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Carisbamate add-on therapy for drug-resistant focal epilepsy (Review)

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[Intervention Review]

Carisbamate add-on therapy for drug-resistant focal epilepsy

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ABSTRACT

Background

Epilepsy is one of the most common neurological disorders. Many people with epilepsy are drug-resistant and require add-on therapy, meaning that they concomitantly take multiple antiepileptic drugs. Carisbamate is a drug which is taken orally and inhibits voltage-gated sodium channels. Carisbamate may be useful for drug-resistant focal epilepsy.

Objectives

To evaluate the efficacy and tolerability of carisbamate when used as an add-on therapy for drug-resistant focal epilepsy.

Search methods

We searched the following databases on 8 April 2021: Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid) 1946 to April 07, 2021. CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, WHO ICTRP, the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane review groups including Epilepsy. We also searched ongoing trials registers, checked reference lists, and contacted authors of the included trials.

Selection criteria

Double-blind randomised controlled trials (RCTs) comparing carisbamate versus placebo or another antiepileptic drug, as add-on therapy for drug-resistant focal epilepsy. Trials could have a parallel-group or cross-over design.

Data collection and analysis

Two review authors independently selected the trials for inclusion, assessed trial quality, and extracted data. The primary outcome was 50% or greater reduction in seizure frequency (responder rate). The secondary outcomes were: seizure freedom, treatment withdrawal (for any reason and due to adverse events); adverse events, and quality of life. We analysed data using the Mantel-Haenszel statistical method and according to the intention-to-treat population. We presented results as risk ratios (RRs) with 95% confidence intervals (CIs).

Main results

We included four RCTs involving a total of 2211 participants. All four trials compared carisbamate with placebo for drug-resistant focal epilepsy. Participants in all trials were over 16 years of age and received at least one other antiepileptic drug concomitantly. We detected substantial risk of bias across the included trials. All four trials were at high risk of attrition bias due to the incomplete reporting of attrition and the high treatment withdrawal rates noted, especially with higher doses. All four trials also had unclear risk of detection bias, as they did not specify whether outcome assessors were blinded.

Meta-analysis suggested that carisbamate produced a higher responder rate compared to placebo (RR 1.36, 95% CI 1.14 to 1.62; 4 studies; moderate-certainty evidence). More participants in the carsibamate group achieved seizure freedom (RR 2.43, 95% CI 0.84 to 7.03; 1 study); withdrew from treatment for any reason (RR 1.32, 95% CI 0.82 to 2.12; 4 studies); and withdrew from treatment due to adverse events (RR 1.80, 95% CI 0.78 to 4.17; 4 studies) than in the placebo group. However, the evidence for the three outcomes was very low-certainty. There was no difference between treatment groups for the proportion of participants experiencing at least one adverse event (RR 1.10, 95% CI 0.93 to 1.30; 2 studies; low-certainty evidence). More participants in the carisbamate group than in the placebo group developed dizziness (RR 2.06, 95% CI 1.23 to 3.44; 4 studies; very low-certainty evidence) and somnolence (RR 1.82, 95% CI 1.28 to 2.58; 4 studies; low-certainty evidence), but not fatigue (RR 1.11, 95% CI 0.73 to 1.68; 3 studies); headache (RR 1.13, 95% CI 0.92 to 1.38; 4 studies); or nausea (RR 1.19, 95% CI 0.81 to 1.75; 3 studies). None of the included trials reported quality of life.

Authors' conclusions

The results suggest that carisbamate may demonstrate efficacy and tolerability as an add-on therapy for drug-resistant focal epilepsy. Importantly, the evidence for all outcomes except responder rate was of low to very low certainty, therefore we are uncertain of the accuracy of the reported effects. The certainty of the evidence is limited by the significant risk of bias associated with the included studies, as well as the statistical heterogeneity detected for some outcomes. Consequently, it is difficult for these findings to inform clinical practice. The studies were all of short duration and only included adult study populations. There is a need for further RCTs with more clear methodology, long-term follow-up, more clinical outcomes, more seizure types, and a broader range of participants.

PLAIN LANGUAGE SUMMARY

Carisbamate add-on therapy for drug-resistant focal epilepsy

Background

Epilepsy is one of the most common chronic disorders of the nervous system. Most people with epilepsy are able to control their condition using a single antiepileptic drug; however, many people with epilepsy are drug-resistant and need to take multiple antiepileptic drugs. Carisbamate may be useful for drug-resistant focal epilepsy (epilepsy where the seizures start in one area of the brain).

Aim of review

This review evaluated the effectiveness and tolerability of carisbamate when used as an add-on treatment (a treatment added to other antiepileptic drugs) for drug-resistant focal epilepsy.

The evidence is current to April 2021.

Key results

We found four studies involving a total of 2211 participants, who were aged 16 years and above. A third more people experienced a 50% or greater reduction in seizure frequency when receiving add-on carisbamate compared to those who received add-on placebo (dummy pill).

Twice as many people in the carisbamate group became free of all seizures compared to the placebo group. More people in the carisbamate group withdrew from treatment for any reason and withdrew due to side effects than in the placebo group. There was no difference in the number of people who experienced one of more adverse events between the carisbamate and placebo groups. Approximately twice as many people in the carisbamate group developed dizziness and drowsiness compared to the placebo group.

Certainty of the evidence

The included studies were at risk of bias due to a high number of participant withdrawals, especially when given high doses of carisbamate. The evidence for 50% or greater reduction in seizure frequency was of moderate certainty, meaning that we are fairly certain that the findings we have reported are accurate. The evidence for the other results (seizure freedom, treatment withdrawal, the number of people experiencing one or more adverse events, dizziness, and drowsiness) was of low to very low certainty, meaning that we are uncertain of the accuracy of these results. We cannot comment on the use of add-on carisbamate in children or on its long-term use because the studies only included adults and were of short duration.

Summary of findings 1. Carisbamate compared to placebo for drug-resistant focal epilepsy

Carisbamate compared to placebo for drug-resistant focal epilepsy

Patient or population: people with drug-resistant focal epilepsy
Setting: outpatients
Intervention: carisbamate (any dose)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with carisbamate				
50% or greater reduction in seizure frequency (responder rate) Follow-up (range): 12 to 16 weeks	**Study population** 197 per 1000	268 per 1000 (225 to 320)	**RR 1.36** (1.14 to 1.62)	**2211** (4 RCTs)	⊕⊕⊕⊖ **MODERATE**[1]	Carisbamate likely increases the proportion of people who will attain a 50% or greater reduction in seizure reduction. The effect was shown to be statistically significant by the test for overall effect.
Seizure freedom Follow-up: 14 weeks	**Study population** 22 per 1000	53 per 1000 (18 to 152)	**RR 2.43** (0.84 to 7.03)	**540** (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[1,2]	Carisbamate may result in a large increase in the number of people who attain seizure freedom, but we are very uncertain of the accuracy of this effect. Furthermore, the overall effect was shown to be statistically insignificant.
Treatment withdrawal for any reason Follow-up (range): 12 to 16 weeks	**Study population** 93 per 1000	122 per 1000 (76 to 196)	**RR 1.32** (0.82 to 2.12)	**2211** (4 RCTs)	⊕⊖⊖⊖ **VERY LOW**[1,3,4]	Carisbamate may increase the number of people who withdraw from treatment for any reason, but we are very uncertain of the accuracy of this effect. Furthermore, the overall effect was shown to be statistically insignificant.
Treatment withdrawal due to adverse events Follow-up (range): 12 to 16 weeks	**Study population** 36 per 1000	65 per 1000 (28 to 150)	**RR 1.80** (0.78 to 4.17)	**2211** (4 RCTs)	⊕⊖⊖⊖ **VERY LOW**[1,3,4]	Carisbamate may increase the number of people who withdraw from treatment due to adverse events, but we are very uncertain of the accuracy of this effect. Furthermore, the overall effect was shown to be statistically insignificant.

Proportion of participants who experienced atleast 1 adverse event Follow-up (range): 14 to 16 weeks	**Study population**		**RR 1.10** (0.93 to 1.30)	**1084** (2 RCTs)	⊕⊕⊖⊖ **LOW**[1,3]	Carisbamate may result in little to no difference in the number of people who experience at least 1 adverse event. The test for overall effect demonstrated that the effect was statistically insignificant.
	690 per 1000	760 per 1000 (642 to 898)				
Adverse events: dizziness Follow-up (range): 12 to 16 weeks	**Study population**		**RR 2.06** (1.23 to 3.44)	**2211** (4 RCTs)	⊕⊖⊖⊖ **VERY LOW**[1,3,4]	Carisbamate may increase the proportion of people who will experience dizziness, but we are very uncertain of the accuracy of this effect. The test for overall effect demonstrated that the effect was statistically significant.
	73 per 1000	151 per 1000 (90 to 252)				
Adverse events: somnolence Follow-up (range): 12 to 16 weeks	**Study population**		**RR 1.82** (1.28 to 2.58)	**2211** (4 RCTs)	⊕⊕⊖⊖ **LOW**[1,4]	Carisbamate may increase the proportion of people who will experience somnolence. The test for overall effect demonstrated that the effect was statistically significant.
	54 per 1000	98 per 1000 (69 to 139)				

*__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:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once for risk of bias due to high attrition rates and insufficient detail provided regarding the blinding of outcome assessors.
[2]Downgraded twice for imprecision due to the low number of events (< 400 events) and because only one study provided useable data for the outcome.
[3]Downgraded once for inconsistency due to the significant statistical heterogeneity detected by the homogeneity test (I^2 between 50% and 100%).
[4]Downgraded once for imprecision due to the low number of events (< 400 events), which did not satisfy the optimal information size.

BACKGROUND

Description of the condition

Epilepsy is one of the most common chronic neurological disorders. It is estimated that there are at least 65 million people with epilepsy worldwide. The annual incidence rate of epilepsy is approximately 50 per 100,000 population, and the annual prevalence is nearly 700 per 100,000 in the developed world (Thurman 2011). Although a number of antiepileptic drugs have been in use for a long time, it remains difficult to decide whether a person will respond to a drug favourably. Moreover, about 30% of people with epilepsy are drug-resistant and often require add-on therapy with other antiepileptic drugs (Privitera 2011; Schuele 2008). Uncontrolled seizures may result in memory and cognitive problems, reduced quality of life and social function, and psychosocial and psychiatric disorders (Lawn 2004; Schmidt 2002; Villeneuve 2004). Treatment with newer, more effective and more tolerable antiepileptic drugs is therefore required. Currently, new antiepileptic drugs are initially approved as add-on therapy for drug-resistant focal epilepsy.

Description of the intervention

Carisbamate (RWJ-333369; (S)-2-O-carbamoyl-1-o-chlorophenyl-ethanol) is a novel orally antiepileptic drug currently undergoing clinical evaluation (Liu 2009). When administered orally, it can be quickly absorbed, and the time to reach a peak plasma concentration is one to three hours. Its plasma elimination half-life is approximately 12 hours, allowing twice-daily dosing. Carisbamate is metabolised by uridine diphosphate glucuronosyltransferase and shows minimal first-pass hepatic metabolism (Mannens 2007; Yao 2006). Current research shows that there are no clinically significant interactions between carisbamate and valproic acid or lamotrigine (Chien 2007), whilst drug metabolism enzyme-inducing antiepileptic drugs such as carbamazepine, phenytoin, phenobarbital, and primidone can increase the clearance, shorten half-life, and reduce the plasma concentration of carisbamate through induction of uridine diphosphate glucuronosyltransferase (Chien 2006; Faught 2008). The most frequent adverse events include somnolence, insomnia, headache, and dizziness (Yao 2006).

How the intervention might work

It has been confirmed that carisbamate inhibits voltage-gated sodium channels ($Na_V1.2$ isoform) highly expressed in the hippocampus (Liu 2009). Voltage-gated sodium channels are responsible for the initial inwards current during the depolarisation phase of action potential in excitable cells, which is crucial for nerve function (Denac 2000). Many antiepileptic drugs, such as phenytoin, lamotrigine, carbamazepine, felbamate, and topiramate, have been shown to exert their antiepileptic effects by modulating these channels (Kohling 2002). Furthermore, another study demonstrated that carisbamate has an antiglutamatergic effect, as reductions in glutamate transmission have been found in the granule cell of the dentate gyrus, which helps draw a complete picture of carisbamate antiepileptic mechanism (Lee 2011).

