobson Mercedes P, Pazdera Ladislav, Gough Mallory, Cheng Hailong, et al. Conversion to eslicarbazepine acetate monotherapy: A pooled analysis of 2 phase III studies. *Neurology* 2016;**86**:1095-102.

Zaccara 2015 {published data only}

Zaccara Gaetano, Giovannelli Fabio, Cincotta Massimo, Carelli Alessia, Verrotti Alberto. Clinical utility of eslicarbazepine: current evidence. *Drug design, development & therapy* 2015;**9**:781-9.

References to ongoing studies

NCT00988429 {unpublished data only}

NCT00988429. Efficacy and safety study of eslicarbazepine acetate (BIA 2 093) as adjunctive therapy for refractory partial seizures in children. <https://clinicaltrials.gov/ct2/show/NCT00988429> (first received 01 October 1999).

Additional references

Almeida 2007

Almeida L, Soares-da-Silva P. Eslicarbazepine acetate (BIA 2-093). *Neurotherapeutics* 2007;**4**(1):88-96.

GRADEpro 2004 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro Version 3.6 for Windows. Hamilton (ON): GRADE Working Group, McMaster University, 2004.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

McCormack 2009

McCormack PL, Robinson DM. Eslicarbazepine acetate. *CNS Drugs* 2009;**23**(1):71-9.

McCullagh 1989

McCullagh P, Nelder JA. Generalized Linear Models. 2nd Edition. London (UK): Chapman and Hall, 1989.

Mestre 2009

Mestre T, Ferreira J. Eslicarbazepine acetate: a new option for the treatment of focal epilepsy. *Expert Opinion on Investigational Drugs* 2009;**18**(2):221-9.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sander 2003

Sander JW. The epidemiology of epilepsy revisited. *Current Opinion in Neurology* 2003;**16**(2):165-70.

Schuele 2008

Schuele SU, Luders HO. Intractable epilepsy: management and therapeutic alternatives. *Lancet Neurology* 2008;**7**(6):514-24.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editors(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Walker 1997

Walker MC, Sander JW. Difficulties in extrapolating from clinical trial data to clinical practice: the case of antiepileptic drugs. *Neurology* 1997;**49**(2):333-7.

References to other published versions of this review

Chang 2010

Chang XC, Yuan H, Wang Y, Xu HQ, Zheng RY. Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: [10.1002/14651858.CD008907](https://doi.org/10.1002/14651858.CD008907)]

Chang 2011

Chang XC, Yuan H, Wang Y, Xu HQ, Zheng RY. Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: [10.1002/14651858.CD008907.pub2](https://doi.org/10.1002/14651858.CD008907.pub2)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ben-Menachem 2010

Methods	Randomized double-blind placebo-controlled parallel multi-centre (45 sites in 13 countries) trial. Duration of baseline period: 8 weeks. Treatment period: 14 weeks. Only ESL 1200 mg group had 2 weeks titration period.
Participants	395 people randomized, 100 to placebo group, 96 to ESL 400 mg group, 101 to ESL 800 mg group, 98 to ESL 1200 mg group. Taking 1-3 AEDs. Age range: 18-69 years (median age: 35 years). Gender: 51% women.
Interventions	Group 1: placebo once daily. Group 2: ESL 400 mg once daily.

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Ben-Menachem 2010 (Continued)

Group 3: ESL 800 mg once daily.

Group 4: ESL 1200 mg once daily.

Outcomes	<p>≥ 50% reduction in seizure frequency.</p> <p>Freedom from seizures.</p> <p>Treatment withdrawal.</p> <p>Adverse effects.</p>
Notes	2 participants without postbaseline efficacy data excluded from published analyses: 1 from ESL 800 mg group and 1 from ESL 1200 mg group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes were generated using SAS® software (PROC PLAN procedure).
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical shape and appearance.
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was performed in a double-blind fashion, neither the investigator or his/her staff, nor did the patient know which treatment he/she was assigned to. This was achieved using identical study medication.
Incomplete outcome data (attrition bias) 50% or greater reduction in seizure frequency	High risk	<p>19 participants (19%) missing from placebo group; 26 participants (27%) from ESL 400 mg group; 26 participants (26%) from ESL 800 mg group; 44 participants (45%) from ESL 1200 mg group.</p> <p>2 participants (1 from ESL 800 mg group; 1 from ESL 1200 mg group) excluded from ITT population because they had no postbaseline efficacy data.</p> <p>ITT analysis used by concerns regarding attrition bias due to high proportions of missing data, particularly in the ESL 1200 mg group</p>
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but appears all expected and prespecified outcomes were reported.
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Elger 2007

Methods	<p>Randomized double-blind placebo-controlled parallel multi-centre (19 centres in 5 countries) trial.</p> <p>Baseline period: retrospective 2 months.</p> <p>Treatment period: 16 weeks.</p>
Participants	<p>144 participants randomized, 47 to placebo group, 50 to ESL once daily group, 47 to ESL twice daily group.</p> <p>Taking 1 or 2 AEDs.</p> <p>Age range: 18-65 years.</p>

Elger 2007 (Continued)

Interventions	<p>Group 1: placebo.</p> <p>Group 2: ESL once daily.</p> <p>Group 3: ESL twice daily.</p> <p>Daily doses of ESL were increased from 400 mg to 800 mg to 1200 mg at 4-week intervals.</p>
Outcomes	<p>≥ 50% reduction in seizure frequency.</p> <p>Freedom from seizures.</p> <p>Treatment withdrawal.</p> <p>Adverse effects.</p>
Notes	1 participant in ESL twice daily group excluded from published analyses because he did not take study medication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization carried out by computerized techniques by the biostatistics department of contract research organization in charge of the process.
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical shape and appearance.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study performed using double-blind method where investigator, staff and participants did not.
Incomplete outcome data (attrition bias) 50% or greater reduction in seizure frequency	High risk	<p>11 participants (23%) missing from placebo group; 8 participants (16%) from ESL once daily group; 12 participants (26%) from ESL twice daily group.</p> <p>1 participant (from ESL twice daily group) excluded from ITT population because he did not take study medication.</p> <p>ITT analysis used by concerns regarding attrition bias due to relatively high proportions of missing data</p>
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appeared all expected and prespecified outcomes were reported.
Other bias	Low risk	Comment: the study appeared free of other sources of bias.

Elger 2009

Methods	<p>Randomized double-blind placebo-controlled parallel multi-centre (40 sites in 11 countries) trial.</p> <p>Duration of baseline period: 8 weeks.</p> <p>Treatment period: 18-weeks including 2-week titration period, 12-week maintenance period and 4-week tapering-off period.</p>
Participants	402 participants randomized, 102 to placebo group, 100 to ESL 400 mg group, 98 to ESL 800 mg group, 102 to ESL 1200 group.

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Elger 2009 (Continued)

Taking 1 or 2 AEDs.

Age range: 18-76 years (median age: 39 years).

Gender: 51% women.

Interventions	<p>Group 1: placebo.</p> <p>Group 2: ESL 400 mg once daily.</p> <p>Group 3: ESL 800 mg once daily.</p> <p>Group 4: ESL 1200 mg once daily.</p>
Outcomes	<p>≥ 50% reduction in seizure frequency.</p> <p>Freedom from seizures.</p> <p>Treatment withdrawal.</p> <p>Adverse effects.</p>
Notes	5 participants excluded from published analyses: 1 from ESL 400 group and 4 from ESL 1200 mg group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes generated using computerized techniques.
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical shape and appearance.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study performed using double-blind method where investigator, staff and participants did not know which treatment was assigned. Achieved using identical study medication.
Incomplete outcome data (attrition bias) 50% or greater reduction in seizure frequency	High risk	<p>18 participants (18%) missing from placebo group; 10 participants (10%) from ESL 400 mg group; 13 participants (13%) from ESL 800 mg group; 31 participants (30%) from ESL 1200 mg group.</p> <p>5 participants (1 from ESL 400 mg group; 4 from ESL 1200 mg group) excluded from ITT population because they had no postbaseline efficacy data.</p> <p>ITT analysis used by concerns regarding attrition bias due to relatively high proportions of missing data, particularly in the ESL 1200 mg group</p>
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appeared all expected and prespecified outcomes were reported.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Gil-Nagel 2009

Methods

Randomized double-blind placebo controlled parallel multi-centre (39 sites in 3 countries) trial.

Duration of baseline period: 8 weeks.

Gil-Nagel 2009 (Continued)

Treatment period: 18-weeks including 2-week titration period, 12-week maintenance period and 4-week tapering-off period.