Why it is important to do this review

Carisbamate has been shown to have a highly potent efficacy in inhibiting various seizure types in animal models (Francois 2008; Grabenstatter 2008). Several recent randomised controlled trials (RCTs) have indicated the possible efficacy and good tolerability of carisbamate when used as an add-on treatment for people with focal epilepsy (Faught 2008; Halford 2011; Sperling 2010). However, to date there has been no Cochrane Review to investigate its use. We therefore aimed in this review to evaluate the use of carisbamate as an add-on therapy for focal epilepsy, by summarising the evidence regarding efficacy and tolerability from those RCTs.

OBJECTIVES

To evaluate the efficacy and tolerability of carisbamate when used as an add-on therapy for drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with no language restrictions as follows:

1. RCTs using adequate methods of randomisation;
2. double-blinded trials in which both participants and treating personnel or outcome assessors were blinded to the treatment;
3. placebo- or active-controlled trials;
4. parallel-group or cross-over trials; for cross-over studies, we planned to use the first treatment period as a parallel trial.

Types of participants

People of any age with drug-resistant (defined in this review as uncontrolled seizures despite treatment with one or more antiepileptic drugs) focal epilepsy, including: simple focal seizures, complex focal seizures, or secondary generalised seizures.

Types of interventions

1. The treatment groups received carisbamate in addition to one or more existing antiepileptic drugs.
2. The control group received placebo or another antiepileptic agent in addition to one or more existing antiepileptic drugs.

Types of outcome measures

Primary outcomes

1. 50% or greater reduction in seizure frequency (responder rate)
   a. The proportion of participants with ≥ 50% reduction in focal seizure frequency during the treatment period versus the baseline phase.
   b. We used this as the primary outcome because it is commonly measured in this type of study. For studies not reporting responder rate, this information could be calculated provided that baseline seizure data were recorded and reported.

Secondary outcomes

1. Seizure freedom
   a. The proportion of people with seizure freedom during the whole treatment period.

2. Treatment withdrawal
   a. We used the proportion of people who withdrew from treatment for any reason during the course of the treatment as a measure of 'global effectiveness'.
   b. Treatment may be withdrawn due to adverse events, lack of efficacy, or a combination of both. The main reason for treatment withdrawal is usually adverse events, therefore we also assessed treatment withdrawal due to adverse events.
3. Adverse events
   a. The proportion of participants experiencing at least one adverse event.
   b. The proportion of participants experiencing the following adverse events: dizziness, headache, somnolence, fatigue, nausea. We chose these adverse events as we consider them to be common or clinically important adverse events often associated with antiepileptic drugs.
   c. The proportion of participants experiencing the five most common adverse events mentioned in the included trials, if different from those described above.
4. Quality of life
   a. There is currently no consensus as to which instruments (commonly Quality of Life in Epilepsy Inventory (QOLIE)-89, QOLIE-31, or QOLIE-10; Epilepsy Surgery Inventory 55 Survey (ESI-55)) should be used to assess quality of life.
   b. We planned to tabulate the results where a specific instrument was used to assess the effects of carisbamate on quality of life. We did not plan to combine the results in a meta-analysis.

Search methods for identification of studies

Electronic searches

We searched the following databases on 8 April 2021:

1. Cochrane Register of Studies (CRS Web) using the search strategy shown in Appendix 1;
2. MEDLINE (Ovid 1946 to April 07, 2021) using the search strategy shown in Appendix 2.

CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane review groups including Epilepsy. We did not impose any language restrictions.

Searching other resources

We checked the reference lists of included studies and review articles to identify additional reports of relevant studies. We contacted the manufacturers of carisbamate and the original investigators of relevant studies to obtain additional published or unpublished data. We also searched Chinese Clinical Trial Register (www.chictr.org/cn/proj/search.aspx) for ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (CL and YC until 2019, RB and KMM thereafter) independently screened the titles and abstracts of the articles identified by the search. During the initial title and abstract screening phase, the review authors firstly eliminated obviously ineligible reports. The review authors then retrieved the full texts of any potentially relevant reports and independently evaluated them for inclusion in the review. Any disagreements were resolved by discussion or by consulting a third review author (JZ) if necessary.

Data extraction and management

We did not undertake an individual patient data review. Instead, two review authors (CL and YC) independently extracted the following information and aggregate data from the included trials. Any disagreements were resolved by discussion.

1. Methodological/trial design:
   a. method of randomisation and allocation concealment;
   b. method of double-blinding;
   c. duration of baseline period;
   d. duration of treatment period;
   e. dose(s) of carisbamate tested;
   f. description of treatment withdrawals.
2. Participant/demographic information:
   a. total number of participants allocated to each treatment group;
   b. age/sex;
   c. number with focal/generalised epilepsy;
   d. ethnicity;
   e. seizure types;
   f. number of background drugs.
3. Interventions:
   a. dosage;
   b. administration method.
4. Outcomes:
   a. number of participants experiencing each outcome per randomised group (see Types of outcome measures).

We predict that an individual patient data analysis approach will not be appropriate for the subsequent review update unless more high-certainty evidence is available at the time of conduct. The low-certainty evidence available at present (see Summary of findings 1) is unable to justify the time-costs and expenses associated with conducting an individual patient data review (Tudur Smith 2016).

Assessment of risk of bias in included studies

Two review authors (CL and JZ) independently assessed the risk of bias of the included studies using Cochrane's tool for assessing risk of bias as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The tool considers the following seven specific parameters:

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective reporting (reporting bias);
7. other bias.

Any disagreements were resolved by discussion between the two review authors.

Measures of treatment effect

We managed data according to the intention-to-treat principle. For dichotomous data, we presented treatment effect measures as risk ratios (RRs) with 95% confidence intervals (CIs) using the Mantel-Haenszel statistical method. All the outcomes listed in Types of outcome measures, except for quality of life, are dichotomous data. Had we obtained data for quality of life, a continuous data outcome, we would have calculated mean differences (MDs) with 95% CIs. We considered a P value of ≤ 0.05 to indicate statistical significance.

Unit of analysis issues

Two review authors (CL and JZ) dealt with any unit of analysis issues according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. For cross-over trials, we only included data from the first period for meta-analysis.
2. For multi-arm trials:
   a. for multiple-dose-group trials, we combined groups to create a single pair-wise comparison;
   b. for multiple-medication trials, we included one or more correlated comparisons and accounted for the correlation.

Dealing with missing data

There are many potential origins of missing data in a systematic review or meta-analysis. It is important to investigate the sources of missing data. Data may be missing at random (unrelated to actual values of the missing data) or not at random (related to the actual missing data). We attempted to contact the authors of included studies and manufacturers for any missing data. We planned to make explicit assumptions of any methods used to cope with missing data (e.g. the data were assumed to be missing at random or to have a particular value, such as a poor outcome). When data were assumed to be missing at random, we only analysed the available data. For data judged to not be missing at random, we conducted sensitivity analyses to assess how sensitive results are to reasonable changes in the potential impact of missing data.

Assessment of heterogeneity

We visually assessed clinical heterogeneity by comparing the characteristics of the participants and interventions, and methodological heterogeneity by comparing methodological factors (such as study designs, concealment of allocation, blinding, etc.) between studies that met our inclusion criteria. We planned to assess statistical heterogeneity using the I^2 statistic. We assessed the percentage ranges of I^2 statistic as follows (Higgins 2011):

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

Visual inspection of the forest plots also helped us to assess whether or not heterogeneity was present.

Assessment of reporting biases

Had we identified more than 10 studies, we would have visually inspected funnel plots for asymmetry. We would have investigated reasons for asymmetry (if any) including publication bias, outcome reporting bias, language bias, citation bias, poor methodological design, and heterogeneity.

Data synthesis

We analysed the data using Cochrane's statistical software, Review Manager 5 (Review Manager 2014). We used a fixed-effect model where the I^2 statistic indicated no important or moderate heterogeneity (see Assessment of heterogeneity). Where the I^2 statistic indicated substantial or considerable heterogeneity, we employed a random-effects model. We then explored factors that could have produced this heterogeneity and made a determination as to whether to conduct a subgroup analysis.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses, where possible:

1. different ages of participants: children (less than 16 years old) versus adults (16 years old and over);
2. different doses of carisbamate: high dose (over 800 mg/d) versus intermediate (400 mg/d to 800 mg/d) or low dose (less than 400 mg/d);
3. different interventions in control groups: actively controlled or placebo-controlled studies;
4. different ethnicity of the participants: white, black, and Asian;
5. different duration of the intervention: short term (less than 12 months) and long term (12 months or longer).

Sensitivity analysis

We planned to carry out a sensitivity analysis to test the robustness of the evidence by repeating meta-analysis as follows:

1. exclude trials at high risk of bias;
2. exclude studies that were available as abstracts only.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to interpret findings (Schünemann 2011). We used GRADEpro GDT software (GRADEpro GDT) to import data from Review Manager 5 (Review Manager 2014) and to create a 'Summary of findings' table for the main comparison of the review (carisbamate compared to placebo for drug-resistant focal epilepsy). We GRADE assessed the primary outcome, 50% or greater reduction in seizure frequency, and the secondary outcomes of seizure freedom, treatment withdrawal, and adverse events, to provide an overall certainty of evidence judgement, which was then included in the Summary of findings 1. This information is of importance for healthcare decision making and considers eight important 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 overall certainty of evidence judgements to guide our conclusions.

RESULTS

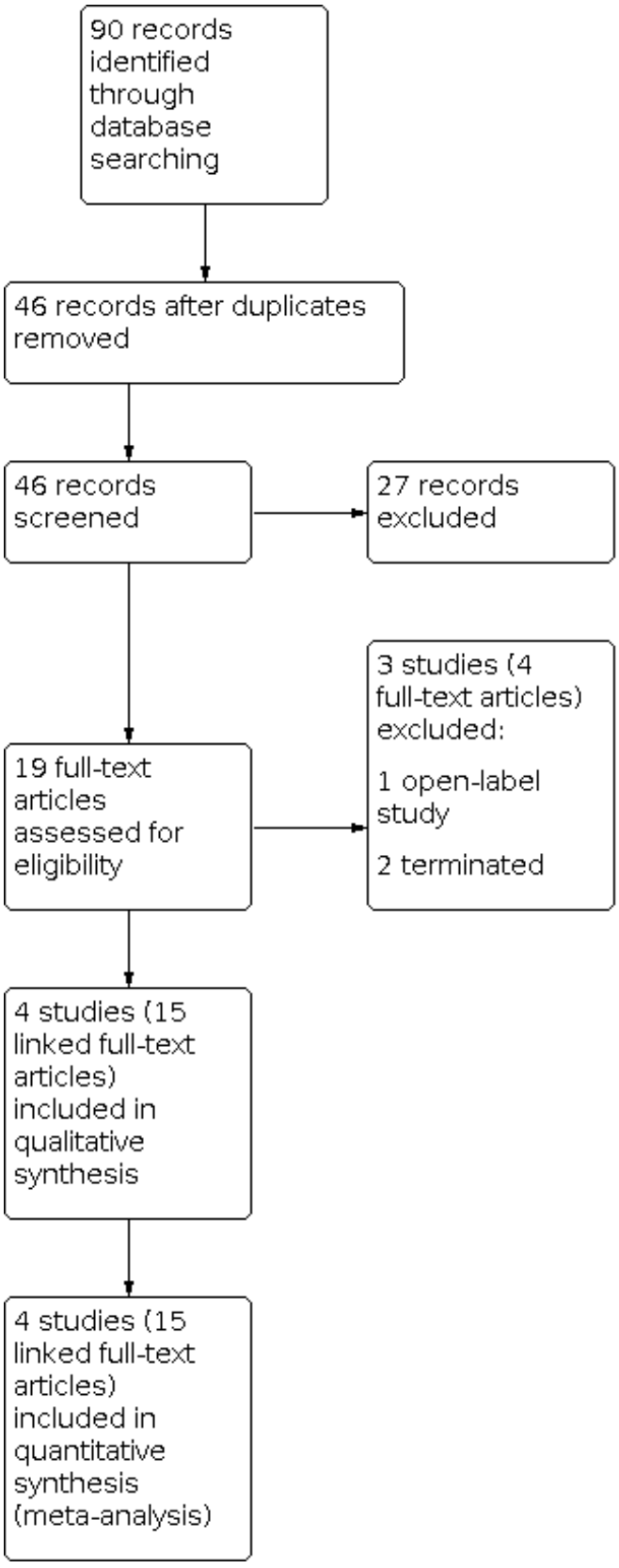
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

A total of 90 references were identified by literature searches, of which 44 were duplicates and 27 were irrelevant. We screened the full-text articles of the remaining 19 records. Of the full-texts screened, we assessed 15 records, linked to a total of four individual studies, as eligible for inclusion in the review. Importantly, one full-text article included the methods and data from two of the included studies (Sperling 2010a; Sperling 2010b). The reference for the full-text article can thus be found duplicated in the reference list of this review. Data extracted from the records regarding the four individual trials were incorporated into both a qualitative and quantitative analysis (see Figure 1).

Figure 1. Study flow diagram.



Included studies

We included four studies (2211 randomised participants) in the review (Faught 2008; Halford 2011; Sperling 2010a; Sperling 2010b). All four studies investigated the efficacy and safety of carisbamate versus placebo add-on therapy in people with focal epilepsy who received concomitant treatment with one to three antiepileptic drugs. For full details of the included trials see Characteristics of included studies.

Faught 2008 was a multicentre, double-blind RCT with parallel-group design. The trial included 537 participants, all of whom were aged between 18 and 70 years old and had focal epilepsy. Following an eight-week baseline phase, participants were randomised to one of five treatment arms: placebo, 100 mg/d, 300 mg/d, 800 mg/d, or 1600 mg/d carisbamate. The allocated treatment was received over a 16-week double-blind treatment phase.

Likewise, Halford 2011 was a multicentre, double-blind RCT with parallel-group design. The inclusion criteria specified that participants must be aged 16 years and over and weigh at least 40 kg. Additionally, participants were required to have an established diagnosis of focal seizures and be on stable doses of one to three antiepileptic drugs. A total of 547 participants were randomised to one of three treatment arms: placebo, 800 mg/d, or 1200 mg/d carisbamate. The trial consisted of an 8-week prospective baseline followed by a 14-week double-blind treatment phase. Upon completion, there was optional entry into an open-label extension study; otherwise, participants underwent a three-week tapering-off phase.

Notably, the results of both Sperling 2010a and Sperling 2010b were published in the same journal article. The two trials had an identical trial design, both being multicentre, double-blind RCTs with parallel-group design, and including participants aged 16 and over (minimum weight 35 kg) with focal seizures. Both trials consisted of an 8-week prospective baseline phase followed by a 12-week double-blind treatment phase without titration. Participants in both studies were randomised to one of three treatment groups: placebo, 200 mg/d, or 400 mg/d carisbamate. At the end of both trials, participants were offered entry into an open-label extension study; otherwise, participants were entered into a two-week double-blind tapering-off phase.

All four included studies were funded by the pharmaceutical company Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, New Jersey, USA.

Excluded studies

We excluded three studies (four linked records) for the reasons provided in the Characteristics of excluded studies tables. Two of the studies, NCT00563459 and NCT00697762, were prematurely terminated. No results were available for either study, therefore they could not be incorporated into the review and were thus excluded. Alternatively, EUCTR2008-007688-17-LT was an open-label study and did not meet our inclusion criteria, hence it was excluded from the review.

Risk of bias in included studies

We have summarised the overall results of all the 'Risk of bias' assessments in Figure 2 and Figure 3. See the 'Risk of bias' tables, located under each Characteristics of included studies table, for more details.

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

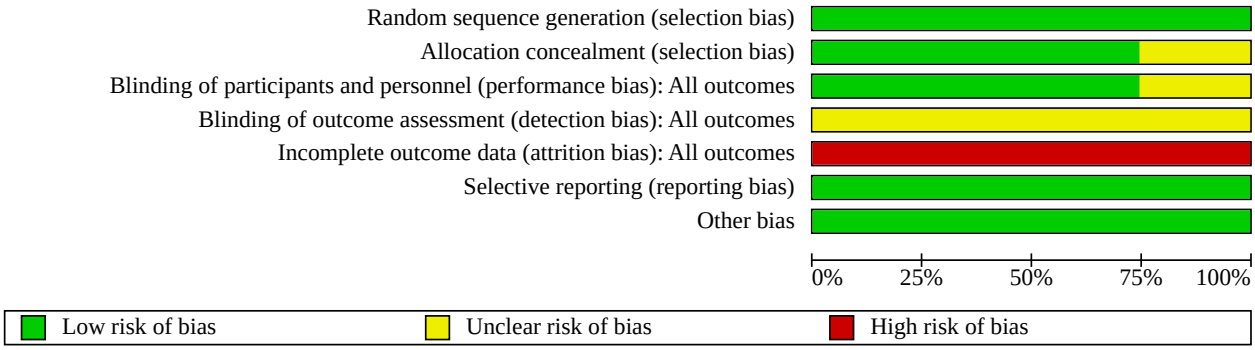
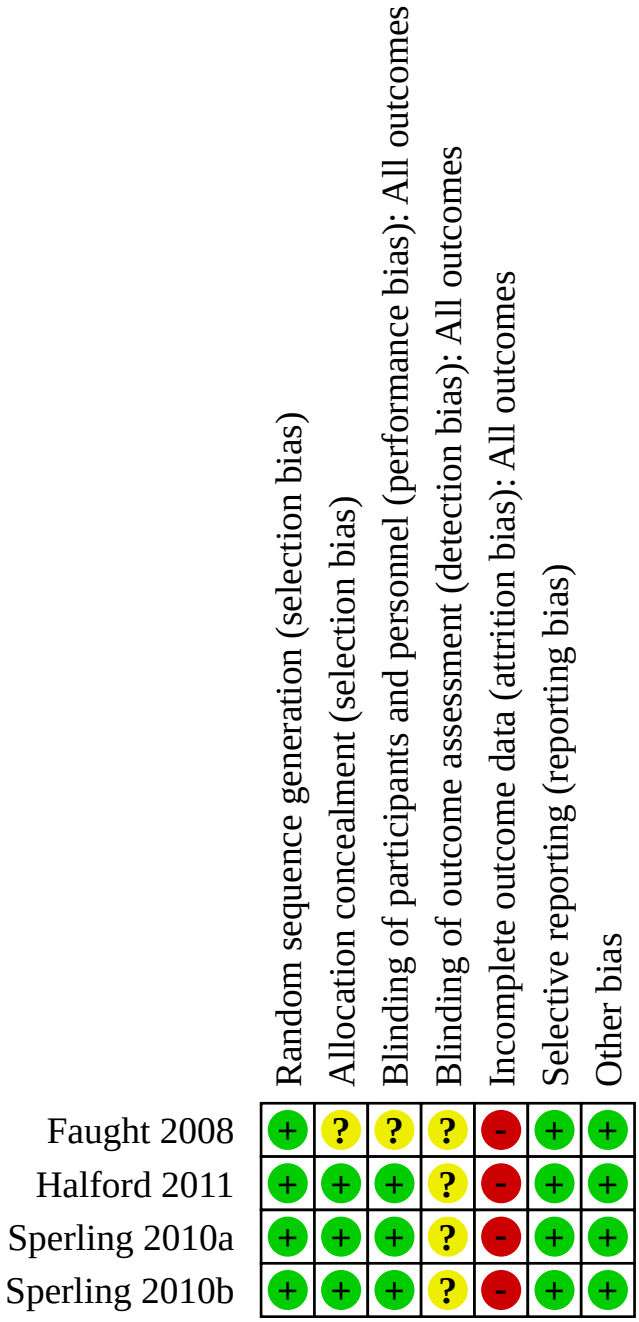


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All of the included studies were reported as using a computer-generated randomisation schedule and were therefore judged to have low risk of selection bias due to random sequence generation. Sperling 2010a, Sperling 2010b, and Halford 2011 used interactive voice response systems to assign a treatment code and matching medication kit for each participant and were thus assessed as at low risk of bias for allocation concealment. In Faught 2008, no further details about allocation concealment were provided, thus

we assessed this study as at unclear risk of selection bias related to allocation concealment.

Blinding

All of the included studies were reported as being double-blind. A placebo was used in all four included studies; however, only three of the studies specified that they used matching placebo as the method to effectively blind participants (Halford 2011; Sperling 2010a; Sperling 2010b). We therefore judged these three studies as at low risk of performance bias. Regarding the remaining study (Faught 2008), we were unsure whether participants and personnel would be able to identify the placebo from the active treatment due to the lack of specific details provided. We therefore judged this study as at unclear risk of performance bias.

None of the four studies described the method of blinding for outcome assessment, hence we were uncertain whether outcome assessors were effectively blinded. We thus assessed all four trials as at unclear risk of detection bias.

Incomplete outcome data

In Faught 2008, the number of, and the reasons for, treatment withdrawals were reported clearly in the article. However, in the 800 mg/d and 1600 mg/d carisbamate groups, 20% (22/108) and 36% (38/106) of the participants withdrew from the study, respectively. Due to the high attrition rate, we judged Faught 2008 to have a high risk of attrition bias.

Similarly, the attrition rates for the treatment groups in Halford 2011 were high. Specifically, the percentage of treatment withdrawals was 20% (36/180) in the 800 mg/d carisbamate group and 31% (56/182) in the 1200 mg/d carisbamate group. Furthermore, one participant withdrew for an unclear reason from the placebo group. We thus also judged Halford 2011 to have a high risk of attrition bias.

In contrast, the treatment withdrawal rates for the treatment groups in Sperling 2010a (200 mg/d: 11/187; 400 mg/d: 12/192) and Sperling 2010b (200 mg/d: 12/188; 400 mg/d: 11/185) were deemed not to be high (< 20%). Although the total number of treatment withdrawals per group were clearly reported, the authors failed to provide the reasons for all withdrawals. Specifically, reasons were not given for 19 out of the 72 treatment withdrawals overall. Consequently, we considered Sperling 2010a and Sperling 2010b to be at high risk of attrition bias.

Selective reporting

We compared the outcomes reported in Sperling 2010a, Sperling 2010b, and Halford 2011 with the set of outcomes listed in their trial registry entries at ClinicalTrials.gov (NCT00425282, NCT00433667, and NCT00740623, respectively). All the outcome measures reported in the studies were the same as in the protocols. We thus considered the three studies to have a low risk of reporting bias.

We could not obtain the protocol or trial registry entry for Faught 2008; however, all outcomes specified in the methods of the full-text publication were fully reported in the results. We therefore judged this study to have a low risk of reporting bias.

Other potential sources of bias

Whilst the researchers of Sperling 2010a, Sperling 2010b, and Halford 2011 confirmed that the reports were consistent with the guidelines of ethical publication, there was no such statement in Faught 2008. We did not consider this to be a valid source of other bias, but nevertheless wished to highlight this shortcoming. We therefore assessed all four studies as at low risk of other bias.