Participants	252 people randomized, 87 to placebo group, 85 to ESL 800 mg group, 80 to ESL 1200 mg group. Taking 1 or 2 AEDs. Age range: 17-77 years (median age: 35 years). Gender: 55.2% women.
Interventions	Group 1: placebo. Group 2: ESL 800 mg once daily. Group 3: ESL 1200 mg once daily.
Outcomes	≥ 50% reduction in seizure frequency. Freedom from seizures. Treatment withdrawal. Adverse effects.
Notes	7 participants excluded from published analyses: 3 from placebo group, 1 from ESL 800 mg group, 3 from ESL 1200 mg group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes prepared by designated, unblinded statistician, generated using SAS software (PROC PLAN procedure).
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical shape and appearance.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study performed with double-blind method where investigator, staff and participants did not know which treatment was assigned. Achieved using identical study medication.
Incomplete outcome data (attrition bias) 50% or greater reduction in seizure frequency	High risk	22 participants (25%) missing from placebo group; 15 participants (18%) from ESL 800 mg group; 21 participants (26%) from ESL 1200 mg group. 7 participants (3 from placebo group; 1 from ESL 800 mg; 3 from ESL 1200 mg group) excluded from ITT population because they had no postbaseline efficacy data. ITT analysis used by concerns regarding attrition bias due to relatively high proportions of missing data, particularly in the ESL 1200 mg group
Selective reporting (reporting bias)	Low risk	Protocol unavailable, but appeared all expected and prespecified outcomes were reported.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Sperling 2015

Methods	<p>Randomized double-blind placebo-controlled parallel multi-centre (173 sites in 19 countries) trial.</p> <p>Duration of baseline period: 8 weeks.</p> <p>Treatment period: 18-weeks including 2-week titration period, 12-week maintenance period and 2-week tapering-off period.</p>
Participants	<p>653 people randomized, 226 to placebo group, 216 to ESL 800 mg group, 211 to ESL 1200 mg group.</p> <p>Taking 1 or 2 AEDs.</p> <p>Age range: 16-71 years (median age: 38.5 years).</p> <p>Gender: 49.8% women.</p>
Interventions	<p>Group 1: placebo.</p> <p>Group 2: ESL 800 mg once daily.</p> <p>Group 3: ESL 1200 mg once daily.</p>
Outcomes	<p>≥ 50% reduction in seizure frequency.</p> <p>Freedom from seizures.</p> <p>Treatment withdrawal.</p> <p>Adverse effects.</p>
Notes	<p>13 participants excluded from published analyses: 6 from placebo group, 1 from ESL 800 mg group and 6 from ESL 1200 mg group.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes were generated using computerized techniques.
Allocation concealment (selection bias)	Low risk	<p>Central randomisation</p> <p>Quote: "Randomization and allocation to treatment group was performed using an interactive voice-response system. The randomisation code was prepared by a third party using a computer-generated schedule,"</p>
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was performed in a double-blind fashion, neither the investigator or his/her staff, nor did the patient know which treatment he/she was assigned to.
Incomplete outcome data (attrition bias) 50% or greater reduction in seizure frequency	High risk	<p>37 participants (16%) missing from placebo group; 43 participants (20%) from ESL 800 mg group; 69 participants (33%) from ESL 1200 mg group.</p> <p>13 participants (6 from ESL placebo group; 1 from ESL 800 mg group; 6 from ESL 1200 mg group) excluded from ITT population because they had no post-baseline efficacy data.</p> <p>ITT analysis used by concerns regarding attrition bias due to relatively high proportions of missing data, particularly in the ESL 1200 mg group</p>
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but appears all expected and prespecified outcomes were reported.

Sperling 2015 (Continued)

Other bias	Low risk	Comment: the study appears to be free of other sources of bias.
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AED: antiepileptic drug; ESL: eslicarbazepine; ITT: intention to treat.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aneja 2013	Not randomised controlled trial.
Cramer 2015	The results of interest have been published in another article (Sperling 2015).
Ermolenko 2014	Not randomised controlled trial.
Grunze 2015	Ineligible population: patients with bipolar disorder.
Jacobson 2015	Monotherapy.
Keating 2014	Not randomised controlled trial.
Moreira 2012	Monotherapy
Sperling 2015a	Monotherapy
Sperling 2016	Not randomised controlled trial.
Zaccara 2015	Not randomised controlled trial.