Effects of interventions

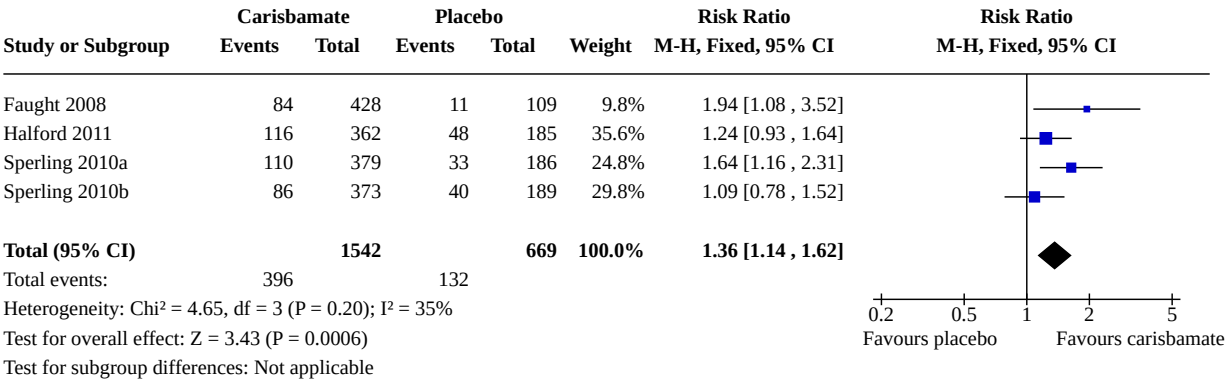
See: **Summary of findings 1** Carisbamate compared to placebo for drug-resistant focal epilepsy

Primary outcomes

50% or greater reduction in seizure frequency (responder rate)

All four trials (2211 participants) reported this outcome. There was a significant difference between carisbamate and placebo groups, with a risk ratio (RR) 1.36 (95% confidence interval (CI) 1.14 to 1.62; Analysis 1.1; Figure 4) indicating a clinical advantage with carisbamate compared to placebo.

Figure 4. Forest plot of comparison: 1 Carisbamate versus placebo, outcome: 1.1 50% or greater reduction in seizure frequency (responder rate).



Secondary outcomes

Seizure freedom

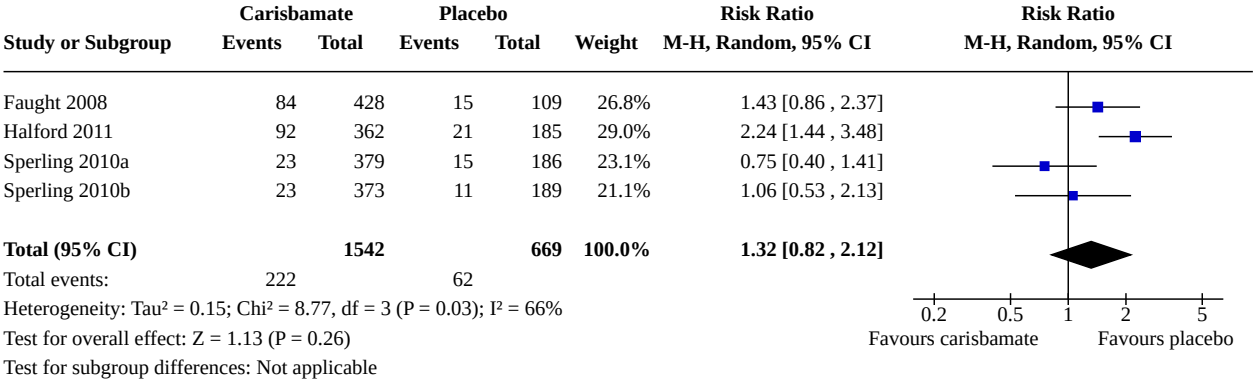
We attempted to investigate the proportion of participants with seizure freedom during the whole treatment period, as stated in our protocol. However, only the study by Halford 2011, consisting of 540 participants, contributed to this outcome analysis.

We could not use data from Faught 2008 in this meta-analysis because the study only reported the percentage of participants who became seizure-free during the last eight weeks of double-blind treatment, rather than during the whole treatment period. Equally, Sperling 2010a and Sperling 2010b only described that the seizure freedom rates were similar in the carisbamate and placebo treatment groups, without providing any numerical values to support this claim. Using the only data extracted from Halford 2011, the RR of 2.43 (95% CI 0.84 to 7.03; Analysis 1.2) suggested that there may be a clinical advantage of add-on carisbamate compared to placebo for seizure freedom. However, the evidence was graded as very low-certainty (Summary of findings 1).

Treatment withdrawal for any reason

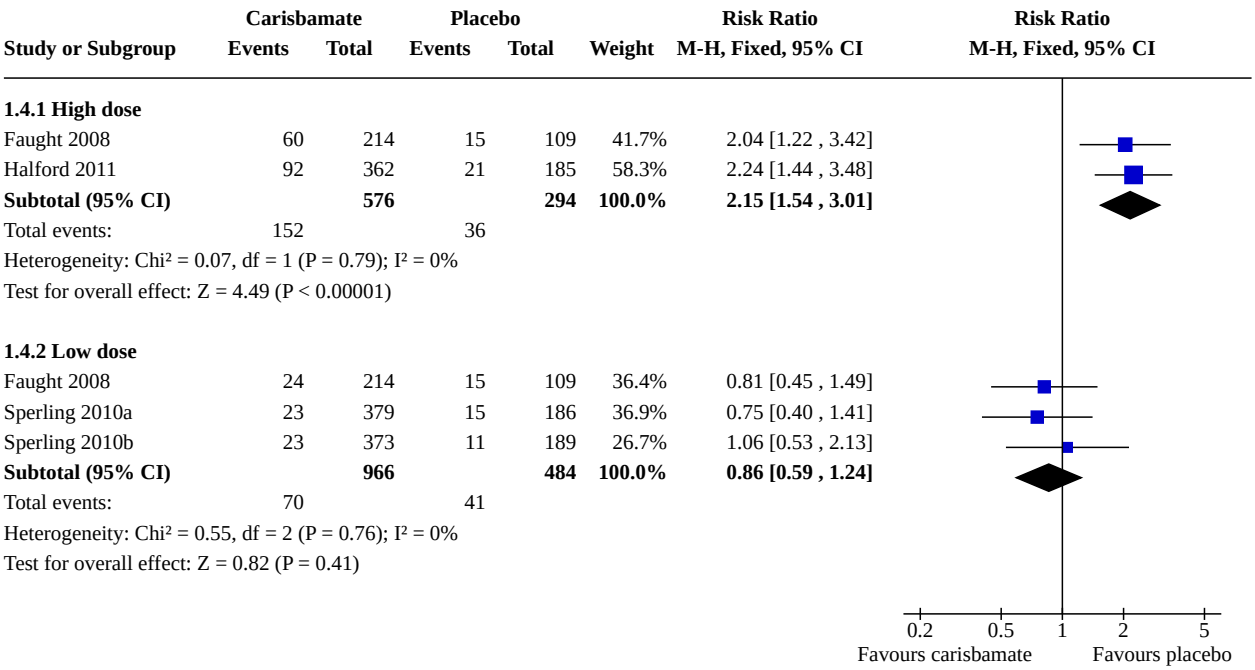
All four studies (2211 participants) reported this outcome and contributed data to the meta-analysis. More participants in carisbamate group withdrew from treatment for any reason compared to the placebo group (RR 1.32, 95% CI 0.82 to 2.12; Analysis 1.3; Figure 5), however, the difference was relatively small and the evidence was very low-certainty. The homogeneity test indicated significant heterogeneity (I^2 = 66%), therefore we employed the random-effects model.

Figure 5. Forest plot of comparison: 1 Carisbamate versus placebo, outcome: 1.3 Treatment withdrawal for any reason.



We suspected that the heterogeneity might have been due to the different carisbamate dosages used in the studies. We therefore conducted a subgroup analysis according to dose. For the purposes of this subgroup analysis, we categorised the doses used as either high or low doses. We considered the high-dose group as ranging from 800 mg/d to 1600 mg/d, and the low-dose group from 100 mg/d to 400 mg/d. In the high-dose group, there was a significant difference between the carisbamate and placebo group (RR 2.15, 95% CI 1.54 to 3.01, 2 trials, 870 participants; Analysis 1.4; Figure 6). In the low-dose group, there was no significant difference between the carisbamate and placebo group (RR 0.86, 95% CI 0.59 to 1.24, 3 trials, 1450 participants; Analysis 1.4; Figure 6). We did not detect significant statistical heterogeneity in either the high- or low-dose subgroup.

Figure 6. Forest plot of comparison: 1 Carisbamate versus placebo, outcome: 1.4 Treatment withdrawal for any reason (subgroup analysis).



Data regarding the ethnicity of participants were insufficient to conduct subgroup analysis stratified by this population characteristic. Moreover, all of the included studies only recruited adult participants and were of short duration, therefore we were unable to conduct subgroup analyses stratified by age or study duration.

Treatment withdrawal due to adverse events

All four included studies (2211 participants) reported treatment withdrawals due to adverse events. Overall, more participants in the carisbamate withdrew from treatment due to adverse events than in the placebo group (RR 1.80, 95% CI 0.78 to 4.17; Analysis 1.5). However, we detected significant heterogeneity (I^2 = 67%), so we applied the random-effects model.

We again conducted subgroup analysis according to dose, using the same ranges to categorise doses into the relevant subgroup. For the high-dose group, there was a significant difference between carisbamate and placebo groups (RR 2.71, 95% CI 1.62 to 4.54, 2 trials, 870 participants; Analysis 1.6). This indicates a significant increase in treatment withdrawal due to adverse events with high-dose add-on carisbamate compared to placebo. There was no significant difference between the carisbamate and placebo groups in the low-dose group (RR 0.94, 95% CI 0.53 to 1.68, 3 trials, 1450 participants; Analysis 1.6), indicating no significant difference in treatment withdrawal due to adverse events with low-dose carisbamate.

Adverse events

The proportion of participants experiencing at least one adverse event

All of the included trials reported adverse events. However, Sperling 2010a and Sperling 2010b did not provide the specific proportion of participants who experienced each individual adverse event, instead only reporting that the incidence of all adverse events was similar (52% to 59%) between the placebo and carisbamate groups. Consequently, only data from Faught 2008 and Halford 2011 were included in this analysis. We used the random-effects model because the homogeneity test indicated significant heterogeneity (I^2 = 75%). There was no significant difference between carisbamate and placebo groups for this outcome (RR 1.10, 95% CI 0.93 to 1.30; Analysis 1.7), indicating that participants are equally likely to experience one or more adverse events, regardless of group allocation. Regarding subgroup analysis according to dose, there was also no significant difference between the carisbamate and placebo groups when comparing either the high-dose (RR 1.14, 95% CI 1.04 to 1.24; Analysis 1.8) or low-dose carisbamate subgroups (RR 0.98, 95% CI 0.87 to 1.11; Analysis 1.8) to placebo.

The proportion of participants experiencing the five most common adverse events mentioned in the carisbamate group

We concluded from the included trials that the five most commonly reported adverse events in the carisbamate groups were dizziness, headache, somnolence, fatigue, and nausea. When compared with placebo, carisbamate was associated with increased rates of dizziness (RR 2.06, 95% CI 1.23 to 3.44, I^2 = 64%; Analysis 1.9) and somnolence (RR 1.82, 95% CI 1.28 to 2.58, I^2 = 0%; Analysis 1.13). There were no significant differences in the occurrence of headache (RR 1.13, 95% CI 0.92 to 1.38, I^2 = 0%; Analysis 1.11), fatigue (RR 1.11, 95% CI 0.73 to 1.68, I^2 = 11%; Analysis 1.15), or nausea (RR 1.19, 95% CI 0.81 to 1.75, I^2 = 38%; Analysis 1.17) between carisbamate and placebo groups.

Due to the significant heterogeneity detected following the homogeneity test for the adverse event nausea, we decided to conduct subgroup analysis according to dose for all of the adverse

events investigated. High-dose carisbamate (800 to 1600 mg/d) was associated with significantly increased rates of dizziness (RR 3.53, 95% CI 2.33 to 5.34; Analysis 1.10), headache (RR 1.37, 95% CI 1.05 to 1.79; Analysis 1.12), and somnolence (RR 1.55, 95% CI 1.02 to 2.36; Analysis 1.14), whilst low-dose carisbamate was only associated with increased rates of somnolence (RR 2.21, 95% CI 1.35 to 3.64; Analysis 1.14).

Quality of life

None of the four included trials reported this outcome.

Sensitivity analysis

We did not conduct either of our planned sensitivity analyses. Notably, all of the included studies were at high overall risk of bias, and all were published as full-text journal articles. Consequently, the planned sensitivity analyses were redundant.

DISCUSSION

Summary of main results

We included four RCTs involving a total of 2211 participants comparing carisbamate with placebo for drug-resistant focal epilepsy (Faught 2008; Halford 2011; Sperling 2010a; Sperling 2010b). There was a significant difference between carisbamate and placebo groups for responder rate after 12 to 16 weeks of treatment for epilepsy. Specifically, 36% more people are expected to be responders and experience a 50% or greater reduction in seizure frequency when given add-on carisbamate compared to those given add-on placebo. For seizure freedom, we were unable to perform a meta-analysis to synthesise the results as planned, because only one study reported this outcome (Halford 2011). Consequently, we are very uncertain whether the large effect reported for seizure freedom is accurate. We therefore cannot comment on the efficacy of carisbamate with regard to seizure freedom.

For the safety outcomes, carisbamate seems to be well-tolerated, except for a higher rate of participants with dizziness and somnolence in the carisbamate group compared to the placebo group. Interestingly, high-dose carisbamate was associated with an increased rate of treatment withdrawal for any reason as well as an increased rate of treatment withdrawal due specifically to adverse events. There was also as an increased incidence of dizziness, headache, and somnolence amongst participants receiving high-dose carisbamate compared to placebo. In contrast, low-dose carisbamate was only associated with an increased incidence of somnolence. The results suggest that any issues with tolerability could be related to dose.

Overall completeness and applicability of evidence

The available evidence was limited in terms of size and applicability.

Firstly, all of the participants were adults. As a result, data to assess the effectiveness of add-on carisbamate for children and adolescents were lacking.

Secondly, we did not identify an actively controlled trial for inclusion in the review. As a result, we are unable to comment on how carisbamate might compare in efficacy or tolerability to an alternative antiepileptic drug.

Thirdly, most of the participants from the included studies were of white or Asian ethnicity. Data to perform subgroup analysis by ethnicity were unavailable, and the number of other ethnicities evaluated was limited. We therefore could not assess the profile of effectiveness by ethnicity.

Finally, the treatment phases of the trials were of short duration. As epilepsy is a chronic disease, further investigation in longer-term trials is needed to the demonstrate effectiveness and tolerability of carisbamate. Importantly, none of the included trials reported the important outcome of quality of life.

Quality of the evidence

The study by Faught 2008 had some limitations relating to reporting quality. There was no description of the method used to conceal the allocation of participants or to achieve the blinding of outcome assessment. This study was assessed as at high risk of attrition bias due to the increased withdrawal rate in the higher-dose treatment groups.

In contrast, the other three included studies demonstrated clear methodological reporting (Halford 2011; Sperling 2010a; Sperling 2010b). Methods of randomisation, allocation concealment, and blinding were all adequately described. All outcomes listed in the study details section of the ClinicalTrials.gov entry were reported in the published studies. However, in Sperling 2010a and Sperling 2010b, there were a number of treatment withdrawals that the authors failed to provide details for, and in Halford 2011, attrition rates in the treatment groups were higher (20% in the 800 mg/d carisbamate group and 31% in 1200 mg/d carisbamate group). We therefore judged the three studies as at high risk of attrition bias.

We downgraded the certainty of evidence once for all of the GRADE assessed outcomes due to risk of bias (Summary of findings 1). We downgraded the certainty of the evidence a further level for four outcomes (treatment withdrawal for any reason; treatment withdrawal due to adverse events; proportion of participants experiencing at least one adverse event; dizziness) due to the statistical heterogeneity detected. There were also issues with imprecision for five of the outcomes (seizure freedom; treatment withdrawal for any reason; treatment withdrawal due to adverse events; dizziness; somnolence) (Summary of findings 1). The limited number of events included in the analysis produced wide confidence intervals and did not satisfy the optimal information size, resulting in the downgrading of the evidence by one level. We downgraded the certainty of evidence for seizure freedom twice for imprecision because only one study reported useable data for the outcome.

Overall, we assessed two of the outcomes presented in the Summary of findings 1 as derived from low-certainty evidence (proportion of participants experiencing at least one adverse event; somnolence); four from very low-certainty evidence (seizure freedom; treatment withdrawal for any reason; treatment withdrawal due to adverse events; dizziness); and only one outcome from moderate-certainty evidence (50% or greater reduction in seizure frequency).

Potential biases in the review process

We undertook an extensive and comprehensive literature search based on electronic databases for trials. We searched the specialised register of Cochrane Epilepsy, CENTRAL via Cochrane

Register of Studies Online (CRSO), MEDLINE, ClinicalTrials.gov, and the WHO ICTRP. We identified some unpublished trials, but none of the them met our inclusion criteria. It is possible that there are unpublished trials or data of which we are not aware. Furthermore, we were unable to obtain data that we considered to be important but that were not reported sufficiently by the included trials.

Agreements and disagreements with other studies or reviews

To our knowledge, the efficacy and tolerability of carisbamate add-on therapy for drug-resistant focal epilepsy has not been previously systematically reviewed.

We excluded EUCTR2008-007688-17-LT from this review because it was an open-label study. Nevertheless, we examined the findings of the study to compare them with the results of our own review. In the EUCTR2008-007688-17-LT study, participants received up to 1200 mg/d carisbamate. Similar to our review, the study found a degree of efficacy with carisbamate. Notably, 36.1% of participants reported a 50% or greater reduction in seizure frequency, with the median change in seizure frequency being 28.22% (range: −865.52 to 100%). The study also found that 5.4% of participants became seizure-free. Similarly, in the study by Halford 2011 (included in this review), 5.2% of carisbamate-randomised participants became seizure-free compared to only 2.2% of placebo-randomised participants. In the open-label study EUCTR2008-007688-17-LT, no participants received placebo, so we were unable to compare the incidence rate to a control group.

With regard to tolerability outcomes, we determined that the proportion of participants experiencing at least one adverse event was fairly similar between treatment groups (78.0% of carisbamate-randomised participants versus 69.0% of placebo-randomised participants) and between high- and low-dose subgroups (78.5% versus 76.6%, respectively). In contrast, in the open-label study EUCTR2008-007688-17-LT, it appeared that a higher proportion of participants receiving low-dose carisbamate (< 400 mg/d: 75.0%) reported one or more adverse events compared to participants receiving high-dose carisbamate (800 to 1000 mg/d: 68.6%; 1000 to 1200 mg/d: 56.3%). Again, there was no control group to compare these data to, so we could not determine the significance of this finding.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review demonstrate that carisbamate may display efficacy and tolerability as an add-on therapy for drug-resistant focal epilepsy. However, the evidence from which these findings were derived was mainly of low to very low certainty, meaning that we are unsure whether the effects that we have reported are representative of the true effect of carisbamate. The evidence was limited by risk of bias associated with the included studies, specifically attrition bias, as well as by inconsistency (heterogeneity) present within the data sets for some outcomes. It is therefore difficult to use these findings to reliably inform clinical decisions. Given the short duration of the eligible trials and adult study populations evaluated, we are unable to comment on the long-term effectiveness of add-on carisbamate or its efficacy and tolerability in children and adolescents.

Implications for research

More randomised controlled trials are required to assess longer-term outcomes and adverse events associated with the prolonged use of add-on carisbamate for drug-resistant focal epilepsy. In future clinical studies, more clinical outcomes (such as quality of life), more types of seizure (such as generalised onset tonic-clonic seizures), and a broader range of participants (such as children and adolescents) should be included in order to comprehensively inform clinical decisions regarding the use of carisbamate as an add-on therapy.

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Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* 2011;**52**(Suppl 7):2-26. [PMID: 21899536]

Tudur Smith 2016

Tudur Smith C, Marcucci M, Nolan SJ, Iorio A, Sudell M, Riley R, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No: MR000007. [DOI: 10.1002/14651858.MR000007.pub3]

Villeneuve 2004

Villeneuve N. Quality-of-life scales for patients with drug-resistant partial epilepsy [Quelles echelles de qualite de vie pour les patients ayant une epilepsie partielle pharmaco-resistante]. *Revue Neurologique* 2004;**160**(Spec No 1):5S376-93. [PMID: 15331986]

Yao 2006

Yao C, Doose DR, Novak G, Bialer M. Pharmacokinetics of the new antiepileptic and CNS drug RWJ-333369 following single and multiple dosing to humans. *Epilepsia* 2006;**47**(11):1822-9. [PMID: 17116021]

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Lu 2016

Lu C, Zheng J, Cao Y. Carisbamate add-on therapy for drug-resistant partial epilepsy. *Cochrane Database of*

Systematic Reviews 2016, Issue 3. Art. No: CD012121. [DOI: 10.1002/14651858.CD012121]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Faught 2008

Study characteristics	
Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled add-on study (101 centres in 12 countries including: Argentina, Hungary, the Netherlands, Poland, Russia, Spain, the UK, the USA) **Duration:** 8-week baseline phase and 16-week double-blind phase (4-week titration period plus 12-week maintenance period), optional entry into an open-label extension study or mandatory 3-week tapering phase
Participants	623 participants aged 18 to 70 years with focal epilepsy who also had 1 to 3 AEDs were screened, of which 537 were randomised. The ITT population used in the study report was 533, and the safety population was 536. **Number of participants randomised:** Placebo: 109 Carisbamate 100 mg/day: 107 Carisbamate 300 mg/day: 107 Carisbamate 800 mg/day: 108 Carisbamate 1600 mg/day: 106 **Age (mean ± SD years):** Placebo: 38 ± 9.9 Carisbamate 100 mg/day: 37 ± 10.7 Carisbamate 300 mg/day: 36 ± 13.1 Carisbamate 800 mg/day: 38 ± 12.4 Carisbamate 1600 mg/day: 36 ± 11.5 **Sex (female):** Placebo: 55% Carisbamate 100 mg/day: 52% Carisbamate 300 mg/day: 55% Carisbamate 800 mg/day: 51% Carisbamate 1600 mg/day: 49% **Number of concomitant AEDs:** Placebo: 1 (17%), 2 (44%), 3 (39%) Carisbamate 100 mg/day: 1 (7%), 2 (55%), 3 (38%) Carisbamate 300 mg/day: 1 (17%), 2 (51%), 3 (32%)

Faught 2008 *(Continued)*

	Carisbamate 800 mg/day: 1 (10%), 2 (53%), 3 (37%) Carisbamate 1600 mg/day: 1 (18%), 2 (50%), 3 (32%)
Interventions	**Group 1:** placebo **Group 2:** carisbamate 100 mg/d add-on therapy during double-blind treatment phase **Group 3:** carisbamate 300 mg/d add-on therapy during double-blind treatment phase **Group 4:** carisbamate 800 mg/d add-on therapy during double-blind treatment phase **Group 5:** carisbamate 1600 mg/d add-on therapy during double-blind treatment phase
Outcomes	1. The per cent reduction in frequency of focal seizures 2. The per cent of participants with ≥ 50% reduction in frequency of focal seizures 3. Adverse events
Notes	Trial funded by Johnson & Johnson Pharmaceutical Research and Development.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was via a sponsor-prepared computer-generated scheme"
Allocation concealment (selection bias)	Unclear risk	Comment: no description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the study was reported to be double-blinded, but no specific information was provided regarding how participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study was reported to be double-blinded, but no specific information was provided regarding how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the number of and the reasons for treatment withdrawals were reported clearly in the article. The data showed that most withdrawals from treatment were due to adverse events, and ITT analysis was used. In the 800 mg/d and 1600 mg/d groups, however, 20% (22/108) and 36% (38/106) of the participants, respectively, withdrew from treatment, attrition rates that were much higher than in the other groups.
Selective reporting (reporting bias)	Low risk	Comment: neither the trial protocol nor the ClinicalTrials.gov registry entry could be located; however, all outcomes specified in the methods section were fully reported in the results section
Other bias	Low risk	Comment: none identified

Halford 2011

Study characteristics

Halford 2011 *(Continued)*

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled add-on study (106 centres in 20 countries: Australia, Belgium, Croatia, Finland, Germany, Hong Kong, India, Italy, Lithuania, Mexico, the Netherlands, Republic of Korea, Russia, Serbia, Singapore, Spain, Sweden, Taiwan, Thailand, and the USA) **Duration:** 8-week prospective baseline phase, 14-week double-blind phase (2-week titration period plus 12-week maintenance period), optional entry into an open-label extension study or mandatory double-blind 3-week tapering phase
Participants	743 participants aged ≥ 16 years with focal epilepsy who received concomitant treatment 1 to 3 AEDs were screened, of which 547 were randomised. In the double-blind phase, the ITT population used in the study report was 540, and the safety population was 544. **Number of participants randomised:** Placebo: 185 Carisbamate 800 mg/day: 180 Carisbamate 1200 mg/day: 182 **Age (mean ± SD years):** Placebo: 37 ± 12.2 Carisbamate 800 mg/day: 37 ± 12.0 Carisbamate 1200 mg/day: 37 ± 12.5 **Sex (female):** Placebo: 52% Carisbamate 800 mg/day: 51% Carisbamate 1200 mg/day: 49% **Number of concomitant AEDs:** Placebo: 1 (12%), 2 (48%), 3 (37%), > 3 (1%) Carisbamate 800 mg/day: 1 (14%), 2 (46%), 3 (41%), > 3 (0%) Carisbamate 1200 mg/day: 1 (13%), 2 (49%), 3 (38%), > 3 (1%)
Interventions	**Group 1:** placebo **Group 2:** carisbamate 800 mg/d add-on therapy during double-blind treatment phase **Group 3:** carisbamate 1200 mg/d add-on therapy during double-blind treatment phase
Outcomes	1. The per cent reduction in frequency of focal seizures 2. The per cent of participants with ≥ 50% reduction in frequency of focal seizure 3. Seizure freedom rates 4. Adverse events
Notes	Trial funded by Johnson & Johnson Pharmaceutical Research and Development.