Characteristics of ongoing studies [ordered by study ID]

NCT00988429

Trial name or title	Eslicarbazepine Acetate (BIA 2 093) as Therapy for Refractory Partial Seizures in Children.
Methods	Randomized, double-blind, placebo-controlled parallel multi-centre trial. 8-week observational baseline period followed by a 6-week double-blind titration period, a 12-week double-blind maintenance period, a double-blind tapering-off period and a 4-week observational period.
Participants	Age: 2-16 years. Taking 1 or 2 antiepileptic drugs. ≥4 focal-onset seizures during each 4-week interval of the 8-week baseline period.
Interventions	Group 1: placebo. Group 2: eslicarbazepine acetate.
Outcomes	Responder rate, relative reduction in standardized seizure frequency, adverse effects.
Starting date	December 2007.
Contact information	Teresa Nunes, MD, tel: 351 229866100, teresa.nunes@bial.com .

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NCT00988429 (Continued)

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Notes

DATA AND ANALYSES

Comparison 1. 50% or greater reduction in seizure frequency

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary analysis	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.80, 1.85]
1.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.34, 2.07]
1.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.56, 2.37]
1.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.42, 2.05]
2 Best-case scenario	5	1799	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [2.47, 3.49]
3 Worst-case scenario	5	1799	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.00]

Analysis 1.1. Comparison 1 50% or greater reduction in seizure frequency, Outcome 1 Primary analysis.

Study or subgroup	ESL n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Eslicarbazepine acetate 400 mg/day versus placebo					
Ben-Menachem 2010	16/96	13/100		39.14%	1.28[0.65,2.52]
Elger 2009	23/100	20/102		60.86%	1.17[0.69,2]
Subtotal (95% CI)	196	202		100%	1.22[0.8,1.85]
Total events: 39 (ESL), 33 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.04, df=1(P=0.84); I ² =0%					
Test for overall effect: Z=0.92(P=0.36)					
1.1.2 Eslicarbazepine acetate 800 mg/day versus placebo					
Ben-Menachem 2010	40/101	13/100		13.15%	3.05[1.74,5.34]
Elger 2009	33/98	20/102		19.73%	1.72[1.06,2.78]
Gil_x002d_Nagel 2009	29/85	19/87		18.9%	1.56[0.95,2.56]
			Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours ESL

Analysis 1.2. Comparison 1 50% or greater reduction in seizure frequency, Outcome 2 Best-case scenario.

Analysis 1.3. Comparison 1 50% or greater reduction in seizure frequency, Outcome 3 Worst-case scenario.

Comparison 2. Freedom from seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.21, 5.02]
2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [1.38, 8.46]
3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [1.40, 8.54]
4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [1.49, 5.68]

Analysis 2.1. Comparison 2 Freedom from seizures, Outcome 1 Eslicarbazepine acetate 400 mg/day versus placebo.

Analysis 2.2. Comparison 2 Freedom from seizures, Outcome 2 Eslicarbazepine acetate 800 mg/day versus placebo.

Analysis 2.3. Comparison 2 Freedom from seizures, Outcome 3 Eslicarbazepine acetate 1200 mg/day versus placebo.

Analysis 2.4. Comparison 2 Freedom from seizures, Outcome 4 Eslicarbazepine acetate any dose versus placebo.

Comparison 3. Treatment withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment withdrawal (any reason)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.38, 2.30]
1.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.39]
1.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.26, 2.41]
1.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.86, 1.64]
2 Treatment withdrawal (adverse effect)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Random, 95% CI)	2.12 [0.53, 8.48]
2.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Random, 95% CI)	2.52 [1.47, 4.35]
2.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Random, 95% CI)	4.66 [2.68, 8.09]
2.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.42, 4.96]

Analysis 3.1. Comparison 3 Treatment withdrawal, Outcome 1 Treatment withdrawal (any reason).

Analysis 3.2. Comparison 3 Treatment withdrawal, Outcome 2 Treatment withdrawal (adverse effect).