Risk of bias

Bias	Authors' judgement	Support for judgement

Halford 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was based on a computer-generated randomization schedule balanced by using randomly permuted blocks across the three treatment groups and was stratified"
Allocation concealment (selection bias)	Low risk	Quote: "An interactive voice response system assigned a treatment code and matching medication kit for each patient."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Carisbamate was supplied as 100, 200, or 400 mg tablets with matching placebo" Comment: effective double-blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study was reported to be double-blinded, but no specific information was provided regarding how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the number of and reasons for withdrawals were reported clearly but were unbalanced across groups. The percentage of treatment withdrawals was 20% (36/180) in the 800 mg/d carisbamate group, 31% (56/182) in the 1200 mg/d carisbamate group, and 11% (21/185) in the placebo group. The data showed that most withdrawals from treatment were due to adverse events; however, there was 1 participant withdrawal from placebo treatment with unclear reason. We considered that the authors had made a mistake in the record. ITT analysis was employed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes listed in the study details section of the ClinicalTrials.gov registry entry were reported
Other bias	Low risk	Comment: none identified

Sperling 2010a

Study characteristics	
Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled add-on study (91 centres in 13 countries: Argentina, Australia, China, Croatia, the Czech Republic, Finland, Germany, India, Malaysia, Republic of Korea, Russia, Sweden, and the USA) **Duration:** 8-week prospective baseline phase and 12-week double-blind phase without titration, optional entry into an open-label extension study or mandatory 2-week double-blind tapering-off phase
Participants	713 participants aged ≥ 16 years with focal epilepsy who received concomitant treatment 1 to 2 AEDs were screened, of which 565 were randomised. The ITT population used in the study report was 561, and the safety population was 565. **Number of participants randomised:** Placebo: 186 Carisbamate 200 mg/day: 187 Carisbamate 400 mg/day: 192 **Age (mean ± SD years):** Placebo: 36 ± 13.6 Carisbamate 200 mg/day: 35 ± 12.11

Sperling 2010a *(Continued)*

	Carisbamate 400 mg/day: 35 ± 12.87 **Sex (female):** Placebo: 54% Carisbamate 200 mg/day: 51% Carisbamate 400 mg/day: 45% **Number of concomitant AEDs:** Placebo: 1 (25%), 2 (75%) Carisbamate 200 mg/day: 1 (23%), 2 (76%) Carisbamate 400 mg/day: 1 (20%), 2 (79%)
Interventions	**Group 1:** placebo **Group 2:** carisbamate 200 mg/d add-on therapy during double-blind treatment phase **Group 3:** carisbamate 400 mg/d add-on therapy during double-blind treatment phase
Outcomes	1. The per cent reduction in frequency of focal seizures 2. The per cent of participants with ≥ 50% reduction in frequency of focal seizures 3. Seizure freedom rates 4. Adverse events
Notes	There are 2 separate RCTs reported in the same journal article (Sperling 2010a and Sperling 2010b). Trial funded by Johnson & Johnson Pharmaceutical Research and Development.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was via a computer-generated scheme, balanced using permuted blocks across treatment groups, stratified by country."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was... implemented using an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Carisbamate was formulated in tablets of 100 and 200 mg, with identical-appearing placebo comparators for each tablet size."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study was reported to be double-blinded, but no specific information was provided regarding how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the number of treatment withdrawals was clearly reported and similar across groups. However, the reasons for withdrawal were not provided in all cases. ITT analysis was used.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes listed in the study details section of the ClinicalTrials.gov registry entry were reported
Other bias	Low risk	Comment: none identified

Sperling 2010b

Study characteristics	
Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled add-on study (83 centres in 12 countries: Bulgaria, Canada, China, Hong Kong, Hungary, India, Norway, Poland, Taiwan, Thailand, Ukraine, and the USA) **Duration:** 8-week prospective baseline phase, 12-week double-blind phase without titration, optional entry into an open-label extension study or mandatory 2-week double-blind tapering-off phase
Participants	721 participants aged ≥ 16 years with focal epilepsy who received concomitant treatment 1 to 2 AEDs were screened, of which 562 were randomised. The ITT population used in the study report was 555, and the safety population was 562. **Number of participants randomised:** Placebo: 189 Carisbamate 200 mg/day: 188 Carisbamate 400 mg/day: 185 **Age (mean ± SD years):** Placebo: 36 ± 12.21 Carisbamate 200 mg/day: 36 ± 11.7 Carisbamate 400 mg/day: 35 ± 13.94 **Sex (female):** Placebo: 58% Carisbamate 200 mg/day: 49% Carisbamate 400 mg/day: 48% **Number of concomitant AEDs:** Placebo: 1 (33%), 2 (67%) Carisbamate 200 mg/day: 1 (33%), 2 (67%) Carisbamate 400 mg/day: 1 (27%), 2 (73%)
Interventions	**Group 1:** placebo **Group 2:** carisbamate 200 mg/d add-on therapy during double-blind treatment phase **Group 3:** carisbamate 400 mg/d add-on therapy during double-blind treatment phase
Outcomes	1. The per cent reduction in frequency of focal seizures 2. The per cent of participants with ≥ 50% reduction in frequency of focal seizures 3. Seizure freedom rates 4. Adverse events
Notes	There are 2 separate RCTs reported in the same journal article (Sperling 2010a and Sperling 2010b). Trial funded by Johnson & Johnson Pharmaceutical Research and Development.

Sperling 2010b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was via a computer-generated scheme, balanced using permuted blocks across treatment groups, stratified by country."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was... implemented using an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Carisbamate was formulated in tablets of 100 and 200 mg, with identical-appearing placebo comparators for each tablet size."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study was reported to be double-blinded, but no specific information was provided regarding how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the number of treatment withdrawals was clearly reported and similar across groups. However, the reasons for withdrawal were not provided in all cases. ITT analysis was used.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes listed in the study details section of the ClinicalTrials.gov registry entry were reported
Other bias	Low risk	Comment: none identified

AED: antiepileptic drug; ITT: intention-to-treat; RCT: randomised controlled trial; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
EUCTR2008-007688-17-LT	An open-label study. The study was not randomised, controlled, or blinded.
NCT00563459	Study was terminated for lack of consistent efficacy data.
NCT00697762	Study was terminated.

DATA AND ANALYSES

Comparison 1. Carisbamate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 50% or greater reduction in seizure frequency (responder rate)	4	2211	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.14, 1.62]

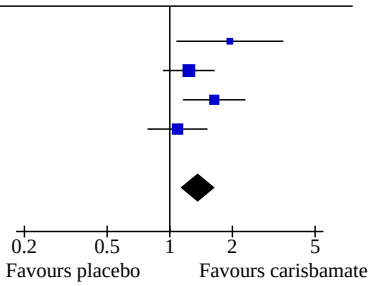
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Seizure freedom	1	547	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.84, 7.03]
1.3 Treatment withdrawal for any reason	4	2211	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.82, 2.12]
1.4 Treatment withdrawal for any reason (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.54, 3.01]
1.4.2 Low dose	3	1450	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.24]
1.5 Treatment withdrawal due to adverse events	4	2211	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.78, 4.17]
1.5.1 New Subgroup	4	2211	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.78, 4.17]
1.6 Treatment withdrawal due to adverse events (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [1.62, 4.54]
1.6.2 Low dose	3	1450	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.53, 1.68]
1.7 At least 1 adverse event	2	1084	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.93, 1.30]
1.8 At least 1 adverse event (subgroup analysis)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.04, 1.24]
1.8.2 Low dose	1	323	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.11]
1.9 Adverse events: dizziness	4	2211	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.23, 3.44]
1.10 Adverse events: dizziness (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [2.33, 5.34]
1.10.2 Low dose	3	1450	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.97, 2.10]
1.11 Adverse events: headache	4	2211	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.92, 1.38]
1.12 Adverse events: headache (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.05, 1.79]
1.12.2 Low dose	3	1450	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.26]
1.13 Adverse events: somnolence	4	2211	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.28, 2.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Adverse events: somnolence (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.14.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.02, 2.36]
1.14.2 Low dose	3	1450	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.35, 3.64]
1.15 Adverse events: fatigue	3	1649	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.73, 1.68]
1.16 Adverse events: fatigue (subgroup analysis)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.16.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.67, 1.90]
1.16.2 Low dose	2	888	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.70, 2.42]
1.17 Adverse events: nausea	3	1649	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.81, 1.75]
1.18 Adverse events: nausea (subgroup analysis)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.18.1 High dose	2	870	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.96, 2.43]
1.18.2 Low dose	2	888	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.64]

Analysis 1.1. Comparison 1: Carisbamate versus placebo, Outcome 1: 50% or greater reduction in seizure frequency (responder rate)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Faught 2008	84	428	11	109	9.8%	1.94 [1.08 , 3.52]
Halford 2011	116	362	48	185	35.6%	1.24 [0.93 , 1.64]
Sperling 2010a	110	379	33	186	24.8%	1.64 [1.16 , 2.31]
Sperling 2010b	86	373	40	189	29.8%	1.09 [0.78 , 1.52]
Total (95% CI)		**1542**		**669**	**100.0%**	**1.36 [1.14 , 1.62]**
Total events:	396		132			

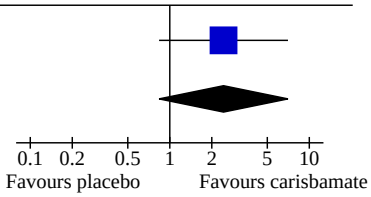
Heterogeneity: Chi² = 4.65, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Carisbamate versus placebo, Outcome 2: Seizure freedom

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Halford 2011	19	362	4	185	100.0%	2.43 [0.84 , 7.03]
Total (95% CI)		**362**		**185**	**100.0%**	**2.43 [0.84 , 7.03]**
Total events:	19		4			

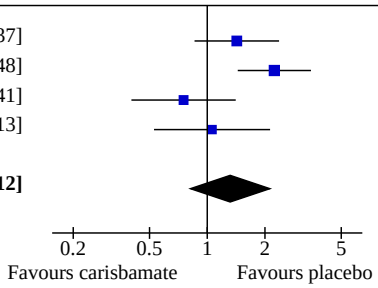
Heterogeneity: Not applicable
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Carisbamate versus placebo, Outcome 3: Treatment withdrawal for any reason

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Faught 2008	84	428	15	109	26.8%	1.43 [0.86 , 2.37]
Halford 2011	92	362	21	185	29.0%	2.24 [1.44 , 3.48]
Sperling 2010a	23	379	15	186	23.1%	0.75 [0.40 , 1.41]
Sperling 2010b	23	373	11	189	21.1%	1.06 [0.53 , 2.13]
Total (95% CI)		**1542**		**669**	**100.0%**	**1.32 [0.82 , 2.12]**
Total events:	222		62			

Heterogeneity: Tau² = 0.15; Chi² = 8.77, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



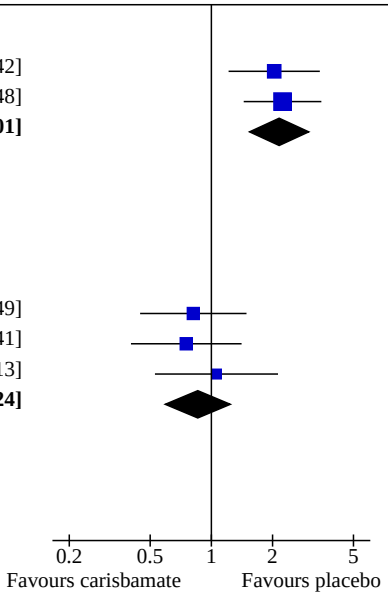
Analysis 1.4. Comparison 1: Carisbamate versus placebo, Outcome 4: Treatment withdrawal for any reason (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 High dose						
Faught 2008	60	214	15	109	41.7%	2.04 [1.22 , 3.42]
Halford 2011	92	362	21	185	58.3%	2.24 [1.44 , 3.48]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**2.15 [1.54 , 3.01]**
Total events:	152		36			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)

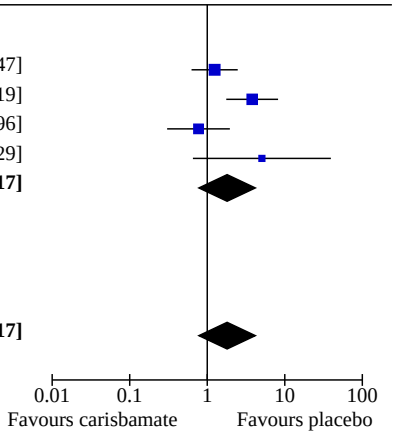
1.4.2 Low dose						
Faught 2008	24	214	15	109	36.4%	0.81 [0.45 , 1.49]
Sperling 2010a	23	379	15	186	36.9%	0.75 [0.40 , 1.41]
Sperling 2010b	23	373	11	189	26.7%	1.06 [0.53 , 2.13]
Subtotal (95% CI)		**966**		**484**	**100.0%**	**0.86 [0.59 , 1.24]**
Total events:	70		41			

Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



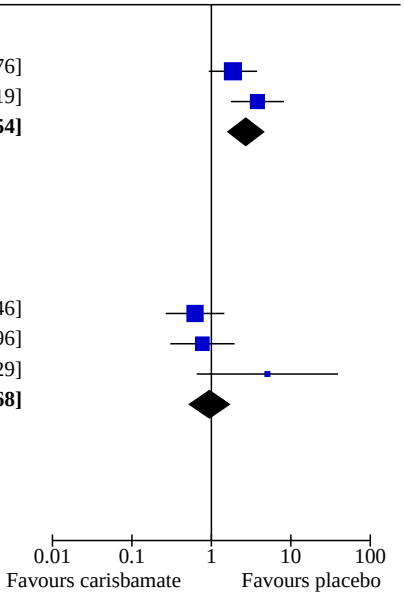
Analysis 1.5. Comparison 1: Carisbamate versus placebo, Outcome 5: Treatment withdrawal due to adverse events

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 New Subgroup						
Faught 2008	44	428	9	109	31.5%	1.25 [0.63 , 2.47]
Halford 2011	52	362	7	185	29.9%	3.80 [1.76 , 8.19]
Sperling 2010a	11	379	7	186	26.8%	0.77 [0.30 , 1.96]
Sperling 2010b	10	373	1	189	11.8%	5.07 [0.65 , 39.29]
Subtotal (95% CI)		**1542**		**669**	**100.0%**	**1.80 [0.78 , 4.17]**
Total events:	117		24			
Heterogeneity: Tau² = 0.46; Chi² = 9.18, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**1542**		**669**	**100.0%**	**1.80 [0.78 , 4.17]**
Total events:	117		24			
Heterogeneity: Tau² = 0.46; Chi² = 9.18, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Test for subgroup differences: Not applicable						



Analysis 1.6. Comparison 1: Carisbamate versus placebo, Outcome 6: Treatment withdrawal due to adverse events (subgroup analysis)

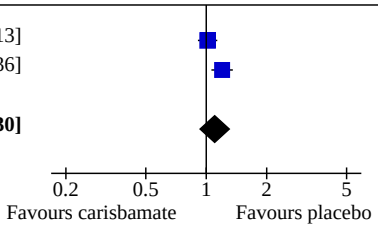
Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 High dose						
Faught 2008	33	214	9	109	56.3%	1.87 [0.93 , 3.76]
Halford 2011	52	362	7	185	43.7%	3.80 [1.76 , 8.19]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**2.71 [1.62 , 4.54]**
Total events:	85		16			
Heterogeneity: Chi² = 1.83, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 3.80 (P = 0.0001)						
1.6.2 Low dose						
Faught 2008	11	214	9	109	52.7%	0.62 [0.27 , 1.46]
Sperling 2010a	11	379	7	186	41.5%	0.77 [0.30 , 1.96]
Sperling 2010b	10	373	1	189	5.9%	5.07 [0.65 , 39.29]
Subtotal (95% CI)		**966**		**484**	**100.0%**	**0.94 [0.53 , 1.68]**
Total events:	32		17			
Heterogeneity: Chi² = 3.69, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 0.19 (P = 0.85)						



Analysis 1.7. Comparison 1: Carisbamate versus placebo, Outcome 7: At least 1 adverse event

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Faught 2008	339	428	85	109	51.2%	1.02 [0.91 , 1.13]
Halford 2011	277	362	118	185	48.8%	1.20 [1.06 , 1.36]
Total (95% CI)		**790**		**294**	**100.0%**	**1.10 [0.93 , 1.30]**
Total events:	616		203			

Heterogeneity: Tau² = 0.01; Chi² = 4.07, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Not applicable



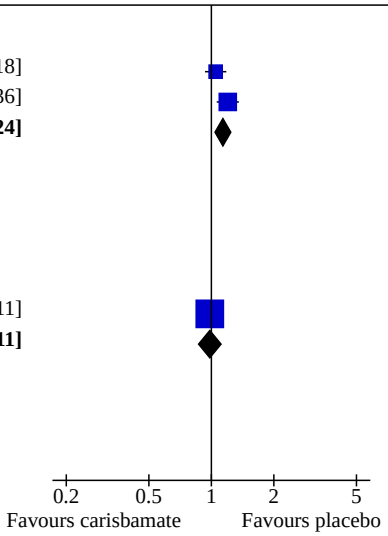
Analysis 1.8. Comparison 1: Carisbamate versus placebo, Outcome 8: At least 1 adverse event (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 High dose						
Faught 2008	175	214	85	109	41.9%	1.05 [0.93 , 1.18]
Halford 2011	277	362	118	185	58.1%	1.20 [1.06 , 1.36]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**1.14 [1.04 , 1.24]**
Total events:	452		203			

Heterogeneity: Chi² = 2.53, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 2.87 (P = 0.004)

1.8.2 Low dose						
Faught 2008	164	214	85	109	100.0%	0.98 [0.87 , 1.11]
Subtotal (95% CI)		**214**		**109**	**100.0%**	**0.98 [0.87 , 1.11]**
Total events:	164		85			

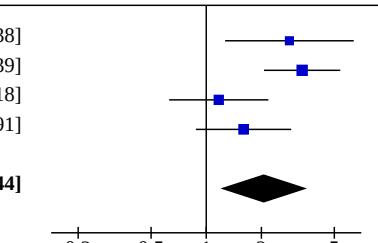
Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.78)



Analysis 1.9. Comparison 1: Carisbamate versus placebo, Outcome 9: Adverse events: dizziness

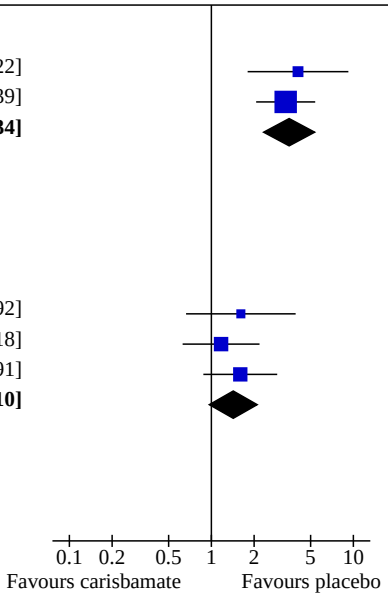
Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Faught 2008	67	428	6	109	20.0%	2.84 [1.27 , 6.38]
Halford 2011	111	362	17	185	29.4%	3.34 [2.07 , 5.39]
Sperling 2010a	31	379	13	186	25.0%	1.17 [0.63 , 2.18]
Sperling 2010b	41	373	13	189	25.7%	1.60 [0.88 , 2.91]
Total (95% CI)		**1542**		**669**	**100.0%**	**2.06 [1.23 , 3.44]**
Total events:	250		49			

Heterogeneity: Tau² = 0.17; Chi² = 8.41, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.76 (P = 0.006)
Test for subgroup differences: Not applicable



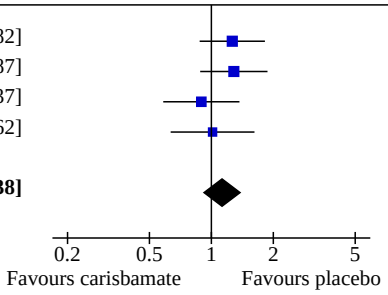
Analysis 1.10. Comparison 1: Carisbamate versus placebo, Outcome 10: Adverse events: dizziness (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 High dose						
Faught 2008	48	214	6	109	26.1%	4.07 [1.80 , 9.22]
Halford 2011	111	362	17	185	73.9%	3.34 [2.07 , 5.39]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**3.53 [2.33 , 5.34]**
Total events:	159		23			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 5.98 (P < 0.00001)						
1.10.2 Low dose						
Faught 2008	19	214	6	109	18.6%	1.61 [0.66 , 3.92]
Sperling 2010a	31	379	13	186	40.9%	1.17 [0.63 , 2.18]
Sperling 2010b	41	373	13	189	40.5%	1.60 [0.88 , 2.91]
Subtotal (95% CI)		**966**		**484**	**100.0%**	**1.43 [0.97 , 2.10]**
Total events:	91		32			
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						



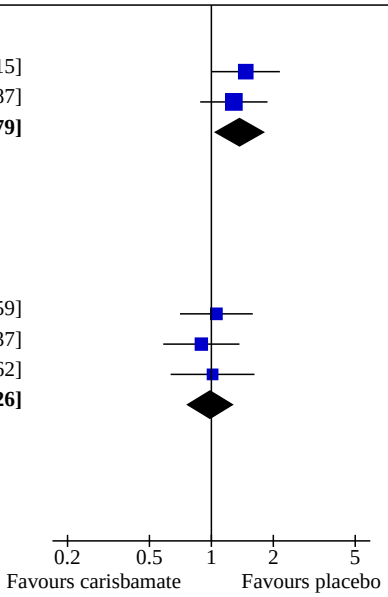
Analysis 1.11. Comparison 1: Carisbamate versus placebo, Outcome 11: Adverse events: headache

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Faught 2008	129	428	26	109	27.5%	1.26 [0.88 , 1.82]
Halford 2011	78	362	31	185	27.3%	1.29 [0.88 , 1.87]
Sperling 2010a	51	379	28	186	24.9%	0.89 [0.58 , 1.37]
Sperling 2010b	46	373	23	189	20.3%	1.01 [0.63 , 1.62]
Total (95% CI)		**1542**		**669**	**100.0%**	**1.13 [0.92 , 1.38]**
Total events:	304		108			
Heterogeneity: Chi² = 2.18, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Not applicable						