Comparison 4. Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ataxia	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.1 Eslicarbazepine acetate 400 mg/day versus placebo	1	196	Risk Ratio (M-H, Fixed, 99% CI)	1.04 [0.21, 5.09]
1.2 Eslicarbazepine acetate 800 mg/day versus placebo	2	373	Risk Ratio (M-H, Fixed, 99% CI)	2.49 [0.75, 8.29]
1.3 Eslicarbazepine acetate 1200 mg/day versus placebo	2	365	Risk Ratio (M-H, Fixed, 99% CI)	2.59 [0.77, 8.64]
1.4 Eslicarbazepine acetate any dose versus placebo	2	647	Risk Ratio (M-H, Fixed, 99% CI)	2.14 [0.71, 6.48]
2 Dizziness	5		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
2.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 99% CI)	2.25 [0.97, 5.22]
2.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 99% CI)	2.41 [1.52, 3.80]
2.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 99% CI)	3.58 [2.33, 5.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Fixed, 99% CI)	2.81 [1.86, 4.27]
3 Fatigue	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
3.1 Eslicarbazepine acetate 400 mg/day versus placebo	1	196	Risk Ratio (M-H, Fixed, 99% CI)	0.83 [0.15, 4.51]
3.2 Eslicarbazepine acetate 800 mg/day versus placebo	2	643	Risk Ratio (M-H, Fixed, 99% CI)	1.21 [0.43, 3.40]
3.3 Eslicarbazepine acetate 1200 mg/day versus placebo	2	635	Risk Ratio (M-H, Fixed, 99% CI)	1.72 [0.66, 4.50]
3.4 Eslicarbazepine acetate any dose versus placebo	2	1048	Risk Ratio (M-H, Fixed, 99% CI)	1.39 [0.58, 3.31]
4 Nausea	4		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
4.1 Eslicarbazepine acetate 400 mg/day versus placebo	1	196	Risk Ratio (M-H, Fixed, 99% CI)	2.08 [0.45, 9.66]
4.2 Eslicarbazepine acetate 800 mg/day versus placebo	3	815	Risk Ratio (M-H, Fixed, 99% CI)	2.12 [0.99, 4.55]
4.3 Eslicarbazepine acetate 1200 mg/day versus placebo	3	802	Risk Ratio (M-H, Fixed, 99% CI)	3.64 [1.80, 7.39]
4.4 Eslicarbazepine acetate any dose versus placebo	4	1397	Risk Ratio (M-H, Fixed, 99% CI)	2.61 [1.36, 5.01]
5 Somnolence	5		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
5.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 99% CI)	1.15 [0.54, 2.45]
5.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 99% CI)	1.39 [0.83, 2.31]
5.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 99% CI)	2.10 [1.31, 3.37]
5.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Fixed, 99% CI)	1.71 [1.11, 2.63]
6 Rash	4		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Eslicarbazepine acetate any dose versus placebo	4	1702	Risk Ratio (M-H, Fixed, 99% CI)	1.24 [0.38, 4.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Headache	5		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 99% CI)	1.17 [0.49, 2.80]
7.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 99% CI)	1.20 [0.71, 2.01]
7.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 99% CI)	1.55 [0.95, 2.53]
7.4 Eslicarbazepine acetate any dose versus placebo	5	1799	Risk Ratio (M-H, Fixed, 99% CI)	1.30 [0.84, 2.02]
8 Diplopia	4		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
8.1 Eslicarbazepine acetate 400 mg/day versus placebo	2	398	Risk Ratio (M-H, Fixed, 99% CI)	2.42 [0.59, 10.01]
8.2 Eslicarbazepine acetate 800 mg/day versus placebo	4	1015	Risk Ratio (M-H, Fixed, 99% CI)	4.03 [1.61, 10.08]
8.3 Eslicarbazepine acetate 1200 mg/day versus placebo	4	1006	Risk Ratio (M-H, Fixed, 99% CI)	5.12 [2.07, 12.62]
8.4 Eslicarbazepine acetate any dose versus placebo	4	1702	Risk Ratio (M-H, Fixed, 99% CI)	4.14 [1.74, 9.84]
9 Vomiting	4		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
9.1 Eslicarbazepine acetate 400 mg/day versus placebo	1	196	Risk Ratio (M-H, Fixed, 99% CI)	1.39 [0.20, 9.59]
9.2 Eslicarbazepine acetate 800 mg/day versus placebo	3	815	Risk Ratio (M-H, Fixed, 99% CI)	2.59 [0.96, 7.02]
9.3 Eslicarbazepine acetate 1200 mg/day versus placebo	3	802	Risk Ratio (M-H, Fixed, 99% CI)	4.59 [1.80, 11.70]
9.4 Eslicarbazepine acetate any dose versus placebo	4	1397	Risk Ratio (M-H, Fixed, 99% CI)	3.30 [1.34, 8.13]

Analysis 4.1. Comparison 4 Adverse effects, Outcome 1 Ataxia.

Study or subgroup	ESL n/N	Placebo n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
4.1.1 Eslicarbazepine acetate 400 mg/day versus placebo					
Ben-Menachem 2010	5/96	5/100		100%	1.04[0.21,5.09]

Analysis 4.2. Comparison 4 Adverse effects, Outcome 2 Dizziness.

Analysis 4.3. Comparison 4 Adverse effects, Outcome 3 Fatigue.

Analysis 4.4. Comparison 4 Adverse effects, Outcome 4 Nausea.

Study or subgroup	ESL n/N	Placebo n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Test for overall effect: $Z=3.78(P=0)$					
<div> <div>More in placebo</div> <div>0.01</div> <div>0.1</div> <div>1</div> <div>10</div> <div>100</div> <div>More in ESL</div> </div>					

Analysis 4.5. Comparison 4 Adverse effects, Outcome 5 Somnolence.

Analysis 4.6. Comparison 4 Adverse effects, Outcome 6 Rash.

Analysis 4.7. Comparison 4 Adverse effects, Outcome 7 Headache.

Analysis 4.8. Comparison 4 Adverse effects, Outcome 8 Diplopia.

Analysis 4.9. Comparison 4 Adverse effects, Outcome 9 Vomiting.

ADDITIONAL TABLES

Table 1. Estimated percentage responders per dose

Dose (mg/day)	Responders (%)	95% Confidence intervals
0	19.0	15.9 to 22.7
400	24.5	19.0 to 30.0
800	30.9	27.1 to 35.2

Table 1. Estimated percentage responders per dose *(Continued)*

1200	38.2	34.1 to 42.7
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Table 2. Percentage difference in responders per dose compared to placebo

Dose (mg/day)	Difference	95% Confidence intervals
400	6	-1 to 12
800	13	7 to 17
1200	21	14 to 25

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 (Eslicarbazepine or Zeb?nix or Exalief or Stedesa or "BIA 2-093") AND >2010:YR

Appendix 2. CENTRAL search strategy

#1 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Epilepsy] explode all trees

#3 MeSH descriptor: [Seizures] explode all trees

#4 (#1 or #2 or #3) in Trials

#5 Eslicarbazepine or Zeb?nix or Exalief or Stedesa or "BIA 2-093"

#6 #4 and #5 from 2011

Below is the search strategy used for the original searches in November 2011.

#1 MeSH descriptor Epilepsy explode all trees

#2 MeSH descriptor Seizures explode all trees

#3 epilep* or seizure* or convulsion*

#4 "eslicarbazepine acetate":ti,ab,kw or (eslicarbazepine):ti,ab,kw or (zebenix):ti,ab,kw or "BIA 2-093":ti,ab,kw

#5 (#1 OR #2 OR #3)

#6 (#4 AND #5)

Appendix 3. MEDLINE search strategy

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

1. (randomized controlled trial or controlled clinical trial).pt. or (randomized 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. (Eslicarbazepine or Zeb#nix or Exalief or Stedesa or BIA 2-093).tw.
12. 6 and 10 and 11
13. limit 12 to ed=20111001-20131114

Below is the search strategy used for the original searches in November 2011.

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Epilepsy/
12. Seizures/
13. (epilep\$ or seizure\$ or convuls\$).tw.
14. 11 or 12 or 13
15. (eslicarbazepine or zeбенix or BIA 2-093).ti,ab.
16. 10 and 14 and 15

WHAT'S NEW

Date	Event	Description
30 January 2018	Amended	Several edits made to the text. Conclusions are unchanged.

HISTORY

Protocol first published: Issue 12, 2010
Review first published: Issue 12, 2011

Date	Event	Description
6 December 2016	New search has been performed	Searches updated 6 December 2016; one new study has been added to the review.
6 December 2016	New citation required but conclusions have not changed	Conclusions are unchanged.

CONTRIBUTIONS OF AUTHORS

XCC: drafting protocol and review versions; selection of trials for inclusion/exclusion; extraction of data; interpretation of data analyses; updating review.

HY: selection of trials for inclusion/exclusion; extraction of data.

YW: methodology expert.

HQX: drafting review versions; updating review.

WKH: drafting review versions; updating review.

RYZ: correspondence; arbiter of selection of trials for inclusion/exclusion.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Dibenzazepines [*therapeutic use]; Drug Resistance; Drug Therapy, Combination [methods]; Epilepsies, Partial [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Humans; Middle Aged; Young Adult