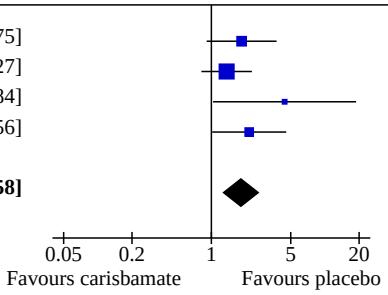
Analysis 1.12. Comparison 1: Carisbamate versus placebo, Outcome 12: Adverse events: headache (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 High dose						
Faught 2008	75	214	26	109	45.6%	1.47 [1.00 , 2.15]
Halford 2011	78	362	31	185	54.4%	1.29 [0.88 , 1.87]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**1.37 [1.05 , 1.79]**
Total events:	153		57			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 2.30 (P = 0.02)						
1.12.2 Low dose						
Faught 2008	54	214	26	109	33.6%	1.06 [0.70 , 1.59]
Sperling 2010a	51	379	28	186	36.6%	0.89 [0.58 , 1.37]
Sperling 2010b	46	373	23	189	29.8%	1.01 [0.63 , 1.62]
Subtotal (95% CI)		**966**		**484**	**100.0%**	**0.98 [0.77 , 1.26]**
Total events:	151		77			
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						



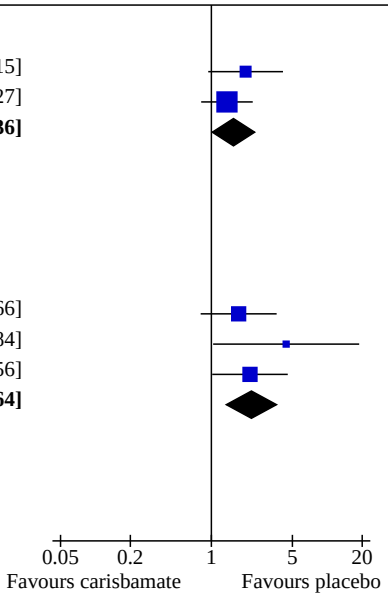
Analysis 1.13. Comparison 1: Carisbamate versus placebo, Outcome 13: Adverse events: somnolence

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Faught 2008	58	428	8	109	25.6%	1.85 [0.91 , 3.75]
Halford 2011	48	362	18	185	47.8%	1.36 [0.82 , 2.27]
Sperling 2010a	18	379	2	186	5.4%	4.42 [1.04 , 18.84]
Sperling 2010b	34	373	8	189	21.3%	2.15 [1.02 , 4.56]
Total (95% CI)		**1542**		**669**	**100.0%**	**1.82 [1.28 , 2.58]**
Total events:	158		36			
Heterogeneity: Chi² = 2.86, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
Test for subgroup differences: Not applicable						



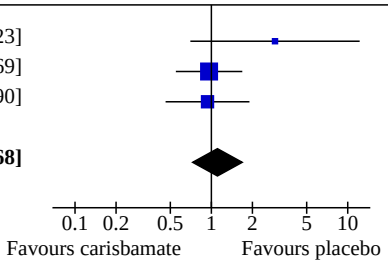
Analysis 1.14. Comparison 1: Carisbamate versus placebo, Outcome 14: Adverse events: somnolence (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 High dose						
Faught 2008	31	214	8	109	30.8%	1.97 [0.94 , 4.15]
Halford 2011	48	362	18	185	69.2%	1.36 [0.82 , 2.27]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**1.55 [1.02 , 2.36]**
Total events:	79		26			
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.14.2 Low dose						
Faught 2008	27	214	8	109	44.3%	1.72 [0.81 , 3.66]
Sperling 2010a	18	379	2	186	11.2%	4.42 [1.04 , 18.84]
Sperling 2010b	34	373	8	189	44.4%	2.15 [1.02 , 4.56]
Subtotal (95% CI)		**966**		**484**	**100.0%**	**2.21 [1.35 , 3.64]**
Total events:	79		18			
Heterogeneity: Chi² = 1.31, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.13 (P = 0.002)						



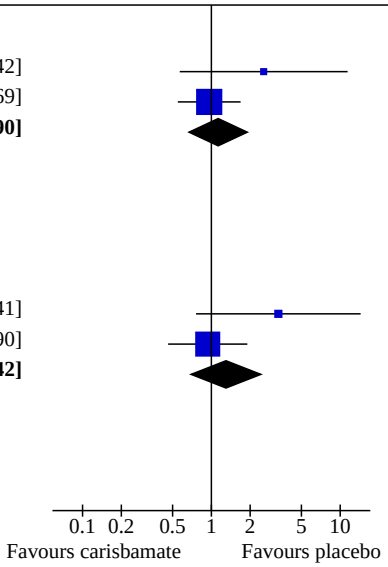
Analysis 1.15. Comparison 1: Carisbamate versus placebo, Outcome 15: Adverse events: fatigue

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Faught 2008	23	428	2	109	7.9%	2.93 [0.70 , 12.23]
Halford 2011	32	362	17	185	55.6%	0.96 [0.55 , 1.69]
Sperling 2010a	21	379	11	186	36.5%	0.94 [0.46 , 1.90]
Total (95% CI)		**1169**		**480**	**100.0%**	**1.11 [0.73 , 1.68]**
Total events:	76		30			
Heterogeneity: Chi² = 2.24, df = 2 (P = 0.33); I² = 11%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Not applicable						



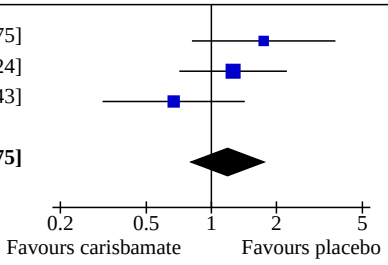
Analysis 1.16. Comparison 1: Carisbamate versus placebo, Outcome 16: Adverse events: fatigue (subgroup analysis)

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 High dose						
Faught 2008	10	214	2	109	10.5%	2.55 [0.57 , 11.42]
Halford 2011	32	362	17	185	89.5%	0.96 [0.55 , 1.69]
Subtotal (95% CI)		**576**		**294**	**100.0%**	**1.13 [0.67 , 1.90]**
Total events:	42		19			
Heterogeneity: Chi² = 1.44, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 0.46 (P = 0.65)						
1.16.2 Low dose						
Faught 2008	13	214	2	109	15.2%	3.31 [0.76 , 14.41]
Sperling 2010a	21	379	11	186	84.8%	0.94 [0.46 , 1.90]
Subtotal (95% CI)		**593**		**295**	**100.0%**	**1.30 [0.70 , 2.42]**
Total events:	34		13			
Heterogeneity: Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.82 (P = 0.41)						

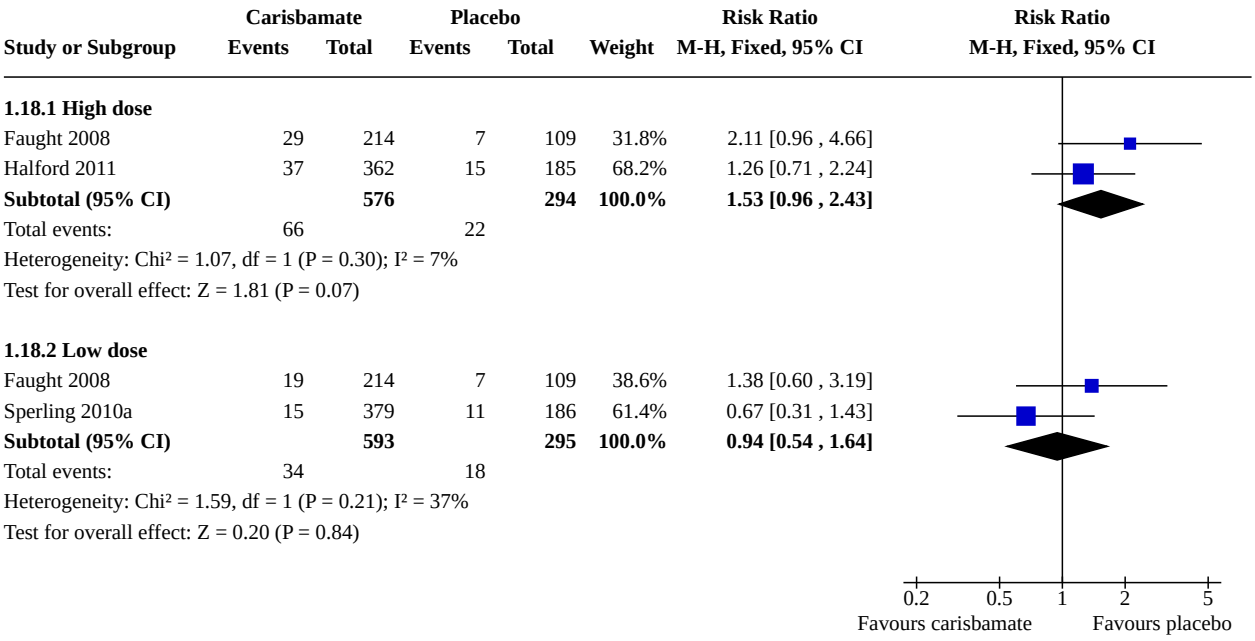


Analysis 1.17. Comparison 1: Carisbamate versus placebo, Outcome 17: Adverse events: nausea

Study or Subgroup	Carisbamate Events	Carisbamate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Faught 2008	48	428	7	109	24.4%	1.75 [0.81 , 3.75]
Halford 2011	37	362	15	185	43.4%	1.26 [0.71 , 2.24]
Sperling 2010a	15	379	11	186	32.2%	0.67 [0.31 , 1.43]
Total (95% CI)		**1169**		**480**	**100.0%**	**1.19 [0.81 , 1.75]**
Total events:	100		33			
Heterogeneity: Chi² = 3.22, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Not applicable						



Analysis 1.18. Comparison 1: Carisbamate versus placebo, Outcome 18: Adverse events: nausea (subgroup analysis)



APPENDICES

Appendix 1. CRS Web search strategy

1. (Carisbamate or "YKP 509" or comfyde or "RWJ-333369"):AB,KW,KY,MC,MH,TI 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*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

5. #2 OR #3 OR #4 AND CENTRAL:TARGET

6. eclampsia:TI AND CENTRAL:TARGET

7. #5 NOT #6 AND CENTRAL:TARGET

8. #1 AND #7

Appendix 2. MEDLINE (Ovid) search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2021).

1. (Carisbamate or "YKP 509" or comfyde or "RWJ-333369").tw.

2. exp Epilepsy/

3. exp Seizures/

4. (epilep$ or seizure$ or convuls$).tw.

5. 2 or 3 or 4

6. exp *Pre-Eclampsia/ or exp *Eclampsia/

7. 5 not 6

8. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 1 and 7 and 13

15. remove duplicates from 14

HISTORY

Protocol first published: Issue 3, 2016

CONTRIBUTIONS OF AUTHORS

Review authors CL, JZ, and YC contributed to the protocol. All five review authors (CL, JZ, YC, RB, and KMM) contributed to the development and conduct of this current version of the review.

DECLARATIONS OF INTEREST

CL: none known.
JZ: none known.
YC: none known.
RB: none known.
KMM: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Two review authors were added to the review team after completion of the April 2016 screening and data extraction. The two additional review authors were then responsible for the June 2019 screening and preparations of the final review.
2. We added information regarding how we planned to measure the treatment effect of the continuous outcome quality of life. This information was not provided in the original review protocol.
3. All bulleted lists were changed to numbered lists for consistency purposes.
4. We only able to conduct one of the planned subgroup analyses (dose). The other four planned subgroup analyses (age of participants, intervention, ethnicity, and study duration) could not be completed. Furthermore, we could not perform any of the planned sensitivity analyses due to the limited number of included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [therapeutic use]; Carbamates; *Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination; *Epilepsies, Partial [drug therapy]; *Pharmaceutical Preparations; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans