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Oxcarbazepine add-on for drug-resistant focal epilepsy (Review)

Bresnahan R, Atim-Oluk M, Marson AG

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[Intervention Review]

Oxcarbazepine add-on for drug-resistant focal epilepsy

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ABSTRACT

Background

Epilepsy is a common neurological disorder. In approximately 30% of epilepsy cases, seizures are uncontrolled by one antiepileptic drug (AED). These people require treatment with a combination of multiple AEDs and are described as having drug-resistant epilepsy. Oxcarbazepine is a keto-analogue of carbamazepine, an established AED, and can be used as an add-on treatment for drug-resistant epilepsy.

Objectives

To assess the efficacy and tolerability of oxcarbazepine as an add-on treatment for people with drug-resistant focal epilepsy.

Search methods

The following databases were searched on 24 September 2018: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL); Medline (Ovid) 1946 to 21 September 2018; ClinicalTrials.gov; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Originally, we also searched SCOPUS as a substitute for Embase, but this is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

Selection criteria

Randomised controlled trials with parallel-group or cross-over design, recruiting people of any age with drug-resistant focal epilepsy. We accepted any level of blinding and trials could be placebo- or active-controlled.

Data collection and analysis

In accordance with the methodological procedures expected by the Cochrane Collaboration, two review authors independently assessed trial eligibility before extracting data and assessing risk of bias. We assessed the primary outcomes: median percentage seizure reduction per 28 days; 50% or greater reduction in seizure frequency; and adverse effects including ataxia, hyponatraemia, and somnolence. We assessed the secondary outcomes: seizure freedom; treatment withdrawal; cognitive effects; and quality of life. We used an intention-to-treat population for all primary analyses. We present results as risk ratios (RR) with 95% confidence intervals (CI), with the exception of adverse effects which we present with 99% CI.

Main results

We identified six eligible studies, involving 1593 participants. We judged that three studies were at unclear risk of bias and three were at high risk of bias. Bias mainly arose from lack of methodological details and from high attrition rates. Participants were aged 1 month to 65

years, with a diagnosis of drug-resistant focal epilepsy. All studies were either placebo- or alternative-dose-controlled with parallel-group design. The treatment period varied from 9 days to 26 weeks.

The median percentage seizure reduction per 28 days (3 studies; moderate-certainty evidence) ranged from 26% to 83.3% for participants randomised to experimental oxcarbazepine compared to 7.6% to 28.7% for participants randomised to control treatment. Oxcarbazepine may increase the responder rate for 50% or greater reduction in seizure frequency compared to control treatment (RR 1.80, 95% CI 1.27 to 2.56; random-effects model; 6 studies; low-certainty evidence). For seizure freedom, the RR was 2.86 (95% CI 1.19 to 6.87; random-effects model; 5 studies; low-certainty evidence), suggesting an advantageous effectiveness of oxcarbazepine over control treatment. Treatment with oxcarbazepine was associated with an increased treatment withdrawal rate compared to control (RR 1.75, 95% CI 1.44 to 2.13; fixed-effect model; 6 studies; moderate-certainty evidence). The largest oxcarbazepine dose used, 2400 mg/d, was associated with a higher treatment withdrawal rate (RR 2.38, 95% CI 1.92 to 2.94; fixed-effect model; 2 studies) compared to control, than 1200 mg/d (RR 1.54, 95% CI 1.21 to 1.95; fixed-effect model; 3 studies) or 600 mg/d oxcarbazepine (RR 0.79, 95% CI 0.55 to 1.15; fixed-effect model; 1 study). Treatment with oxcarbazepine was associated with an increased incidence of multiple adverse effects including: ataxia (RR 2.54, 99% CI 0.86 to 7.54; random-effects model; 5 studies; moderate-certainty evidence); and somnolence (RR 2.03, 99% CI 1.17 to 3.54; random-effects model; 6 studies; low-certainty evidence). Hyponatraemia occurred more frequently with oxcarbazepine treatment but not significantly so (RR 2.53, 99% CI 0.27 to 23.85; fixed-effect model; 6 studies; moderate-certainty evidence).

Authors' conclusions

Oxcarbazepine might be effective at reducing seizure frequency when used as an add-on for drug-resistant focal epilepsy. The efficacy outcomes — 50% or greater seizure reduction and seizure freedom — were derived from low-certainty evidence. We are, therefore, uncertain whether the estimated effect size is representative of the true effect. In contrast, the evidence for median percentage seizure reduction and treatment withdrawal were of moderate certainty: thus, we are fairly certain of the effect estimates' reliability. Overall, we are unsure of the true efficacy of oxcarbazepine, but have concerns about its tolerability.

PLAIN LANGUAGE SUMMARY

Oxcarbazepine add-on for drug-resistant focal epilepsy

Background

Epilepsy is a neurological disorder which causes people to have seizures. Most people can control their epilepsy with a single antiepileptic drug. Some people, however, require multiple antiepileptic drugs to control their epilepsy, and are said to have drug-resistant epilepsy. Oxcarbazepine is an antiepileptic drug and is similar to an older antiepileptic drug, carbamazepine. Oxcarbazepine can be taken as an add-on treatment, alongside other antiepileptic medication, to treat drug-resistant epilepsy.

Aim of the review

This review examined whether oxcarbazepine is tolerable and effective when used alongside other antiepileptic medication by people with drug-resistant focal epilepsy (epilepsy that originates from one area of the brain).

Results

We included six clinical trials that investigated oxcarbazepine as an add-on treatment for people with drug-resistant focal epilepsy. There were 1593 people across the studies and they were aged from 1 month to 65 years.

People who received oxcarbazepine in addition to their normal antiepileptic medication were more likely to have a 50% or greater reduction in the frequency of their seizures compared to people who were on a control treatment, which is believed to have little or no effect. They were also nearly three times more likely to be free from all seizures than those receiving control treatment. Both of these findings suggest that oxcarbazepine is effective at treating drug-resistant focal epilepsy. These findings are, however, based on evidence that was of low certainty. This means that we are not confident that the findings that we have reported are accurate.

People who received oxcarbazepine add-on treatment were also more likely to withdraw from the studies and were more likely to experience side effects, including dizziness and drowsiness, than people receiving control add-on treatment. The evidence for treatment withdrawal was of moderate certainty, and this means that we can be fairly confident that this is a true effect.

Authors' conclusions

As a result of the low-certainty evidence, we cannot be sure that oxcarbazepine is an effective add-on treatment for people with drug-resistant focal epilepsy. Instead, we have concerns about the tolerability of oxcarbazepine because of the increased number of people who withdrew from treatment and who experienced side effects.

The evidence is current to September 2018.

Summary of findings for the main comparison. Oxcarbazepine compared to control for drug-resistant focal epilepsy

Oxcarbazepine compared to control for drug-resistant focal epilepsy

Patient or population: drug-resistant focal epilepsy
Setting: outpatients (except for 1 study which was conducted in a hospital setting to allow EEG-recording)
Intervention: Oxcarbazepine (600 mg/d, 1200 mg/d, 2400 mg/d, 10 mg/kg/d, and 60 mg/kg/d)
Comparison: control (placebo or alternative lower dose of oxcarbazepine)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI for efficacy outcomes and 99% CI for adverse effects)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with Oxcarbazepine				
Median percentage seizure reduction per 28 days Follow-up: 9 days to 26 weeks	The values reported ranged from 7.6% to 28.7% seizure reduction with 2 of the 3 studies specifically reporting percentage reductions of less than 10%. The median percentage seizure reduction for participants randomised to experimental oxcarbazepine treatment ranged from 26% to 83.3%. Importantly, for each study that described this outcome, the median percentage seizure reduction reported was consistently higher in experimental oxcarbazepine treatment group than in the control group.		-	**1494** (5 RCTs)	⊕⊕⊕⊖ **MODERATE**[a]	Oxcarbazepine likely increases the median percentage seizure reduction per 28 days attained by participants.
50% or greater reduction in seizure frequency Follow-up: 9 days to 26 weeks	**Study population**		**RR 1.80** (1.27 to 2.56)	**1593** (6 RCTs)	⊕⊕⊖⊖ **LOW**[a,b]	Oxcarbazepine may increase the number of participants achieving a 50% or greater reduction in seizure frequency but we are uncertain.
	217 per 1000	390 per 1000 (275 to 555)				
Ataxia Follow-up: 9 days to 26 weeks	**Study population**		**RR 2.54** (0.86 to 7.54)	**1227** (5 RCTs)	⊕⊕⊕⊖ **MODERATE**[a,b,d]	Oxcarbazepine likely increases the incidence of ataxia.
	50 per 1000	128 per 1000 (43 to 380)				
Hyponatraemia	**Study population**[#]		**RR 2.53** (0.27 to 23.85)	**1593** (6 RCTs)	⊕⊕⊕⊖ **MODERATE**[a,c,d]	Oxcarbazepine likely increases the incidence of hyponatraemia.

Follow-up: 9 days to 26 weeks	0 per 558	5 per 1035				
Somnolence Follow-up: 9 days to 26 weeks	**Study population**		**RR 2.03** (1.17 to 3.54)	**1593** (6 RCTs)	⊕⊕⊖⊖ **LOW**[a,b,c,d]	Oxcarbazepine may increase the incidence of somnolence but we are uncertain.
	120 per 1000	244 per 1000 (140 to 425)				
Seizure freedom Follow-up: 9 days to 26 weeks	**Study population**		**RR 2.86** (1.19 to 6.87)	**1494** (5 RCTs)	⊕⊕⊖⊖ **LOW**[a,b,c,d]	Oxcarbazepine may increase the incidence of seizure freedom amongst participants but we are uncertain.
	36 per 1000	102 per 1000 (42 to 244)				
Treatment withdrawal Follow-up: 9 days to 26 weeks	**Study population**		**RR 1.75** (1.44 to 2.13)	**1593** (6 RCTs)	⊕⊕⊕⊖ **MODERATE**[a]	Oxcarbazepine likely increases treatment withdrawal.
	167 per 1000	292 per 1000 (240 to 355)				

*__The risk in the intervention group__ (and its 95% CI for efficacy outcomes, including treatment withdrawal, and 99% CI for adverse effects) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI for efficacy outcomes, including treatment withdrawal, and 99% CI for adverse effects).

[#] For the adverse event, __Hyponatraemia__, we have reported the __Number of events recorded per number of randomised participants__ rather than the __Anticipated absolute effects__. Under the circumstances, this measure was considered more informative.

CI: Confidence interval; **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

[a] Evidence downgraded once for risk of bias: 3 of the studies had unclear risk of bias and 3 studies had high risk of bias. This was largely due to studies not specifying their methods for randomisation and allocation concealment, as well as due to high attrition rates noted in some studies.
[b] Evidence downgraded once due to inconsistency: significant heterogeneity between studies detected.
[c] Evidence downgraded once due to imprecision: wide confidence intervals and sub-optimal number of events included in analysis.
[d] Evidence upgraded once for large effect: large effect size (RR > 2.00).

BACKGROUND

Description of the condition

Epilepsy is a disease arising from an enduring and pathological excessive discharge of a set of neurons in the brain, clinically characterised by recurrent unprovoked epileptic seizures or in the context of an epilepsy syndrome. There are many causes alongside several clinical and electroencephalographic manifestations that can result in epilepsy (Fisher 2014). The condition is associated with considerable physical, cognitive, psychiatric and psychological co-morbidity (LaFrance 2008; Burton 2012).

Epilepsy is common worldwide. A meta-analysis of 65 studies estimated lifetime prevalence in high-income countries as 5.8 per 1000; whereas in resource-poor countries the estimate was 10.3 per 1000 in urban areas, and in rural areas the estimate was 15.4 per 1000 (Bell 2014).

The United Kingdom General Practice Study of Epilepsy found 60% of epilepsies to be convulsive, of which around two-thirds comprised focal seizures or focal seizures with secondary generalisation (Sander 1990; Shorvon 2014). Epilepsy is commonly treated with antiepileptic drugs (AEDs), with many patients rendered seizure-free. Unfortunately, an estimated 30% of epilepsy cases are resistant to conventional AED regimens and can require several agents to control seizures (Cockerell 1995; Kwan 2000). This is especially prevalent with focal seizures which originate from one area of the brain. Drug-resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (ILAE 2009). There are also non-medical interventions available for epilepsy, such as vagal nerve stimulation or surgery (Panebianco 2015; West 2019).

Description of the intervention

Oxcarbazepine is an analogue of carbamazepine. Oxcarbazepine is thought to have certain advantages over carbamazepine. In particular, there are fewer side effects associated with oxcarbazepine and the dose can be titrated to a therapeutic dose more quickly (Grant 1992). Oxcarbazepine is an AED used as monotherapy for children and adults with focal-onset seizures. It is established as an efficacious initial monotherapy in children and as a potentially efficacious initial monotherapy for adults (Glauser 2013).

How the intervention might work

AEDs have numerous modes of action. Generally, they inhibit generation of seizure discharge by communicating with several molecular targets in the brain to reduce neuronal excitation or increase inhibition (Porter 2018). Oxcarbazepine has been shown to exert antiepileptic activity by blockade of voltage-dependent sodium channels in the brain. Based on in vitro and in vivo findings and compared with antiepileptic drugs such as carbamazepine, phenytoin and phenobarbital, oxcarbazepine has a low propensity for drug–drug interactions (Flesch 2004). Oxcarbazepine is, however, metabolised hepatically and is rapidly reduced by cytosolic enzymes in the liver to its monohydroxy derivative (MHD), which is responsible for the pharmacological effect of the drug. Oxcarbazepine could, therefore, potentiate other AEDs that are metabolised hepatically. At oxcarbazepine doses above 1.2 g, a 40% increase in the concentration of phenytoin and a 15% increase in phenobarbital levels are observed. Furthermore, oxcarbazepine is associated with decreased clearance with moderate to severe renal impairment. Dose adjustments are thus necessary in situations of AED polypharmacy and in instances of moderate to severe renal impairment (Flesch 2004).

Why it is important to do this review

A large amount of evidence has been accrued regarding the efficacy and tolerability of new AEDs. The International League Against Epilepsy and other organisations have produced guidelines on how to select new AEDs (UK Oxcarbazepine Advisory Board 2001; Kang 2012). New AEDs have been tested and used with success, mainly as add-on therapies to standard drugs such as phenytoin, carbamazepine and valproate. The majority of trials investigating add-on therapy with AEDs have recruited patients with focal epilepsy (experiencing simple focal and/or complex focal and/or secondary generalised tonic-clonic seizures; ILAE 1989) that have been resistant to antiepileptic drug treatment.

The introduction of several new AEDs means that systematic reviews are needed to determine their effect as add-on agents for people with focal seizures. These reviews will help inform clinicians on the best add-on agents to use for their patients (Marson 1997; Privitera 1999). We therefore present a systematic review focusing on the effects of oxcarbazepine on seizures, side effects, cognition and quality of life when used as an add-on treatment for patients with drug-resistant focal epilepsy.

OBJECTIVES

To assess the efficacy and tolerability of oxcarbazepine as an add-on treatment for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review, we required studies to meet the following criteria.

1. Randomised controlled trials (RCTs), including quasi-randomised trials.
2. Double, single or unblinded trials.
3. Placebo-controlled or active-controlled studies.
4. Parallel group or cross-over studies. For cross-over studies, we planned to use the first treatment period as a parallel trial.

Types of participants

Adults and children with drug-resistant focal epilepsy, as defined by the International League Against Epilepsy (ILAE 2009). We included participants who had undergone other interventions to treat epilepsy, such as surgery, vagal nerve stimulation or ketogenic diet.

Types of interventions

1. The active treatment group received therapy with oxcarbazepine, in addition to their usual treatment.
2. The control group received placebo, an alternative antiepileptic drug or a different dose of oxcarbazepine, in addition to their usual treatment.

Types of outcome measures

Primary outcomes

(1) Median percentage seizure reduction per 28 days

The median percentage seizure reduction every four weeks in the treatment period compared to the pre-randomisation baseline period.

(2) 50% or greater reduction in seizure frequency

The proportion of participants with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period.

(3) Adverse effects

The proportion of participants who experienced any of the following adverse effects.

1. Ataxia
2. Dizziness
3. Fatigue
4. Nausea
5. Somnolence
6. Headache
7. Hyponatraemia
8. Vertigo
9. Diplopia
10. Rash
11. Tremor
12. Pyrexia
13. Abnormal gait
14. Abdominal pain
15. Nystagmus
16. Viral infection
17. Vomiting
18. Abnormal vision
19. Any other adverse effect

Secondary outcomes

(1) Seizure freedom

The proportion of participants who had complete cessation of seizures during the treatment period.

(2) Treatment withdrawal

We chose the proportion of participants who withdrew from the treatment during the course of the treatment period as a 'global measure of tolerability'. In studies of relatively short duration, treatment is unlikely to be withdrawn due to lack of efficacy and any treatment withdrawal is likely due to side effects.

(3) Cognitive effects

At present, there is no consensus as to which instruments should be used to assess the effects of AEDs on cognition. As a result, we approached the assessment of cognitive effects in a heterogeneous way (Cochrane 1998).

(4) Quality of life

Once again, there is no consensus as to which instruments should be used to assess this and we expected to see significant heterogeneity in the outcome measures used.

Search methods for identification of studies

Electronic searches

We ran the first searches for this review in July 2014. We ran subsequent searches in December 2016; and we ran the most recent searches on 24 September 2018, when we searched the following databases. There were no language restrictions.

1. Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the search strategy set out in Appendix 1.
2. MEDLINE (Ovid) 1946 to 21 September 2018 using the search strategy set out in Appendix 2.
3. ClinicalTrials.gov using the search strategy set out in Appendix 3.
4. WHO International Clinical Trials Registry Platform (ICTRP) using the search strategy set out in Appendix 4.

Previously SCOPUS was searched as an alternative to Embase but this is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

Searching other resources

References from published studies

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Efforts to identify unpublished studies

We sought unpublished data from Novartis (the manufacturer of oxcarbazepine); we were unable to obtain any, however.

Other

We asked colleagues if they were aware of any studies that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (RB and MO) independently assessed the titles and abstracts identified from the searches and excluded any irrelevant studies. The same two authors then reviewed the full-text papers for inclusion. We resolved any disagreements by discussion; or, if necessary, by asking the third author (AGM) to arbitrate.

Data extraction and management

The review authors extracted the following information from included trials. Again, we resolved any disagreements by discussion.

Methodological trial design

1. Method of concealing randomisation.
2. Method of blinding.

3. Whether any participants had been excluded from reported analyses.
4. Duration of baseline period.
5. Duration of treatment period.
6. Dose(s) of oxcarbazepine tested and potential comparator AED treatment type and dose.

Patient/demographic information

1. Number of participants allocated to each treatment group.
2. Age/sex.
3. Seizure types.
4. Seizure frequency during baseline period.
5. Number of background drugs.

Where necessary, we asked original authors to confirm:

1. the method of randomisation;
2. the total number of participants randomised to each group;
3. the number of participants in each group achieving a 50% or greater reduction in seizure frequency per treatment group;
4. the number of participants having treatment withdrawn post randomisation per treatment group.

And for those excluded:

1. the reason for exclusion;
2. whether any of those excluded completed the treatment phase;
3. whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Outcomes

We recorded the number of participants experiencing each outcome per randomised group (see Types of outcome measures).

Assessment of risk of bias in included studies

Two review authors (RB, MO) independently assessed the risk of bias for each trial in accordance with the Cochrane 'Risk of bias' tool, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We discussed any disagreements and, if necessary, sought the opinion of a third review author (AGM). Studies were rated as having a high, low or unclear risk of bias for six domains applicable to RCTs: randomisation sequence; allocation concealment; blinding; incomplete data outcome; selective outcome reporting; and other sources of bias. We also assessed the potential impact of outcome reporting bias by including an Outcome Reporting Bias in Trials (ORBIT) table in the review (Kirkham 2010).

Measures of treatment effect

For dichotomous outcomes, such as seizure reduction, seizure freedom, and treatment withdrawal we reported risk ratios (RRs) using 95% confidence intervals. We presented the proportion of participants reporting individual adverse effects as an RR but using 99% confidence intervals in an attempt to compensate for multiple outcome testing.

For continuous outcomes — such as cognitive effects and quality of life — in a meta-analysis, we had ideally planned to report the mean difference. Only one study reported either of these outcomes: it was not necessary or possible, therefore, to complete a meta-analysis.

Unit of analysis issues

We did not include any cross-over studies in the review; therefore we did not encounter any unit of analysis issues in this regard, and did not require any compensatory methods.

For trials with more than one treatment arm (for example, different doses of oxcarbazepine versus a control group), we combined the treatment groups for the main meta-analysis and then investigated the dosage effects separately during subgroup analysis.

Dealing with missing data

In the event of missing data, we sought reasons for this by contacting study authors in order to conclude whether data were missing at random or not.

Assessment of heterogeneity

Two authors (RB, MO) independently assessed clinical and methodological heterogeneity. Although we detected some differences in control groups, outcome measures and time scales, we did not detect significant clinical or methodological heterogeneity to the degree to which meta-analysis would be inappropriate.

We visually assessed the clinical and methodological heterogeneity of the included studies. We used the I^2 statistic and a Chi^2 test, where applicable, to assess statistical heterogeneity. We judged a Chi^2 P value of less than 0.10 or I^2 greater than 50% to indicate statistical heterogeneity.

Assessment of reporting biases

We requested protocols from study authors and investigated outcome reporting bias using the ORBIT matrix system (Kirkham 2010).

To examine publication bias, we searched for unpublished data by carrying out a comprehensive search of multiple sources and requested any unpublished data from study authors. We also looked for small-study effects to establish the likelihood of publication bias.

Data synthesis

We combined data in a fixed-effect meta-analysis. Where there was significant clinical, methodological or statistical heterogeneity, however, we combined data in a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

Where possible, we stratified subgroup analysis by type of control group, age group (adults or children), duration of treatment, and experimental treatment dose.

Sensitivity analysis

We did not conduct any sensitivity analyses as part of this review.

Summary of findings and assessment of the certainty of the evidence

We (RB, MO) used the GRADE approach to interpret findings and to assess the certainty of evidence used in the review (Schunemann

2011). We used GRADE Profiler Software (GRADEPro GDT 2015); and imported data from Review Manager 5 (RevMan 5) to create a 'Summary of findings' table for the main comparison in the review: oxcarbazepine versus control, including the primary and secondary outcomes (see Summary of findings for the main comparison; Review Manager 2014). We evaluated the evidence across eight criteria (risk of bias; inconsistency; indirectness; imprecision; publication bias; effect size; presence of plausible confounding factors; and dose-response gradient), according to the GRADE approach, to determine the certainty of evidence. The 'Summary of findings' table thus includes information on overall certainty of the evidence from the trials and information of importance for healthcare decision making.

RESULTS

Description of studies

Results of the search

The search identified 592 records for potential inclusion; and we found one additional record through other sources (Figure 1). We contacted Novartis for additional unpublished data, including any unpublished studies that we may not have been aware of. Unfortunately, we received no correspondence. We removed 125 duplicate records; followed by a further 368 records due to irrelevance. We then screened the remaining 100 records to assess their eligibility for inclusion, according to the information provided in the title and abstract of each record. Next, we attempted to retrieve the full texts for the 38 records that remained after the initial screening for the full-text screening stage. We assessed that 20 records remained eligible for inclusion following the two screening exercises. The 20 records related to six individual trials (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; NCT00975715; French 2014). We extracted the data from these six studies and included them in the subsequent meta-analysis.

Figure 1. Study flow diagram. OXC: Oxcarbazepine

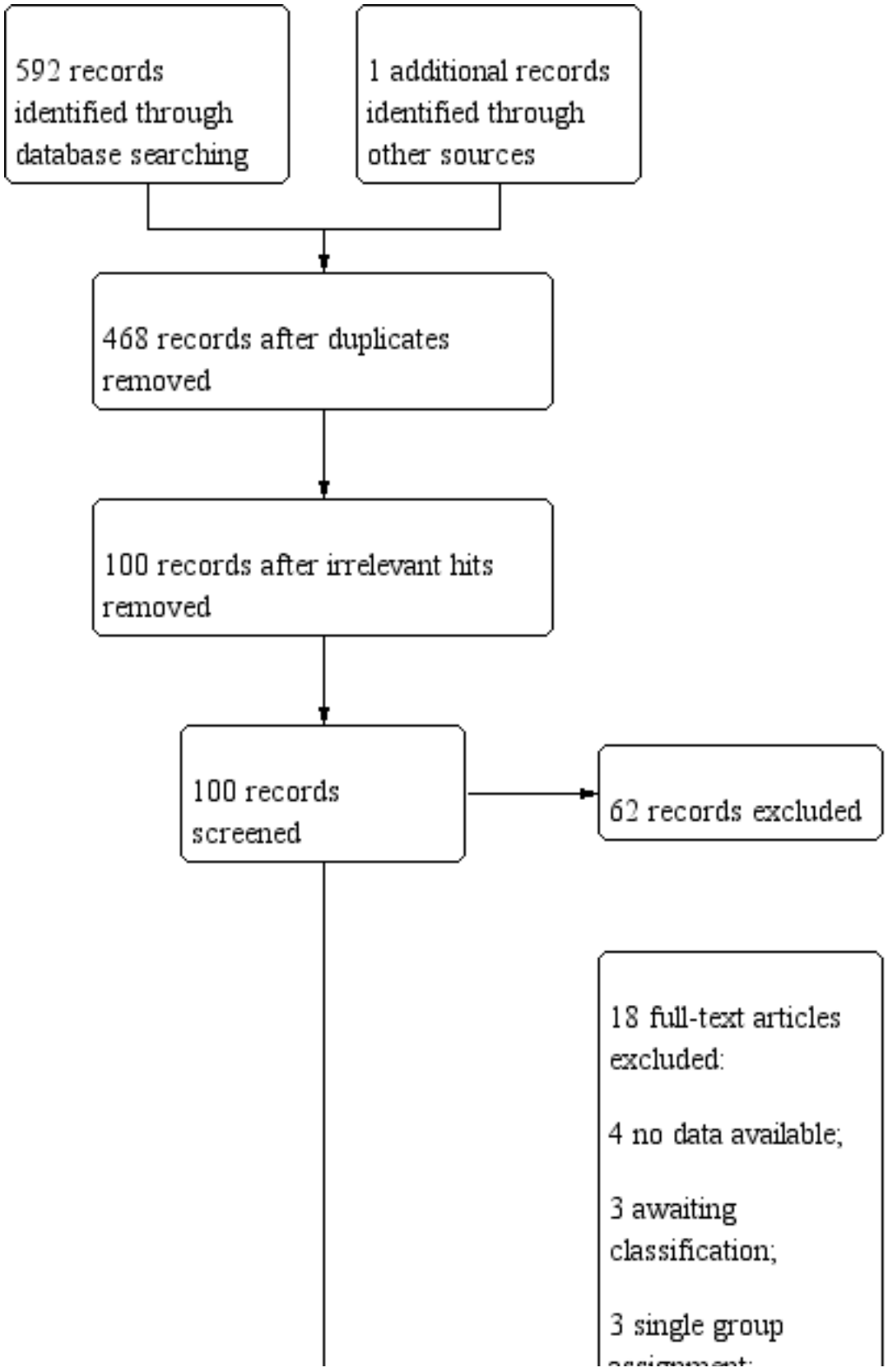
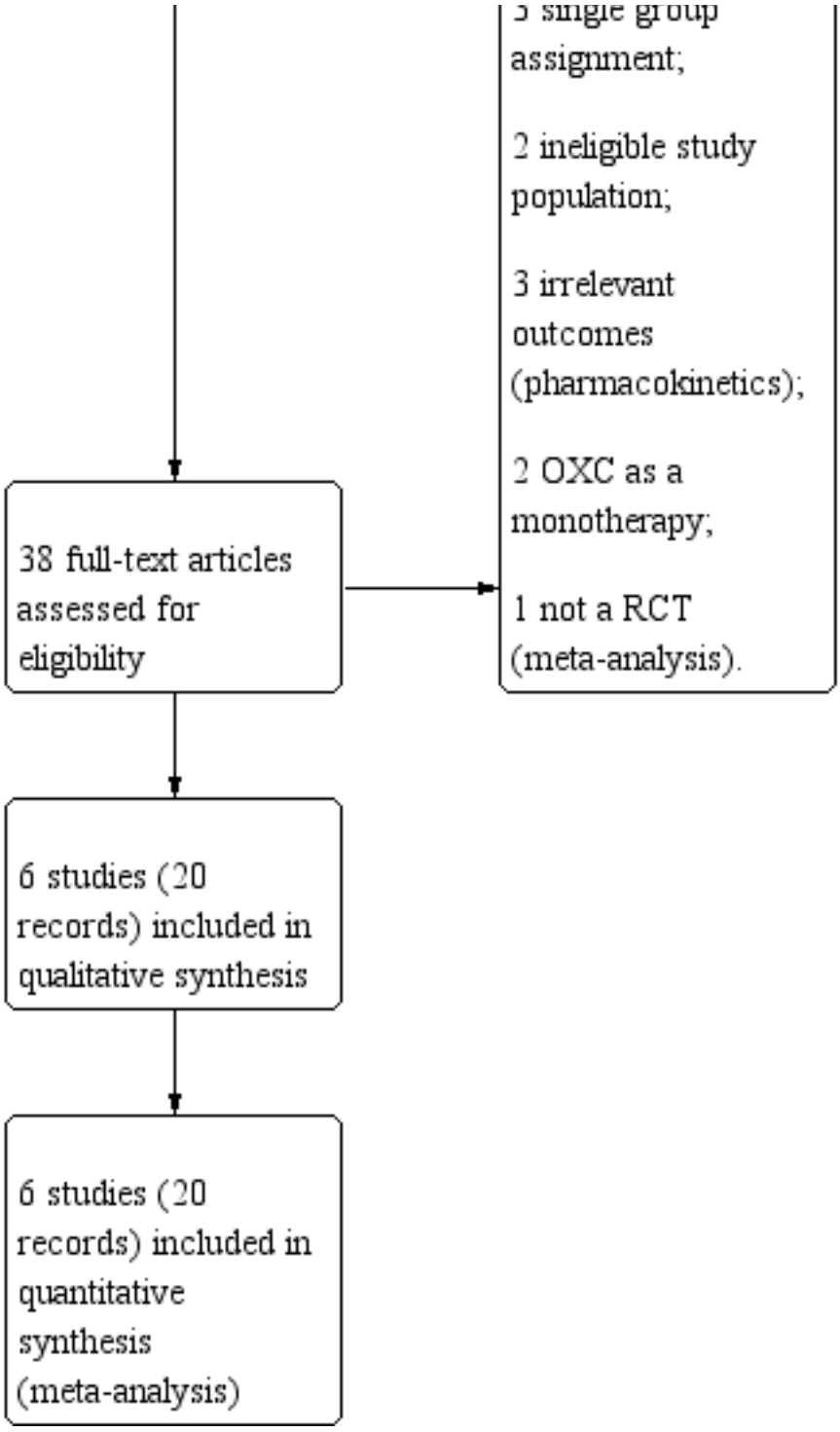


Figure 1. (Continued)



Included studies

The six included studies were all randomised, controlled trials with parallel group design (Barcs 2000; French 2014; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; NCT00975715). Four of the included studies were placebo-controlled (Barcs 2000; Glauser 2000; French 2014; NCT00975715); whilst two of the studies were alternative-dose-controlled (Kraiprab 2005; Pina-Garza 2005). All of the included studies, with the exception of one — Kraiprab 2005 — were multi-centre studies; and all but one study — Pina-Garza 2005 — were double-blind. Pina-Garza 2005 was instead rater-blind. We provide specific details regarding the demographic of the individual treatment groups for each study in the Characteristics of included studies tables.

Barcs 2000 was a multi-centre, placebo-controlled, double-blind study, conducted across 11 countries in 73 centres.

Eligible participants were aged 15 to 65 and had drug-resistant focal epilepsy. Focal seizures could be simple or complex in nature, with or without secondary generalisation. The study consisted of a prospective baseline period, following which participants were randomised to one of four treatment groups: 600 mg/d oxcarbazepine; 1200 mg/d oxcarbazepine; 2400 mg/d oxcarbazepine; or placebo. After randomisation, participants entered a 2-week up-titration period followed by a 24-week maintenance period. Following completion of the trial, there was the option for participants to enter an open-label extension study.

French 2014 was similarly a multi-centre, placebo-controlled, double-blind study. Eighty-eight sites were involved in the study and they were located across eight countries: USA, Mexico, Canada, Russia, Poland, Bulgaria, Croatia, and Romania. Participants were aged 18 to 65 and all participants had drug-resistant focal epilepsy, characterised by uncontrolled focal-onset seizures, with or without secondary generalisation. The majority of participants were taking two concomitant AEDs during their involvement in the study. Again, this study included an 8-week prospective baseline period that preceded participant randomisation. Participants were randomised to one of three treatment groups: 1200 mg/d oxcarbazepine; 2400 mg/d oxcarbazepine; or placebo. After randomisation, participants underwent a 4-week up-titration period followed by a 12-week maintenance period. After completing the trial, participants chose whether to enter a 3-week conversion period which led into an open-label extension study; or whether to undergo a tapering period to return to their baseline therapy.

Glauser 2000 was also a multi-centre, placebo-controlled, double-blind study. The trial included 47 sites, distributed across eight countries: Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, and USA. In contrast to the other studies, Glauser 2000 only included participants aged 3 to 17 years and thus focused on the efficacy of oxcarbazepine in children. Again, participants were required to have drug-resistant focal epilepsy, despite receiving one or two concomitant AEDs. Following an 8-week prospective baseline period, participants were randomised to one of two treatment groups: 30 to 46 mg/kg/d oxcarbazepine or placebo. After being randomised, participants underwent a 2-week titration period before entering into a 14-week maintenance period. The study also included optional entry into an open-label extension study.

Kraiprab 2005 was a double-blind study, similar to the other studies described. In contrast to the other studies, this study was performed at a single centre in Thailand and was an alternative-dose-controlled study rather than a placebo-controlled study. Participants were again recruited from an adult population, aged 18 to 65, who had drug-resistant focal epilepsy. Focal seizures could be simple, complex, or focal seizures evolving into secondarily generalised seizures. The study likewise had an 8-week prospective baseline period, following which participants were randomised to one of two treatment groups: either 1200 mg/d or 2400 mg/d oxcarbazepine. Participants then entered a 2-week up-titration period which then led into a 14-week maintenance period. After completion, participants were offered entry into an open-label extension study.

NCT00975715 was a multi-centre, placebo-controlled, double-blind study conducted at multiple sites, all of which were located in Japan. Similar to Glauser 2000, this trial studied the efficacy of oxcarbazepine in children. Specifically, participants were aged 4 to 14 years with a diagnosis of focal onset seizures which could include simple, complex, and secondarily generalised seizures. Participants were randomised to receive either an oral suspension of either oxcarbazepine (60 mg/ml) or placebo, although information on the precise dosage was not provided. The study comprised an 8-week prospective baseline period, followed by an 8-week treatment period. The treatment period included a 2-week up-titration phase and a 6-week maintenance phase. Participants then completed a 3- to 5-week follow-up period.

Pina-Garza 2005 was also a multi-centre study involving 56 centres, distributed across seven countries: USA, Argentina, France, Germany, Brazil, Mexico, and Lithuania. Rather than being placebo-controlled, the study was instead alternative-dose-controlled and participants were randomised to receive either a high dose of oxcarbazepine (60 mg/kg/d) or a low dose of oxcarbazepine (10 mg/kg/d). Interestingly, the study was not double-blind, but was instead rater-blind, meaning that the outcome assessor was blinded to treatment. Participants and their caregivers were not blinded. This study was, however, conducted in a very young population of participants, aged one month to four years old. All participants had a diagnosis of focal seizures which included subtypes: simple, complex, and focal evolving to secondarily generalised seizures. Participants were initially screened over a 72-hour period, prior to commencing a 24- to 72-hour baseline period. The subsequent treatment periods varied in length, dependent on the treatment group. Participants randomised to high-dose oxcarbazepine (60 mg/kg/d) completed a 26-day titration period followed by a 9-day maintenance period, whereas participants randomised to low-dose oxcarbazepine (10 mg/kg/d) were not required to undergo the 26-day titration period and, instead, only completed the 9-day maintenance period. Following the treatment period, there was then a 6-month open-label extension phase, included in the study design.

Excluded studies

We excluded 15 records at the full-text screening stage. The 15 excluded records related to 13 individual studies. The reasons for exclusion varied (see summarised in the Characteristics of excluded studies tables). Notably, three records are still awaiting classification.

We excluded three records from the review as they were open-label extension studies with single-group assignment, and thus lacked a control group (EUCTR2008-003334-19-BG; Glauser 2001; NCT00918424). We excluded a further two records as they studied oxcarbazepine as a monotherapy (NCT00050947; NCT01891890); whilst another record used oxcarbazepine to replace carbamazepine in participants' drug regime and was therefore deemed irrelevant (Houtkooper 1987). The latter study also included a number of participants with generalised-onset seizures which did not comply with the review inclusion criteria. We found another record, Gillham 1993, to be linked to another record, a study by McKee 1994. We excluded both records from the review as they were deemed to be irrelevant. The study primarily focused on investigating the pharmacokinetics of oxcarbazepine and initially used oxcarbazepine as a monotherapy rather than as an adjunctive therapy. We excluded an additional record, a trial by Rey 2004, and a linked record, a poster abstract by Dulac 2001, after it was revealed that the full-text record — Rey 2004 — did not provide data for any of the outcomes defined in the review and also

focused on the pharmacokinetics of oxcarbazepine. This study also included participants with generalised epilepsy, which again made it ineligible for inclusion as the authors did not report the outcomes stratified by primary seizure type. We excluded one record because, upon inspection of the full-text, we discovered that the record was a meta-analysis of safety data taken from 21 studies, and was not a randomised controlled trial (Kutluay 2003).

We excluded the remaining four studies because there were no results available for the studies (EUCTR2004-002260-25-AT; EUCTR2006-003834-14-DE; NCT00391534; Steinhoff 2012). Notably, three records corresponded to studies which had been terminated early due to low recruitment and, therefore, no data were available (EUCTR2006-003834-14-DE; NCT00391534; Steinhoff 2012). Similarly results were not reported for the other record; consequently we also had to exclude this record from the review (EUCTR2004-002260-25-AT). Additionally, after we studied the EU clinical trial registration for the latter record (EUCTR2004-002260-25-AT), it appeared that a certain proportion of participants on the study received oxcarbazepine as a monotherapy, not as an add-on — therefore we suspected that the study was ineligible for inclusion, regardless.

We further recognised that for another three of the records highlighted in the searches, we required additional information before being able to decide whether they were eligible for inclusion in the review (CTRI/2010/091/000100; CTRI/2010/091/001194; CTRI/2010/091/006085). These records have, therefore, been acknowledged under studies awaiting classification (See Characteristics of studies awaiting classification tables). At the time of publication of this review, we had requested additional information for the studies awaiting classification but had not yet received it.

Risk of bias in included studies

We judged that three of the included studies were at an unclear risk of bias overall (Glauser 2000; Kraiprab 2005; NCT00975715), and rated that the remaining three studies were at a high risk of bias (Barcs 2000; Pina-Garza 2005; French 2014). The rating for the risk of bias, according to each bias domain, for each individual study included, is described in detail below and can be found summarised in Figure 2 and Figure 3 as well as in the 'Risk of bias' tables within the Characteristics of included studies tables.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

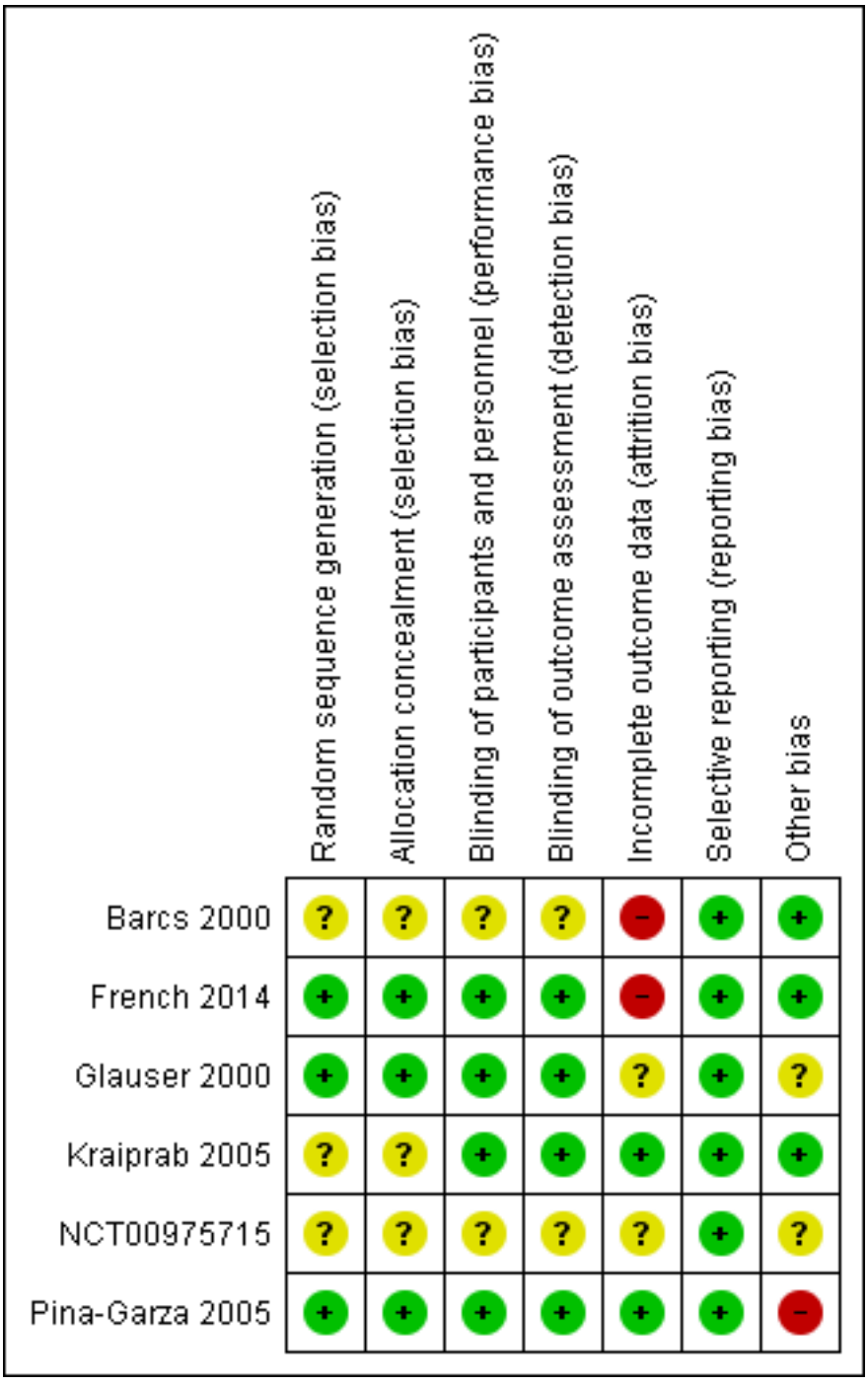
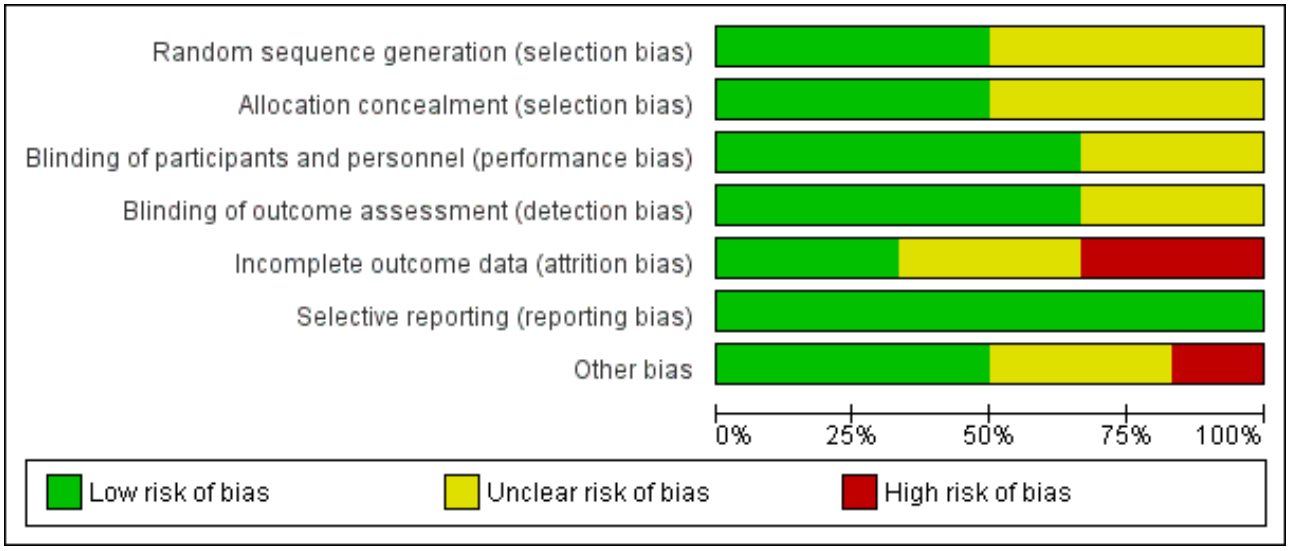


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We judged that three of the included studies had a low risk of bias with regards to random sequence generation (Glauser 2000; Pina-Garza 2005; French 2014). One study specified that a pseudo-random number generator was used (French 2014); whilst another study stated use of a computer-generated schedule for randomisation (Glauser 2000). The third study claimed that randomisation was automated by an interactive voice response system which automated the successful randomisation of participants (Pina-Garza 2005).

Similarly, we assessed these three studies to be at low risk of bias, resulting from allocation concealment (Glauser 2000; Pina-Garza 2005; French 2014). Two studies used an interactive voice response system which guarantees allocation concealment (Pina-Garza 2005; French 2014). The other study employed a phone call system were the investigator would call the central office for allocation of a participant, again ensuring allocation concealment (Glauser 2000).

We determined the other three studies to be at unclear risk of bias across the two selection bias domains — random sequence generation and allocation concealment — as no information regarding either domain was provided by the study publications (Barcs 2000; Kraiprab 2005; NCT00975715).

Blinding

We assessed that four of the included studies were at low risk of performance and detection bias (Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014). Three of the studies used matching placebo, achieved by using capsules and tablets identical in appearance to the active oxcarbazepine tablets (Glauser 2000; Kraiprab 2005; French 2014). For these three studies, participants were required to keep a seizure diary and therefore acted as the outcome assessors (Glauser 2000; Kraiprab 2005; French 2014). Given the successful blinding of both participants and personnel, specifically those responsible for data entry and analysis ensured by the matching placebo, we judged that outcome assessment would be effectively blinded. For this reason, we judged that these three studies were at low risk of both performance and detection bias (Glauser 2000; Kraiprab 2005; French 2014).

The fourth study did not use any blinding method but the participants involved in the study were all below the age of four so we agreed that blinding was unlikely to influence the responsiveness of this population of participants (Pina-Garza 2005). Accordingly, we awarded the study a low risk of bias judgement for performance bias. With regards to outcome assessment, an independent paediatric neurologist, not otherwise involved in the study, assessed and recorded seizures. Consequently, we also judged this study to be at low risk of detection bias (Pina-Garza 2005).

No information regarding the blinding of either participants or of outcome assessors was provided by a further two of the study publications (Barcs 2000; NCT00975715). Notably, Barcs 2000 included adult participants and NCT00975715 included children up to the age of 14 who could have been affected by a lack of or inadequate blinding. We thus assessed that these two studies were at unclear risk of bias for the two domains of performance bias and detection bias.

Incomplete outcome data

Although five of the included studies utilised a modified intention-to-treat population for their efficacy analysis and all fully reported attrition (Barcs 2000; Glauser 2000; Pina-Garza 2005; French 2014; NCT00975715), we only rated one of these studies to be at low risk of attrition bias (Pina-Garza 2005). The study by Pina-Garza 2005 featured an overall attrition rate of 10.2% and the attrition was evenly distributed between the two treatment groups — high-dose and low-dose oxcarbazepine. In contrast two of the studies, Barcs 2000 and French 2014, reported very high attrition rates overall (42.5% and 32.2%, respectively). Most notably, the rate of attrition was not evenly distributed between the treatment groups. In both studies, the attrition rate was considerably higher in the highest oxcarbazepine dose group. For example in the study by Barcs 2000, the attrition rate was 73.6% for the treatment group receiving 2400

mg/d oxcarbazepine compared to 22.5% in the group given the lowest dose, 600 mg/d oxcarbazepine. Additionally, French 2014 employed a highly modified intention-to-treat population for their efficacy analyses which excluded nearly 8% of the study population from their subsequent analyses. As a result we judged that both Barcs 2000 and French 2014 were at high risk of attrition bias.

Furthermore, in both Barcs 2000 and French 2014 approximately a quarter of the participants who were randomised to the highest dose treatment group (2400 mg/d oxcarbazepine) actually received a lower dose of 1800 mg/d oxcarbazepine after being down-titrated. As a consequence, the data reported regarding the tolerability and efficacy of 2400 mg/d oxcarbazepine is likely misrepresented, and could potentially be regarded as misleading.

The remaining two studies, Glauser 2000 and NCT00975715, had acceptable study attrition rates — 11.6% and 10.1% attrition, respectively. Attrition was not evenly distributed between the two treatment groups in either study, however. In the study by Glauser 2000, the attrition rate for the oxcarbazepine treatment group was double that of the placebo treatment group. For the NCT00975715 study, the rate of attrition was nine times higher in the oxcarbazepine group than in the placebo group (nine versus one participant). For both studies the attrition rate remained below 20%, even in the oxcarbazepine treatment group (Glauser 2000; NCT00975715). For this reason we judged the two studies to be at unclear risk of bias, rather than at high risk of bias (Glauser 2000; NCT00975715).

Despite not conducting an intention-to-treat efficacy analysis, we deemed the study by Kraiprab 2005 to be at low risk of attrition bias. Kraiprab 2005 conducted a 'per protocol' analysis, rather than an intention-to-treat analysis. This, however, only excluded four participants from the study analyses. The overall attrition rate for this study was relatively low (10.3%) and was evenly distributed between treatment groups. Furthermore, we were able to reinstate the excluded participants in our intention-to-treat analysis conducted in this review and, therefore, the attrition did not influence our findings or conclusions. As a result, we assessed the risk of attrition bias as low for Kraiprab 2005.

Selective reporting

We judged all six included studies to be at low risk of reporting bias (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014; NCT00975715). Although we were unable to retrieve trial protocols for any of the studies, the outcomes defined in the Methods section for each of the five published studies were all clearly and fully reported in the respective Results sections (Figure 4) (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014). Similarly for the NCT00975715 study, the results of the outcomes defined under the 'study details' of the relevant ClinicalTrials.gov web page were then fully reported under the 'Results' tab. We therefore had no reason to suspect reporting bias in either instance.

Figure 4. ORBIT Matrix for primary, secondary and harm (safety) outcomes to investigate reporting bias

		Study ID (Author, date of publication)						
		Barcs 2000	French 2014	Glauser 2000	Kraiprab 2005	NCT0097-5715	Pina-Garza 2005	Rey 2004*
Review primary outcomes	Median per cent reduction in seizure frequency	✓	✓	✓	✓	○(E)	✓	✱(H)
	50% or greater reduction in seizure frequency	✓	✓	✓	✓	✓	✓	✱(H)
Review harm outcomes	Ataxia	✓	✗(T1)	✓	✓	✓	✓	✱(S2)
	Dizziness	✓	✓	✓	✓	✗(T1)	✗(T1)	✱(S2)
	Fatigue	✓	✓	✓	✓	✗(T1)	✗(T1)	✱(S2)
	Nausea	✓	✓	✓	✓	✓	✗(T1)	✱(S2)
	Somnolence	✓	✓	✓	✓	✓	✓	✱(S2)
	Headache	✓	✓	✓	✓	✗(T1)	✗(T1)	✱(S2)
	Hyponatraemia	✓	✓	✓	✓	✓	✓	✱(S2)
	Vertigo	✓	✗(T1)	✗(T1)	✗(T1)	✓	✗(T1)	✱(S2)
	Diplopia	✓	✓	✓	✓	✓	✗(T1)	✱(S2)
	Rash	✗(T1)	✗(T1)	✓	✓	✓	✗(T1)	✱(S2)
	Tremor	✓	✗(T1)	✗(T1)	✗(T1)	✗(T1)	✗(T1)	✱(S2)
	Pyrexia	✗	✗(T1)	✓	✗(T1)	✓	✓	✱(S2)
	Abnormal gait	✓	✗(T1)	✓	✗(T1)	✗(T1)	✗(T1)	✱(S2)
	Abdominal pain	✓	✗(T1)	✓	✗(T1)	✗(T1)	✗(T1)	✱(S2)
	Nystagmus	✓	✗(T1)	✓	✗(T1)	✗(T1)	✗(T1)	✱(S2)
	Viral infection	✓	✗(T1)	✓	✗(T1)	✗(T1)	✗(T1)	✱(S2)
	Vomiting	✓	✓	✓	✓	✓	✓	✱(S2)
	Abnormal vision	✓	✗(T1)	✓	✓	✗(T1)	✗(T1)	✱(S2)
	Upper respiratory tract infection	✗(T1)	✗(T1)	✓	✗(T1)	✓	✗(T1)	✱(S2)
Review secondary outcomes	Seizure freedom	✓	✓	✓	✓	✗(G)	✓	✱(H)
	Treatment withdrawal	✓	✓	✓	✓	✓	✓	✱(H)
	Cognitive effects	✱(I)	✱(I)	✱(I)	✱(I)	✱(I)	✱(I)	✱(I)
	Quality of life	✱(I)	✓	✱(I)	✱(I)	✱(I)	✱(I)	✱(I)

* Excluded study

✗ Outcome not reported; ○ Outcome partially reported; ✓ Outcome fully reported; ✱ Outcome not measured;

(E) Clear that the outcome was measured. Judgment says outcome likely to have been analysed but not reported.

(G) Not mentioned but clinical judgment says unlikely to have been measured.

(H) Not mentioned but clinical judgment says unlikely to have been measured at all.

Figure 4. (Continued)

(H) Not mentioned but clinical judgment says unlikely to have been measured at all.

(I) Clear that the outcome was not measured.

(S2) No harm outcomes mentioned or reported. Clinical judgment says likely measured and compared across treatment groups.

(T1) Specific harm not mentioned but all other specific harms fully reported. Clinical judgment says likely measured but no events.

Other potential sources of bias

We determined that three of the included studies were free of any other sources of bias (Barcs 2000; Kraiprab 2005; French 2014). We therefore awarded these three studies a low risk of bias rating for this domain.

By contrast, we rated the NCT00975715 study as being at an unclear risk of bias regarding other sources of bias. We do not have a full, detailed publication for this study, hence we are unable to either identify or dismiss any other potential sources of bias. We also assessed Glauser 2000 to be at unclear risk of other bias because the range of doses used was notably different to the target dose specified in the Methods section. Specifically, the lowest dose used was 6.4 mg/kg/d which is dramatically lower than the 30 mg/kg/d suggested dose. Additionally, we assessed the study by Pina-Garza 2005 to be at high risk of other potential sources of bias due to the significantly longer treatment period noted for the high-dose oxcarbazepine group, compared to the low-dose oxcarbazepine group.

Effects of interventions

See: **Summary of findings for the main comparison** Oxcarbazepine compared to control for drug-resistant focal epilepsy

Importantly, for the purposes of our analyses in this review we reinstated any participants that had previously been excluded from the analyses conducted within the original trial publications to fully adhere to the intention-to-treat population principle. Within the trial publications, modified intention-to-treat populations had been implemented which incorrectly excluded participants who would normally be eligible for inclusion in intention-to-treat analyses. Unless specified, a fixed-effect model was used for the analyses performed. In instances where we identified significant heterogeneity, we used a random-effects model; this is declared in the text below.

A summary of the most important outcomes for the main comparison, oxcarbazepine versus control, are presented in the Summary of findings for the main comparison. For the purposes of this comparison, control treatment could be placebo, an alternative antiepileptic drug, or a different dose of oxcarbazepine. Specifically, for the studies included in this review the control treatment was either placebo or a different dose of oxcarbazepine. We did not identify any eligible studies that compared oxcarbazepine to an alternative antiepileptic drug. For this comparison, we pooled all data regardless of dose of oxcarbazepine used, age of participants, or treatment duration.

Subsequent to completing the meta-analysis for the main comparison, we then considered how these variables might have affected the effect size estimates and whether these variables were possible sources of heterogeneity by conducting various subgroup analyses. Based on the study data collected, we stratified data for the subgroup analyses according to: control group used (placebo and alternative oxcarbazepine dose subgroups); age group included (adults and children); duration of treatment period (8 weeks or less, 16 weeks, and 26 weeks); and oxcarbazepine dose (600 mg, 1200 mg, and 2400 mg oxcarbazepine).

Median percentage seizure reduction per 28 days

Median values cannot be incorporated into a meta-analysis. As a result the outcome — median percentage seizure reduction — must be described narratively. Five studies, consisting of 1494 participants, reported median percentage seizure reduction per 28 days for participants randomised to oxcarbazepine (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014). The median percentage seizure reduction for participants randomised to placebo add-on treatment was reported by three studies (Barcs 2000; Glauser 2000; French 2014). The values reported ranged from 7.6% to 28.7% seizure reduction, with two of the three studies specifically reporting percentage reductions of less than 10% (Barcs 2000; Glauser 2000). The median percentage seizure reduction for participants randomised to experimental oxcarbazepine treatment ranged from 26% to 83.3%. Notably, in studies which tested multiple doses of oxcarbazepine (Barcs 2000; Kraiprab 2005; Pina-Garza 2005; French 2014), the higher doses were associated with a greater median percentage reduction in seizure frequency. For example in the Barcs 2000 study, the median percentage seizure reductions were 26%, 40% and 50% for participants allocated to 600 mg/d, 1200 mg/d and 2400 mg/d oxcarbazepine, respectively. Importantly, for each study that described this outcome the median percentage seizure reduction reported was consistently higher in experimental oxcarbazepine treatment group than in the control group.

50% or greater reduction in seizure frequency

All six studies (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014; NCT00975715), involving 1593 participants, contributed to Analysis 1.1. We detected significant heterogeneity within the data set (P = 0.006, I^2 = 70%) and consequently used a random-effects model to combine the data. The responder rate was significantly higher in the experimental oxcarbazepine group, compared to the control group (RR 1.80, 95% CI 1.27 to 2.56, P < 0.001). We completed subgroup analysis stratified by the nature of the control group (Analysis 2.1); the age of the clinical sample (Analysis 3.1); the duration of the treatment period (Analysis 4.1); and the dose of experimental oxcarbazepine (Analysis 5.1).

Subgroup analyses stratified by the type of control group (P = 0.03, I^2 = 79.8%; Analysis 2.1) and by the duration of the treatment

period (P = 0.01, I^2 = 77.9%; Analysis 4.1) demonstrated a significant subgroup effect for the responder rate. This implies that both the type of control group used and the duration of the treatment period might explain some of the statistical heterogeneity observed. Interestingly, a substantial amount of statistical heterogeneity remained despite stratifying the data according to the clinical and design-dependent subgroups. With respect to the control group used, a much larger, statistically significant treatment effect was observed in studies utilising a placebo-controlled design (RR 2.09, 95% CI 1.69 to 2.59, P < 0.001) compared to the insignificant effect observed in studies using an alternative-dose-controlled study design (RR 1.36, 95% CI 0.99 to 1.86, P = 0.06; Analysis 2.1). Notably, only two small-sample studies contributed data to the alternative-dose-controlled subgroup. The results between the two studies were nevertheless very consistent. Specifically, the magnitude of the effect size observed was much greater with a treatment period of 26 weeks (RR 3.09, 95% CI 2.06 to 4.64, P < 0.001) than with a treatment period of 16 weeks or less (RR 1.51, 95% CI 1.20 to 1.92, P < 0.001; Analysis 4.1). It should be noted, however, that the data for the 26-week duration subgroup was taken from a single study (Barcs 2000). Subgroup analysis stratified by the age of participants did not reveal a significant subgroup effect (P = 0.49) (Analysis 3.1). Although it was not possible to conduct a test for subgroup differences for Analysis 5.1 (subgroup analysis stratified by the dose of experimental oxcarbazepine used), the magnitude of change in risk ratios between doses was not sufficiently great. Notably, the confidence intervals for each risk ratio calculated considerably overlapped and there was no clear clustering of data points for each subgroup. This suggests that there is not a dose-dependent subgroup effect for the outcome of 50% or greater reduction in seizure frequency.

Adverse effects

We investigated the incidence rate of 19 different adverse effects. There was no statistically significant difference in the incidence of 11 of the suggested adverse effects detected between participants randomised to the experimental oxcarbazepine group and those randomised to the control group. The 11 adverse effects were: ataxia (Analysis 1.2), nausea (Analysis 1.5), headache (Analysis 1.7), hyponatraemia (Analysis 1.8), rash (Analysis 1.11), tremor (Analysis 1.12), pyrexia (Analysis 1.13), abdominal pain (Analysis 1.15), viral infection (Analysis 1.17), abnormal vision (Analysis 1.19), and upper respiratory tract infection (Analysis 1.20).

The remaining eight adverse effects investigated are described below.

1. Dizziness was reported in four studies, consisting of 1336 participants (Analysis 1.3). The incidence of dizziness was significantly greater in the experimental oxcarbazepine group compared to the control group (RR 2.58, 99% CI 1.81 to 3.68, P < 0.001).
2. Fatigue was reported in four studies, consisting of 1336 participants (Analysis 1.4). The incidence of fatigue was significantly higher in the experimental oxcarbazepine group than in the control group (RR 1.88, 99% CI 1.07 to 3.32, P = 0.004).
3. Somnolence was reported by all six studies, involving a total of 1593 participants (Analysis 1.6). Significant heterogeneity (P = 0.03, I^2 = 59%) was detected within the data set. Consequently, a random-effects model was used for the analysis. Participants in the experimental oxcarbazepine group were twice as likely to experience somnolence as participants in the control group (RR 2.03, 99% CI 1.17 to 3.54, P = 0.001).
4. Vertigo was reported in two studies, involving 793 participants (Analysis 1.9). Participants in the experimental oxcarbazepine group were over four times more likely to experience vertigo than those in the control group (RR 4.62, 99% CI 1.32 to 16.13, P = 0.002).
5. Diplopia was reported by five studies, including 1465 participants (Analysis 1.10). Participants in the experimental oxcarbazepine group were over five times more at risk of experiencing diplopia than those in the control group (RR 5.50, 99% CI 2.83 to 10.68, P < 0.001).
6. Abnormal gait was reported by only two studies with 961 participants included in the analysis (Analysis 1.14). Participants in the experimental oxcarbazepine group were over five times more likely to experience abnormal gait changes than those in the control group (RR 5.53, 99% CI 1.74 to 17.61, P < 0.001).
7. Nystagmus was reported by two studies, involving 961 participants (Analysis 1.16). The incidence of nystagmus was over four times greater in the experimental oxcarbazepine group than in the control group (RR 4.56, 99% CI 1.90 to 10.94, P < 0.001).
8. Vomiting was reported in all six studies, including a total of 1593 participants (Analysis 1.18). Significant heterogeneity (P = 0.06, I^2 = 54%) was detected within the data set. A random-effects model was, therefore, used for the analysis. Participants receiving experimental oxcarbazepine treatment were significantly more likely to experience vomiting than participants receiving control treatment (RR 2.55, 99% CI 1.20 to 5.42, P = 0.001).

Seizure freedom

Five of the included studies involving 1494 participants contributed to the following outcome analysis (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014). Significant heterogeneity was detected within the data set (P = 0.08, I^2 = 51%); therefore, we utilised a random-effects model for the outcome analysis. Participants randomised to the experimental oxcarbazepine group were nearly three times more likely to attain seizure freedom than were participants randomised to a control group (RR 2.86, 95% CI 1.19 to 6.87, P = 0.02).

We conducted multiple subgroup analyses to explore the possible reasons for the observed heterogeneity. Subgroup analysis stratified by control group, specifically whether the study was placebo-controlled or alternative-dose-controlled, displayed significant heterogeneity between the two subgroups (P = 0.02, I^2 = 81.1%, Analysis 2.2). Notably, in placebo-controlled studies participants receiving oxcarbazepine were six times more likely to achieve seizure freedom than participants receiving placebo (RR 6.14, 95% CI 2.62 to 14.41, P < 0.01). In contrast, a significant difference in the likelihood of achieving seizure freedom was not detected between participants receiving high-dose versus low-dose oxcarbazepine in alternative-dose-controlled studies (RR 1.45, 95% CI 0.58 to 3.62, P = 0.08).

Subgroup analysis stratified by age of study population (P = 0.10; Analysis 3.2) and duration of treatment period (P = 0.08; Analysis 4.2) did not display a significant subgroup effect for the outcome 'seizure freedom'. Despite this, the risk ratio calculated for adults (RR 5.19, 95% CI 2.29 to 11.75) was notably larger compared

to that calculated for children (RR 2.16, 95% CI 1.13 to 4.14). Likewise, within the treatment period subgroup analysis, 26 weeks' treatment period demonstrated a much larger treatment effect (RR 20.26, 95% CI 2.83 to 145.02) for oxcarbazepine compared to placebo over the shorter treatment duration lengths (8 weeks or less: RR 1.90, 95% CI 0.96 to 3.76; 16 weeks: RR 2.41, 95% CI 1.05 to 5.52). Specifically, Barcs 2000 was the only study to supply data to the 26-week treatment period subgroup and was also one of only three studies to contribute data to the adult subgroup. Barcs 2000 predicted a very large risk ratio (RR 20.26, 95% CI 2.83 to 145.02) which most likely skewed the adult subgroup. Whilst it is clear that this result is an outlier compared to the other results within the adult subgroup, it is still worth considering that adults could potentially respond better to oxcarbazepine than children. Similar observation apply to treatment duration for seizure freedom.

Subgroup analysis stratified by dose of experimental oxcarbazepine did not demonstrate a clear effect of dose on the estimated effect (Analysis 5.2). Again, Barcs 2000 predicted much larger treatment effects, dependent on dose, compared to the other included studies in the subgroups. Due to the heterogeneity and inconsistency of the data within the individual dose subgroups, we did not consider that dose explained the heterogeneity observed across the entire dataset.

Treatment withdrawal

All six included studies (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; NCT00975715; French 2014), comprising 1593 participants, contributed to this outcome analysis. We did not detect significant heterogeneity (P = 0.55, I^2 = 0%) within this data set for the main comparison — oxcarbazepine versus control — and therefore we continued to utilise the fixed-effect model for this outcome analysis. Participants receiving experimental oxcarbazepine treatment were significantly more likely to withdraw from treatment. Specifically, participants receiving experimental oxcarbazepine were 75% more likely than participants receiving the control treatment to withdraw from treatment (RR 1.75, 95% CI 1.44 to 2.13, P < 0.001; Analysis 1.22).

Although we did not detect any statistical heterogeneity within the data set, we continued to conduct subgroup analysis to determine whether any undetected clinical or methodological heterogeneity might exist. Although we were unable to conduct the test for subgroup differences for the subgroup analysis stratified by the experimental dose of oxcarbazepine used (Analysis 5.3), due to the overlap in placebo participants between subgroups, we were able to identify clear differences between the subgroups, based on the risk ratios calculated. The rate of treatment withdrawal was significantly higher for participants randomised to both 1200 mg/d (RR 1.95, 95% CI 1.50 to 2.52, P < 0.001) and 2400 mg/d oxcarbazepine (RR 2.38, 95% CI 1.92 to 2.94, P < 0.001). Participants randomised to both treatment groups were approximately twice as likely to withdraw from treatment as those receiving placebo. On the other hand, the treatment withdrawal rates for participants receiving 600 mg/d oxcarbazepine and those receiving control were not significantly different (RR 0.79, 95% CI 0.55 to 1.15, P = 0.22).

Subgroup analysis stratified by the type of control group (P = 0.52; Analysis 2.3), the age of the clinical sample (P = 0.29; Analysis 3.3), and the duration of treatment period (P = 0.51; Analysis 4.3) did not display a significant subgroup effect for the outcome 'treatment withdrawal'.

Quality of life and cognitive effects

Only French 2014, involving 366 participants, measured and reported quality of life. French 2014 used the Quality of Life in Epilepsy (QOLIE-31) questionnaire which includes a subscale score for cognitive functioning. This enabled the study to assess both the quality of life of participants and, potentially, any perceived cognitive effects. French 2014 reported that the mean total QOLIE-31 and subscale scores did not decrease from baseline for any of the treatment groups: 1200 mg/d oxcarbazepine, 2400 mg/d oxcarbazepine, or placebo. This highlights that, most importantly, there was no decrease in quality of life resulting from active treatment. The 1200 mg/d treatment group did, however, demonstrate a significantly smaller increase in the QOLIE-31 subscale of Cognitive Functioning. Additionally, there was a significantly smaller increase in the Medication Effects for both the 1200 mg/d oxcarbazepine and 2400 mg/d oxcarbazepine treatments groups, compared to placebo.

DISCUSSION

Summary of main results

This review included data from six randomised controlled trials (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; French 2014; NCT00975715), involving a total of 1593 participants. We judged that three of the included studies were at unclear risk of bias (Glauser 2000; Kraiprab 2005; NCT00975715); and the other three were at high risk of bias (Barcs 2000; Pina-Garza 2005; French 2014). Most of the concerns about bias arose from the lack of details provided regarding the randomisation and allocation concealment of participants. There were also concerns about the high attrition rate noted in several of the studies. The attrition rate was especially problematic in the treatment groups receiving the higher doses of oxcarbazepine.

Treatment with oxcarbazepine was associated with an increased responder rate (the number of participants achieving a 50% or greater reduction in seizure frequency), as well as an increased incidence of seizure freedom compared to control treatment. Both of these outcomes were, however, derived from low-certainty evidence, according to GRADE assessment, meaning that we cannot be certain about the accuracy of these results. Interestingly, when the data were subjected to subgroup analyses, both outcomes were associated with a statistically significant subgroup effect when stratified by the type of control group utilised (placebo or alternative dose). Specifically, experimental oxcarbazepine was revealed to have a much greater treatment effect with regards to seizure freedom and responder rate when compared to placebo control rather than when compared to an alternative, lower dose of oxcarbazepine.

Additionally, the responder rate also demonstrated a significant subgroup effect when stratified by the duration of the treatment period. Oxcarbazepine given over the longest treatment period (26 weeks) demonstrated a much larger treatment effect size for responder rate than oxcarbazepine given over the shorter treatment periods. Importantly, however, Barcs 2000 was the only study which had a treatment period of 26 weeks and was, therefore, the only study to contribute data to this subgroup for the analysis. Although the study by Barcs 2000 contained a large sample size (694 participants), the fact that the subgroup analysis is derived from a single study should be considered when interpreting the results.

Of further significance, Barcs 2000 was also a placebo-controlled study. As previously described, subgroup analysis according to control group revealed that oxcarbazepine was shown to have a greater therapeutic effect when compared to placebo, and therefore it is possible that these two trial characteristics — the nature of the control group and the treatment duration — could be confounding the results between the two subgroup analyses (Barcs 2000; Pina-Garza 2005; French 2014).

With regards to tolerability, treatment with experimental oxcarbazepine increased the treatment withdrawal rate compared to that observed with control treatment. The evidence was of moderate certainty for this outcome, suggesting that this finding is likely to be accurate. Subgroup analyses for the outcome 'treatment withdrawal' revealed clear differences in the treatment effect predicted for subgroups when the data were stratified according to dose of experimental oxcarbazepine. The largest oxcarbazepine dose, 2400 mg/d, was associated with a larger treatment withdrawal rate compared to control than was 1200 mg/d or 600 mg/d oxcarbazepine. Treatment with experimental oxcarbazepine was furthermore associated with an increased incidence rate for several of the adverse effects included in the review, namely: dizziness, fatigue, somnolence, vertigo, diplopia, abnormal gait, nystagmus, and vomiting.

Notably, we analysed data for a total of 19 adverse effects and consequently the likelihood of type I and type II statistical errors occurring was significantly increased. Although care must therefore be taken when interpreting the results, the findings regarding the adverse effects are consistent with the increased treatment withdrawal rate observed. In short-term studies, treatment withdrawal most commonly relates to adverse effects experienced rather than reflecting a lack of efficacy. This consequently implies that the increased occurrence of adverse effects is a true effect of oxcarbazepine treatment.

To summarise, our review has indicated that oxcarbazepine may display a therapeutic effect, as demonstrated by the significantly increased responder and seizure freedom rate compared to control. Uncertainty about this finding arises, however, from the low-certainty evidence used to derive this finding. Our review has also highlighted issues with the tolerability of oxcarbazepine, specifically at higher dosages, which is reflected in the increased treatment withdrawal rate.

Overall completeness and applicability of evidence

As part of this review, we had hoped to explore the effect of oxcarbazepine on quality of life and cognition. Unfortunately, however, only one of the included studies investigated and reported quality of life (French 2014). Notably, the questionnaire used to assess quality of life did include an element whereby participants were asked to evaluate their own cognition; this clearly requires self-report, however, and is not a thorough examination of cognitive ability. As a result, we are not adequately informed to comment on the effects of oxcarbazepine on either outcome. A thorough neuropsychological assessment with more rigorous cognitive testing, focusing on assessing memory, attention and psychomotor speed, would be necessary to determine whether oxcarbazepine does impact cognitive function.

Separate from this, we had also specified that we would conduct multiple subgroup analyses to investigate any potential clinical or statistical heterogeneity. Given that only six studies were eligible for inclusion in the review originally, the splitting of data into subgroups may have led to some subgroups being underpowered. Some subgroups contained data from only one study, whilst other subgroups contained very low numbers of participants, despite including data from multiple studies. For this reason, caution is required when considering, or applying, any of the findings derived from the subgroup analyses performed in this review.

Certainty of the evidence

For this review, we assessed that three of the studies were at high risk of bias (Barcs 2000; Pina-Garza 2005; French 2014); and the other three studies were at unclear risk of bias (Glauser 2000; Kraiprab 2005; NCT00975715). Three studies failed to provide specific information regarding the method for randomisation and allocation concealment (Glauser 2000; Kraiprab 2005; NCT00975715). A further two studies did not describe how effective blinding was achieved and maintained (Barcs 2000; NCT00975715). There were additional concerns regarding attrition bias. We rated two of the studies as being at high risk of attrition bias, as they both had attrition rates that well exceeded 20% of the randomised population (Barcs 2000; French 2014). By contrast, we deemed another two studies to be at unclear of risk of attrition bias because the attrition rate was below 20% of the randomised population, but was not balanced across the treatment groups (Glauser 2000; NCT00975715).

The serious risk of bias, detected across the studies, led to us downgrading the certainty of evidence to moderate certainty for each of the outcomes included in the GRADE assessment. We rated the evidence as moderate certainty both for the incidence of treatment withdrawal and for the incidence of the adverse effects 'ataxia' and 'hyponatraemia', meaning that we are fairly certain that the conclusions made regarding these outcomes are accurate. Further concerns about the significant statistical heterogeneity detected across the data set for the efficacy outcomes 'responder rate' and 'seizure freedom' resulted in the certainty of evidence being downgraded again to low certainty for these two outcomes. Notably, seizure freedom was downgraded again due to imprecision, based on the sub-optimal number of events constituting the analysis, but was upgraded back to low certainty because of the large effect size recognised. Similarly, the certainty of evidence for the adverse effects 'nausea' and 'somnolence' were further downgraded to very low and low, respectively, due to serious statistically significant heterogeneity and imprecision.

For the outcomes for which the evidence was rated as either low or very low certainty, this means that we are less certain that the effect size calculated, and consequently the conclusions reached, are accurate about the true effect of oxcarbazepine.

Potential biases in the review process

During the screening process, we recognised several studies that appeared to be eligible for inclusion in the review (CTRI/2010/091/000100; CTRI/2010/091/001194; CTRI/2010/091/006085). We were unable to obtain the data or methodological details for the trials, however, despite contacting the relevant authors and pharmaceutical companies. Consequently, we could not assess these studies for inclusion and they are therefore listed in the Studies awaiting classification

section of the text. Additional data would have strengthened the review and improved the robustness of the subgroup analysis. Importantly, additional data could also potentially change the conclusions of the review and, therefore, the missing studies must be regarded as a weakness of this review. Future updates of this review should seek whether the results of these trials have yet been published.

We similarly contacted the study authors and sponsoring pharmaceutical companies of the studies included in the review to request the associated trial protocols. Unfortunately, we were only supplied with the trial protocol for Pina-Garza 2005. This was especially problematic for the NCT00975715 trial, for which the results have not been formally published. This meant that we had limited information regarding the methodological design of the trial. We could have gained this information from the trial protocol, had it been provided.

Another potential issue with this review was alluded to earlier. In this review, we assessed and analysed numerous outcomes. Conducting multiple statistical comparisons increases the risk of type I and type II statistical errors occurring. Additionally, multiple subgroup analyses were also performed which were all largely underpowered. It is therefore possible that some of the conclusions described could be inaccurate, despite displaying statistical significance, as a result of these type I and type II errors. In future revisions of this review, it would be advisable to limit the number of outcomes measured, and impose restrictions on when a subgroup analysis can be conducted, to improve the reliability of these statistical assessments.

Agreements and disagreements with other studies or reviews

Multiple other reviews have similarly reported that oxcarbazepine is efficacious at reducing seizure frequency in drug-resistant epilepsy (Kalis 2001; Bang 2003; Saconato 2009). Specifically, the review by Bang 2003 stated that 20% to 54% of trial participants experience a 50% of greater reduction in seizure frequency whilst receiving oxcarbazepine. Comparably in our review, across the six studies we analysed we found that 23% to 59% of participants experience 50% or greater seizure reduction when randomised to oxcarbazepine. Notably, however, the review by Bang 2003 was a narrative summary of data which collected from four studies, including three non-comparative studies, and was not a meta-analysis.

In contrast, the review by Saconato 2009 did include a meta-analysis of data extracted from four randomised controlled trials to investigate oxcarbazepine for drug-resistant epilepsy. Saconato 2009 similarly emphasised that significantly more participants achieved a 50% or greater reduction in seizure frequency when receiving oxcarbazepine compared to when receiving placebo. During the meta-analysis, however, Saconato 2009 detected an increase in the risk ratio for 50% or greater seizure reduction responder rate with increased dosages of oxcarbazepine (600 mg/d: RR 2.11, 95% CI 1.32 to 3.35; 1200 mg/d: RR 3.24, 95% CI 2.11 to 4.98; 2400 mg/d: RR 3.83; 95% CI 2.59 to 5.97). In our own subgroup analysis according to dosage, we observed that the risk ratio for 50% or greater seizure reduction remained around 2.00, regardless of oxcarbazepine dose; thus we were unable to replicate their finding in our current review.

Importantly, in their review the calculated risk ratios only included data from one study which consisted of a purely adult study population: namely, the RCT by Barcs 2000, which was also included in our current review. In our review, we have included data from up to three studies for each of the subgroups during the subgroup analysis, stratified by dose of experimental oxcarbazepine. Furthermore, with our review being more recently published, it contains more up-to-date evidence for the effect of oxcarbazepine. Specifically, our review contains the latest publication by French 2014, which would not have been available at the time of publication for Saconato 2009. As a result, our calculated risk ratios should provide a more robust and accurate estimation of the oxcarbazepine treatment effect as it incorporates more data from multiple sources.

Similarly, the risk ratios for seizure freedom (1200 mg/d: RR 17.59, 95% CI 2.37 to 130.35; 2400 mg/d: RR 25.41, 95% CI 6.26 to 103.10), calculated by Saconato 2009, were much greater than those reported here. Again, they mainly relied upon data extracted from Barcs 2000 with only the risk ratio calculated for the highest oxcarbazepine dose (2400 mg/d) including data from an additional smaller study. Notably, one of the RCTs included in the meta-analysis by Saconato 2009 utilised oxcarbazepine as a monotherapy rather than as an adjunctive therapy, which could further explain any observed differences in our reported findings.

The review by Saconato 2009 did, however, comment that the trials which were included in the meta-analysis were of medium to poor methodological quality. Saconato 2009 likewise highlighted the lack of methodological details regarding random sequence generation and allocation concealment which led to their judgement. Similarly in this review, there was an issue with the quality and certainty of studies, such that we judged all of the included studies to be at either a high or unclear risk of bias, which is a partial reflection of methodological quality.

In contrast to our review, many other reviews and long-term extension studies report that oxcarbazepine is well tolerated (Beydoun 2002; Walker 2002; Bang 2003). Many reviews specifically emphasise the increased tolerability of oxcarbazepine compared to carbamazepine, the molecule from which oxcarbazepine is structurally derived (Krämer 2000; Arroyo 2001; Kalis 2001; Horga de la Parte 2006). This mainly appears to be due to the reduced potential for drug interactions, resulting from enzyme induction, noted with oxcarbazepine (Kalis 2001). In this review, we have instead highlighted issues with the tolerability of oxcarbazepine, especially when participants are titrated to the higher doses. Notably, treatment withdrawal was less problematic and less prevalent in the lower oxcarbazepine dose subgroups.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides limited information about the efficacy and tolerability of oxcarbazepine as an add-on therapy for people with drug-resistant focal epilepsy. Although the evidence presented here did demonstrate that oxcarbazepine effectively reduces seizure frequency, the evidence for this outcome was of low certainty. Consequently, we cannot be certain that this finding is accurate. By contrast, with regards to tolerability the evidence for treatment withdrawal was of moderate certainty, and thus should be a fairly accurate estimate of the true effect of oxcarbazepine.

This review revealed an increased treatment withdrawal rate for participants who receive oxcarbazepine compared to those who receive control. Moreover, people receiving oxcarbazepine were shown to be more at risk of experiencing several different adverse effects.

We suspect that there are issues with the tolerability of oxcarbazepine that are especially prevalent at the higher doses of oxcarbazepine. We observed higher treatment withdrawal rates with increased oxcarbazepine dose. Of further importance, as we have highlighted in Incomplete outcome data (attrition bias) subsection, tolerability could be underestimated for the highest dose of oxcarbazepine (2400 mg/d), due to the down-titration of approximately a quarter of randomised participants from 2400 mg/d to 1800 mg/d. Consequently, we are unable to provide a reliable interpretation of the tolerability of oxcarbazepine at the highest dose but infer that there are serious issues with tolerability at 2400 mg/d oxcarbazepine.

Implications for research

Additional studies are necessary to correctly inform clinical practice. Specifically, we require more clinical trials which investigate multiple doses of oxcarbazepine to be conducted and which vary in treatment duration and type of control group. The data from these trials could then be incorporated into an updated review in order to adequately power the subgroup analyses presented here. Additional studies incorporating multiple doses are especially important to resolve whether the concerns regarding tolerability are notable with all doses of oxcarbazepine or are solely a feature of the higher doses of oxcarbazepine. Longer-term trials are also desirable as they are able to assess the long-term tolerability of drugs, and can further establish whether drug tolerance develops.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Barcs 2000

Methods	**Study design**

Barcs 2000 *(Continued)*

	Randomised, double-blind, PBO-controlled, 4-arm, parallel-group, multi-centre (73 centres, 11 countries) **Duration** 1. Prospective baseline period (8 weeks) 2. Treatment period with titration (2-week up-titration, 24-week maintenance) 3. 2-week tapering period or entry into open-label extension
Participants	**Randomised population** OXC 600 mg/d: 169 OXC 1200 mg/d: 178 OXC 2400 mg/d: 174 PBO: 173 **ITT population** OXC 600 mg/d: 168 OXC 1200 mg/d: 177 OXC 2400 mg/d: 174 PBO: 173 **Safety population** OXC 600 mg/d: 168 OXC 1200 mg/d: 177 OXC 2400 mg/d: 174 PBO: 173 **No. of participants excluded from analyses** OXC 600 mg/d group: 1 OXC 1200 mg/d group: 1 Excluded due to premature discontinuation before taking any trial medication **Age (mean and range)** ≥ 15 to 65 years OXC 600 mg/d = 34.6 (15 to 65) OXC 1200 mg/d = 33.8 (16 to 64) OXC 2400 mg/d = 35.2 (15 to 66) PBO = 34.3 (15 to 65) **Gender, male, n (%)** OXC 600 mg/d = 86 (51.2) OXC 1200 mg/d = 80 (45.2)

Barcs 2000 *(Continued)*

	OXC 2400 mg/d = 98 (56.3) PBO = 77 (44.5) **Types of seizure** Uncontrolled focal-onset seizures (simple, complex, or focal seizures evolving to secondarily generalised seizures) **Seizure frequency during baseline (median)** OXC 600 mg/d = 9.6 OXC 1200 mg/d = 9.8 OXC 2400 mg/d = 10.0 PBO = 8.6
Interventions	OXC 600 mg/d (twice daily) OXC 1200 mg/d (twice daily) OXC 2400 mg/d (twice daily) PBO (twice daily)
Outcomes	**Primary outcome** 1. Percentage reduction in seizure frequency per 28 days during the treatment period relative to baseline. **Secondary outcomes** 1. Responder rate (≥ 50% reduction in seizure frequency in the treatment period relative to baseline). **Safety and tolerability outcomes** 1. Physical and neurologic examination 2. Vital signs 3. Laboratory tests 4. Adverse events (AEs)
Notes	Sponsored by Novartis Pharma AG and conducted on behalf of International Oxcarbazepine (OT/PE1) Study Group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation was not provided
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment was not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: method of blinding participants and personnel was not provided

Barcs 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Patients kept a diary throughout the maintenance period and recorded the date and time of each seizure." Comment: method of blinding for participants, and therefore outcome assessors, is not provided. No other information regarding the blinding of outcome assessors specifically was provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote from table: “[OXC 2400 mg/d treatment group] Includes 47 patients treated with OXC 1800 mg/d; 43 of the 47 patients were randomized directly to OXC 1800 mg/d, and 4 of the 47 patients were reduced from OXC 2400 to OXC 1800 mg/d. Twelve of 46 patients in the OXC 2400 mg/d group, who completed the trial, were treated with OXC 1800 mg/d” Quote from text: "A protocol amendment was prepared to allow for a blinded reduction to 1800 mg/d OXC in the 2400 mg/d OXC treatment group either directly after randomization or on the occurrence of tolerability problems or AEs... For the primary efficacy variable, no distinction was made between patients who received 2400 mg/d OXC and those who received 1800 mg/d OXC after implementation of the amendment, because these two doses still formed a distinct randomized group; the subdivision was not subject to randomization." Comment: modified intention-to-treat analysis performed and attrition reported; however, study had an attrition rate of 42.5%. Highest attrition rate (73.5%) was reported for the 2400 mg/d oxcarbazepine treatment group. Additionally, categorising data from participants receiving 1800 mg/d under the 2400 mg/d treatment group provides unreliable and misleading data regarding the tolerance and efficacy of OXC at the 2400 mg dose level.
Selective reporting (reporting bias)	Low risk	Comment: protocol was not provided; however, all outcomes defined in Methods were reported in Results
Other bias	Low risk	Comment: none detected

French 2014

Methods	**Study design** Randomised, double-blind, PBO-controlled, parallel-group, multi-centre (88 centres, 8 countries: USA, Mexico, Canada, Russia, Poland, Bulgaria, Croatia, Romania) **Duration** 1. Prospective baseline period (8 weeks) 2. Treatment period with titration (4-week titration, 12-week maintenance period) 3. 3-week blinded conversion period to open-label treatment or tapering to baseline therapy
Participants	**Randomised population** OXC 1200 mg/d: 122 OXC 2400 mg/d: 123 PBO: 121 **ITT population** OXC 1200 mg/d: 109 OXC 2400 mg/d: 111

French 2014 *(Continued)*

	PBO: 117 **Safety population** OXC 1200 mg/d: 122 OXC 2400 mg/d: 123 PBO: 121 **No. of participants excluded from analyses** OXC 1200 mg/d group: 13 OXC 2400 mg/d group: 11 PBO: 4 Excluded due to the absence of analysable data. **Age (mean ± SD)** ≥ 18 to 65 years OXC 1200 mg/d = 39.1 (11.5) OXC 2400 mg/d = 38.5 (11.6) PBO = 39.1 (12.5) **Gender, male, n (%)** OXC 1200 mg/d = 71 (58.2) OXC 2400 mg/d = 64 (52.0) PBO = 67 (55.4) **Types of seizure** Focal-onset seizures with or without secondary generalisation **Seizure frequency during baseline (median)** OXC 1200 mg/d = 6.0 OXC 2400 mg/d = 6.0 PBO = 7.0
Interventions	OXC 1200 mg/d (Once daily) OXC 2400 mg/d (Once daily) PBO (Once daily)
Outcomes	**Primary outcome** 1. Median percentage change in seizure frequency per 28 days during the 16-week treatment period relative to baseline. **Secondary outcomes** 1. Responder rate (≥ 50% reduction in seizure frequency in the treatment period relative to baseline) 2. Proportion of patients seizure free

French 2014 *(Continued)*

	3. Changes in PGIC and QOLIE-31 scores **Safety and tolerability outcomes** 1. Treatment emergent adverse events (TEAEs) 2. Physical and neurologic examination 3. Laboratory tests 4. Vital signs 5. ECG tracings
Notes	Sponsored by Supernus Pharmaceuticals Inc. Trial registration number: NCT00772603

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was managed by a centralized interactive voice response system, with the vendor using a pseudo-random number generator to produce study drug kit numbers for the randomization schedule."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was managed by a centralized interactive voice response system, with the vendor using a pseudo-random number generator to produce study drug kit numbers for the randomization schedule."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study drug blinding was maintained with identical 600-mg SPN-804 or placebo tablets and packaging in blister cards."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "During the double-blind treatment period, patients and all personnel involved with the study's conduct or interpretation remained blinded to study drug codes." Comment: participants were required to keep a seizure diary and therefore acted as the efficacy outcome assessors. Participants and personnel, including data analysts and statisticians, were effectively blinded by matching placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Efficacy was assessed in the intent-to-treat population with analyzable seizure data, that is, all randomized patients with seizure data for ≥21 consecutive days in the baseline phase who received at least one dose of study drug, had at least one on-treatment visit, and ≥14 consecutive days of seizure diary data after study drug receipt." Quote: "After week 4, study drug could be down-titrated if needed by discarding the last tablet on each blister pack row, thereby blindly reducing the dose only in the SPN-804 2400-mg group (reduced to 1800 mg/day)... Patients assigned to SPN-804 2400 mg who were down-titrated to 1800 mg/day were included in the 2400-mg group for all analyses.. .Of the 111 patients in the 2400-mg group with analyzable seizure data, 26 were patients in whom SPN-804 was downtitrated to 1800 mg/day." Comment: although intention-to-treat analysis was performed and attrition was reported, the strict intention-to-treat criteria do not comply with the 'once randomized, always analysed' mantra. Criteria led to the exclusion of 7.9% of the original randomised population from the analyses. The study also had a high attrition rate of 32.2%. Furthermore, data in this study from participants

French 2014 *(Continued)*

		receiving 1800 mg/d was categorised under the 2400 mg/d treatment group after they were down-titrated. This therefore provides unreliable and misleading data regarding the tolerance and efficacy of OXC at the 2400 mg dose level.
Selective reporting (reporting bias)	Low risk	Comment: protocol was not provided; however, all outcomes defined in methods were reported in results.
Other bias	Low risk	Comment: none detected

Glauser 2000

Methods	**Study design** Randomised, double-blind, PBO-controlled, parallel-group, multi-centre (47 centres, 8 countries: Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, and USA) **Duration** 1. Prospective baseline period (8 weeks) 2. Treatment period with titration (2-week titration, 14-week maintenance period) 3. Optional entry to open label extension
Participants	**Randomised population** OXC 30 to 46 mg/kg/d: 138 PBO: 129 **ITT population** OXC 30 to 46 mg/kg/d: 136 PBO: 128 **Safety population** OXC 30 to 46 mg/kg/d: 138 PBO: 129 **No. of participants excluded from analyses** OXC 30 to 46 mg/kg/d: 2 PBO: 1 Excluded due to premature discontinuation of treatment and absence of any seizure data **Age (mean and range)** ≥ 3 to 17 years OXC 30 to 46 mg/kg/d: 11 (3 to 17) PBO: 11 (3 to 17) **Gender, male, n (%)** OXC 30 to 46 mg/kg/d: 70 (51) PBO: 71 (55)

Glauser 2000 *(Continued)*

	Types of seizure: focal seizures (simple, complex, and focal seizures evolving to secondarily generalized seizures) **Seizure frequency during baseline (median and range)** OXC 30 to 46 mg/kg/d: 12 (3 to 1470) PBO: 13 (2 to 554)
Interventions	OXC 30 to 46 mg/kg/d (twice daily) PBO (twice daily)
Outcomes	**Primary outcome** 1. Percentage of reduction from baseline in FOS frequency per 28 days during treatment period **Secondary outcomes** 1. Responder rate (≥ 50% reduction from baseline in focal seizure frequency per 28 days during treatment) 2. Percentage change from baseline in secondarily generalized seizure frequency during treatment **Safety and tolerability outcomes** 1. Adverse events (AEs) 2. Vital signs 3. ECG tracings 4. Physical and neurologic examination 5. Laboratory tests
Notes	Sponsored by Novartis Pharmaceuticals Corporation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized (using a computer-generated schedule)"
Allocation concealment (selection bias)	Low risk	Quote: "allocation was made sequentially following a phone call to the central office."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "OXC and placebo were supplied to study centers as matching tablets of identical appearance for oral administration."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...patients or their parents/legal guardians maintained a diary in which they recorded seizure type and frequency." Comment: patients and their legal guardian were the efficacy outcome assessors and were adequately blinded by the matching tablets. Study personnel, including data analysts and statisticians, were also effectively blinded by the matching tablets.

Glauser 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: modified intention-to-treat analysis performed and attrition reported. The study had a low attrition rate overall; however, the attrition rate was unevenly distributed between treatment groups.
Selective reporting (reporting bias)	Low risk	Comment: protocol was not provided; however, all outcomes defined in Methods were reported in Results section
Other bias	Unclear risk	Quote: "Median daily dose of OXC administered during the Maintenance Period of the Double-blind Treatment Phase was 31.4 mg/kg/day (range: 6.4 to 51.4 mg/kg/day)." Comment: the range of doses, most noticeably the lowest value of the range, was outside of the target dose (30 to 46 mg/kg/d). The methods did, however, specify that all doses were permitted if they did not exceed the target randomised dose for the appropriate weight category.

Kraiprab 2005

Methods	**Study design** Randomised, double-blind, parallel-group, alternative dose-controlled, single centre (Thailand) **Duration** 1. Prospective baseline period (8 weeks) 2. Treatment period with titration (2-week titration, 14-week maintenance period) 3. Optional entry to open label extension
Participants	**Randomised population** OXC 1200 mg/d: 19 OXC 600 mg/d: 20 **Per-protocol population (used for efficacy analysis)** OXC 1200 mg/d: 17 OXC 600 mg/d 18 **Safety population** OXC 1200 mg/d: 19 OXC 600 mg/d: 20 **No. of participants excluded from analyses** OXC 1200 mg/d: 2 OXC 600 mg/d: 2 Excluded due to loss during follow-up and discontinuation due to AEs **Age (mean and range)** ≥ 18 to 65 years OXC 1200 mg/d: 31.7 ± 6.9

Kraiprab 2005 *(Continued)*

	OXC 600 mg/d: 30.4 ± 7.3 **Gender, male, n (%):** OXC 1200 mg/d: 8 (42) OXC 600 mg/d: 12 (60) **Types of seizure** Focal seizures (simple, complex, and focal seizures evolving to secondarily generalised seizures) **Seizure frequency during baseline (median (mean))** OXC 1200 mg/d: 4.0 (7.7) OXC 600 mg/d: 4.5 (7.6)
Interventions	OXC 1200 mg/d (twice daily) OXC 600 mg/d (twice daily)
Outcomes	**Primary outcome** 1. Percentage reduction from baseline in FOS frequency per 28 days during treatment period. **Secondary outcomes** 1. Responder rate (≥ 50% reduction from baseline in focal seizure frequency per 28 days during treatment). **Safety and tolerability outcomes** 1. Adverse events (AEs) 2. Physical and neurologic examination 3. Vital signs 4. Laboratory tests
Notes	Sponsored by Novartis Pharmaceuticals Corporation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information was provided about how patients were randomised
Allocation concealment (selection bias)	Unclear risk	Comment: no information was provided about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both medications were dispensed as identical appearing capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The frequency and seizure patterns of each patient were recorded by the patients themselves or by caregivers in a diary issued by the investigators" Comment: patients and caregivers therefore acted as the efficacy outcome assessors and were effectively blinded by identical capsules. Study personnel, in-

Kraiprab 2005 *(Continued)*

		cluding data analysts and statisticians, were also effectively blinded by identical capsules.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis was performed for the safety analysis but 'per protocol' was used for the efficacy analysis. 'Per protocol' only led to the exclusion of 2 participants per group which were reinstated for analyses in this review
Selective reporting (reporting bias)	Low risk	Comment: protocol was not provided; however, all outcomes defined in Methods were reported in Results section
Other bias	Low risk	Comment: none detected

NCT00975715

Methods	**Study design** Randomised, double-blind, parallel-group, placebo-controlled, multi-centre (multiple centres, Japan) **Duration** 1. Prospective baseline period (8 weeks) 2. Treatment period with titration (2-week titration, 6-week maintenance period) 3. Follow-up period (3 to 5 weeks)
Participants	**Randomised population** OXC 60 mg/ml: 48 PBO: 51 **ITT population** OXC 60 mg/ml: 47 PBO: 51 **Safety population** OXC 60 mg/ml: 47 PBO: 51 **No. of participants excluded from analyses** OXC 60 mg/ml: 1 Excluded due to not receiving study drug **Age (mean ± SD)** ≥ 4 to 14 years OXC 60 mg/ml: 9.8 (2.91) PBO: 9.2 (2.83) **Gender, male, n (%)** OXC 60 mg/ml: 26 (54.2)

NCT00975715 *(Continued)*	PBO: 27 (52.9) **Types of seizure** Focal seizures (simple, complex, and focal seizures evolving to secondarily generalized seizures) **Seizure frequency during baseline (median and range)** OXC 60 mg/ml: not provided PBO: not provided
Interventions	OXC 60 mg/ml oral suspension doses, based on body weight (twice daily) PBO oral suspension doses, based on body weight (twice daily)
Outcomes	**Primary outcome** 1. Percentage of reduction from baseline in FOS frequency per 28 days during treatment period. **Secondary outcomes** 1. FOS frequency per 28 days, by study period (every 28 days) and treatment group 2. Responder rate (≥ 50% reduction in FOS frequency per 28 days from baseline) 3. Percent change in FOS frequency during treatment 4. Number of participants with Clinical Global Impression of Change (CGIC) **Safety and tolerability outcomes** 1. Adverse events (AEs)
Notes	Sponsored by Novartis Pharmaceuticals Trial registration number: NCT00975715

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no protocol provided. Information about randomisation unavailable
Allocation concealment (selection bias)	Unclear risk	Comment: no protocol provided. Information about allocation concealment unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no protocol provided. Information about blinding unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no protocol provided. Information about blinding unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The Full Analysis set included all participants who received study drug."

NCT00975715 *(Continued)*

		Comment: attrition reported and modified intention-to-treat performed. The study had a low attrition rate overall; however, the attrition rate was unevenly distributed between treatment groups.
Selective reporting (reporting bias)	Low risk	Comment: no protocol provided; however, all outcomes defined on the study details tab of the clinicaltrials.gov webpage were subsequently reported on the results tab.
Other bias	Unclear risk	Comment: publication is not available so it is not possible to ascertain or discount any other potential sources of bias

Pina-Garza 2005

Methods	**Study design** Randomised, rater-blind, parallel-group, multi-centre (56 centres, 7 countries: USA, Argentina, France, Germany, Brazil, Mexico, and Lithuania) **Duration** 1. Screening period (72 hours) 2. Baseline period (24 to 72 hours) 3. Treatment period for low dose (10 mg/kg/d) OXC group (9-day maintenance only) or high dose (60 mg/kg/d) OXC group (26-day titration period + 9 days' maintenance) 4. Open-label extensions (6 months)
Participants	**Randomised population** OXC 60 mg/kg/d: 64 OXC 10 mg/kg/d: 64 **Modified ITT population** OXC 60 mg/kg/d: 59 OXC 10 mg/kg/d: 57 **Safety population** OXC 60 mg/kg/d: 64 OXC 10 mg/kg/d: 64 **No. of participants excluded from analyses** OXC 60 mg/kg/d: 5 OXC 10 mg/kg/d: 7 Excluded due to having no video-EEG data available. **Age** ≥ 1 month to < 4 years **Gender, male, n (%)** OXC 60 mg/kg/d: 38 (59)

Pina-Garza 2005 *(Continued)*

	OXC 10 mg/kg/d: 35 (55) **Types of seizure** Focal seizures (simple, complex, and focal seizures evolving to secondarily generalized seizures) **Seizure frequency during baseline (median (mean))** OXC 60 mg/kg/d: 3.83 (10.82) OXC 10 mg/kg/d: 7.00 (14.03)
Interventions	OXC 60 mg/kg/d (high dose) OXC 10 mg/kg/d (low dose)
Outcomes	**Primary outcome** 1. Absolute change in type 1 seizure frequency from baseline per 24 hours during the last 72 hours of continuous video-EEG monitoring in the treatment phase. **Secondary outcomes** 1. Percentage change in type 1 seizure frequency per 24 hours. 2. The absolute change in type 1 and type 2 seizure frequency per 24 hours (a type 2 seizure was electrographically similar to a type 1 seizure without the clinical correlate). 3. Response to treatment (characterized by at least a 50%, 75%, or 100% reduction in type 1 seizure frequency per 24 hours). **Safety and tolerability outcomes** 1. Adverse events (AEs) and serious adverse events (SAEs).
Notes	Sponsored by Novartis Pharmaceuticals Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a validated system (interactive voice response system) that automated the random assignment of treatment groups and age strata."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using a validated system (interactive voice response system)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: participants were not blinded; however, all participants were under 4 years of age so likelihood of this having an impact on efficacy outcomes is low. The study instead used a rater-blind design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...seizures were assessed and recorded by an independent pediatric neurologist not involved in the conduct of the study and who was blind to study treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: attrition was reported and was even between treatment groups. A modified intention-to-treat population was used for efficacy analyses.

Pina-Garza 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: protocol was not provided; however, all outcomes defined in Methods were reported in Results section
Other bias	High risk	Comment: the duration of the treatment period was significantly different for the 2 treatment groups. Quote: "The treatment phase lasted 9 days for the low-dose group and 35 days for the high-dose group."

AEs: Adverse effects; EEG: Electroencephalogram; FOS: Focal-onset seizures; OXC: Oxcarbazepine; PBO: Placebo

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

Study	Reason for exclusion
EUCTR2004-002260-25-AT	No data available and we suspect that the study included a proportion of participants who received oxcarbazepine as a monotherapy rather than as an adjunctive therapy.
EUCTR2006-003834-14-DE	Terminated early due to low recruitment. No data available.
EUCTR2008-003334-19-BG	Open-label extension study with single-group assignment.
Glauser 2001	Open-label extension study with single-group assignment.
Houtkooper 1987	Oxcarbazepine was used as a replacement for carbamazepine rather than as an adjunctive to stable anti-epileptic medication. The study included participants with generalised-onset seizures. Data were not reported separately for participants with focal versus generalised epilepsy, therefore it was not possible to extract the relevant data to permit inclusion.
Kutluay 2003	A meta-analysis of safety data taken from 21 studies.
McKee 1994	The study investigated the pharmacokinetics of oxcarbazepine and initially used oxcarbazepine as a monotherapy rather than as an adjunctive therapy.
NCT00050947	Oxcarbazepine utilised as a monotherapy.
NCT00391534	Terminated early due to low recruitment. No data available.
NCT00918424	Open-label extension study with single-group assignment.
NCT01891890	Oxcarbazepine utilised as a monotherapy.
Rey 2004	The study investigated the pharmacokinetics of oxcarbazepine and therefore consisted of irrelevant outcomes.
Steinhoff 2012	Terminated early due to low recruitment. No data available.

Characteristics of studies awaiting assessment *[ordered by study ID]*

CTRI/2010/091/000100

Methods	**Study design** Randomised, open-label (no blinding), active-controlled, parallel-group, multi-centre.

CTRI/2010/091/000100 *(Continued)*

	Duration 1. No information regarding baseline period 2. treatment period with titration (4 weeks up-titration, up to 12 weeks' maintenance)
Participants	**Randomised population:** 210 participants **Age (range):** ≥ 18 to 65 years **Gender:** male and female **Types of seizure:** drug-resistant epilepsy suffering from focal-onset seizures with or without secondary generalisation **Seizure frequency during baseline:** at least 1 seizure in the past month
Interventions	OXC 1200 mg/d Eslicarbazepine Acetate 1200 mg/d
Outcomes	**Primary outcome** 1. Median percentage reduction in frequency of seizures compared to baseline **Secondary outcomes** 1. Responder rate (defined as proportion of patients with a minimum of 50% reduction in seizure frequency from baseline) 2. Number of seizure-free patients during the treatment period 3. Change in QOLIE-31 score 4. Physician's and patient's global assessment to the treatment
Notes	We requested data from the principal investigator and primary contact person; however, no correspondence had been received by the time of publication.

CTRI/2010/091/001194

Methods	**Study design** Randomised, open-label (no blinding), active-controlled, parallel-group, multi-centre **Duration** 1. No information regarding baseline period 2. 12 week treatment period
Participants	**Randomised population:** 200 participants **Age (range):** ≥ 18 to 65 years **Gender:** male and female **Types of seizure:** simple or complex focal seizures with or without secondary generalization and taking stable doses of antiepileptic drugs.

CTRI/2010/091/001194 *(Continued)*

	Seizure frequency during baseline: at least 2 seizures in the past month or at least 4 seizures in the past 2 months.
Interventions	OXC 600 mg/d (twice daily) Eslicarbazepine 400 mg/d (once daily)
Outcomes	**Primary outcome** 1. ≥ 50% reduction in seizure frequency in the treatment period relative to baseline **Secondary outcomes** 1. Seizure frequency per 4 weeks 2. Number of days with seizures 3. Proportion of seizure free subjects 4. Proportion of subjects with an exacerbation in seizure frequency (≥ 25%) 5. Distribution of seizure reduction (proportion of subjects with seizure reduction of 50%; ≥ 50% to 75%, or > 75%) 6. Subjects' global assessment for efficacy 7. Physicians' global assessment for efficacy
Notes	We requested data from the principal investigator and primary contact person; however, no correspondence had been received by the time of publication.

CTRI/2010/091/006085

Methods	**Study design** Randomised, open-label (no blinding), active-controlled, parallel-group, multi-centre **Duration** 1. 13-week study (do not specify duration of baseline or treatment period)
Participants	**Randomised population:** 270 participants **Age (range):** ≥ 18 to 65 years **Gender:** male and female **Types of seizure:** simple or complex focal seizures with or without secondary generalisation and taking stable doses of antiepileptic drugs. **Seizure frequency during baseline:** at least 2 focal seizures in the past 4 weeks
Interventions	OXC 300 - 900 mg/d IN-AQUL-002 (no information on dosage)
Outcomes	**Primary outcome** 1. Change in the seizure frequency rate **Secondary outcomes**

CTRI/2010/091/006085 *(Continued)*	1. Responder rate 2. Change in number of seizure-free days
Notes	We requested data from the principal investigator and primary contact person; however, no correspondence had been received by the time of publication.

OXC: Oxcarbazepine.

DATA AND ANALYSES

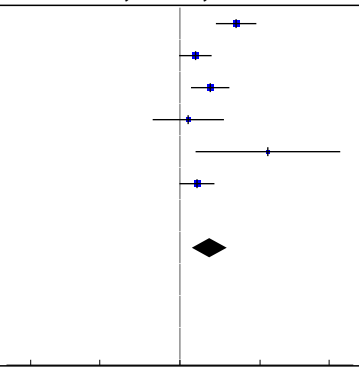
Comparison 1. Oxcarbazepine vs. control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	6	1593	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.27, 2.56]
2 Ataxia	5	1227	Risk Ratio (M-H, Random, 99% CI)	2.54 [0.86, 7.54]
3 Dizziness	4	1366	Risk Ratio (M-H, Fixed, 99% CI)	2.58 [1.81, 3.68]
4 Fatigue	4	1366	Risk Ratio (M-H, Fixed, 99% CI)	1.88 [1.07, 3.32]
5 Nausea	5	1464	Risk Ratio (M-H, Random, 99% CI)	1.87 [0.77, 4.56]
6 Somnolence	6	1593	Risk Ratio (M-H, Random, 99% CI)	2.03 [1.17, 3.54]
7 Headache	4	1366	Risk Ratio (M-H, Fixed, 99% CI)	1.27 [0.94, 1.71]
8 Hyponatraemia	6	1593	Risk Ratio (M-H, Fixed, 99% CI)	2.53 [0.27, 23.85]
9 Vertigo	2	793	Risk Ratio (M-H, Fixed, 99% CI)	4.62 [1.32, 16.13]
10 Diplopia	5	1465	Risk Ratio (M-H, Fixed, 99% CI)	5.50 [2.83, 10.68]
11 Rash	3	405	Risk Ratio (M-H, Fixed, 99% CI)	1.22 [0.38, 3.85]
12 Tremor	1	694	Risk Ratio (M-H, Fixed, 99% CI)	2.13 [0.77, 5.93]
13 Pyrexia	3	524	Risk Ratio (M-H, Fixed, 99% CI)	1.29 [0.71, 2.36]
14 Abnormal gait	2	961	Risk Ratio (M-H, Fixed, 99% CI)	5.53 [1.74, 17.61]
15 Abdominal pain	2	961	Risk Ratio (M-H, Random, 99% CI)	1.37 [0.42, 4.52]
16 Nystagmus	2	961	Risk Ratio (M-H, Fixed, 99% CI)	4.56 [1.90, 10.94]
17 Viral infection	2	961	Risk Ratio (M-H, Random, 99% CI)	2.22 [0.06, 79.48]
18 Vomiting	6	1593	Risk Ratio (M-H, Random, 99% CI)	2.55 [1.20, 5.42]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
19 Abnormal vision	3	1000	Risk Ratio (M-H, Random, 99% CI)	2.77 [0.59, 13.00]
20 Upper respiratory tract infection	2	366	Risk Ratio (M-H, Fixed, 99% CI)	0.68 [0.29, 1.59]
21 Seizure freedom	5	1494	Risk Ratio (M-H, Random, 95% CI)	2.86 [1.19, 6.87]
22 Treatment withdrawal	6	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.44, 2.13]

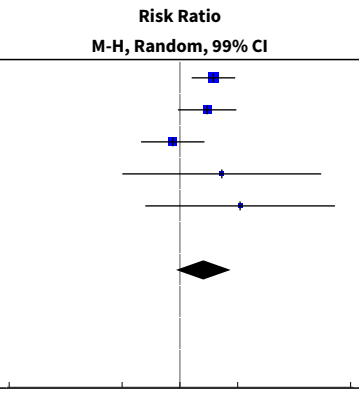
Analysis 1.1. Comparison 1 Oxcarbazepine vs. control, Outcome 1 50% or greater reduction in seizure frequency.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barcs 2000	205/521	22/173		19.7%	3.09[2.06,4.64]
French 2014	94/245	34/121		21.72%	1.37[0.99,1.89]
Glauser 2000	55/138	28/129		20.17%	1.84[1.25,2.7]
Kraiprab 2005	9/19	8/20		12.59%	1.18[0.58,2.42]
NCT00975715	11/48	2/51		4.73%	5.84[1.37,25.02]
Pina-Garza 2005	38/64	27/64		21.08%	1.41[0.99,2]
Total (95% CI)	**1035**	**558**		**100%**	**1.8[1.27,2.56]**
Total events: 412 (Oxcarbazepine), 121 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=16.51, df=5(P=0.01); I^2=69.71%					
Test for overall effect: Z=3.31(P=0)					

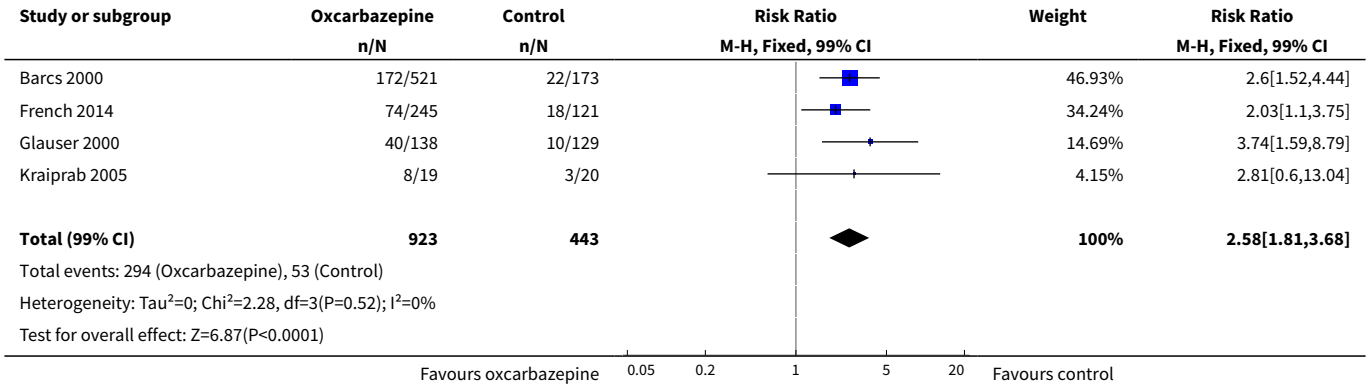


Analysis 1.2. Comparison 1 Oxcarbazepine vs. control, Outcome 2 Ataxia.

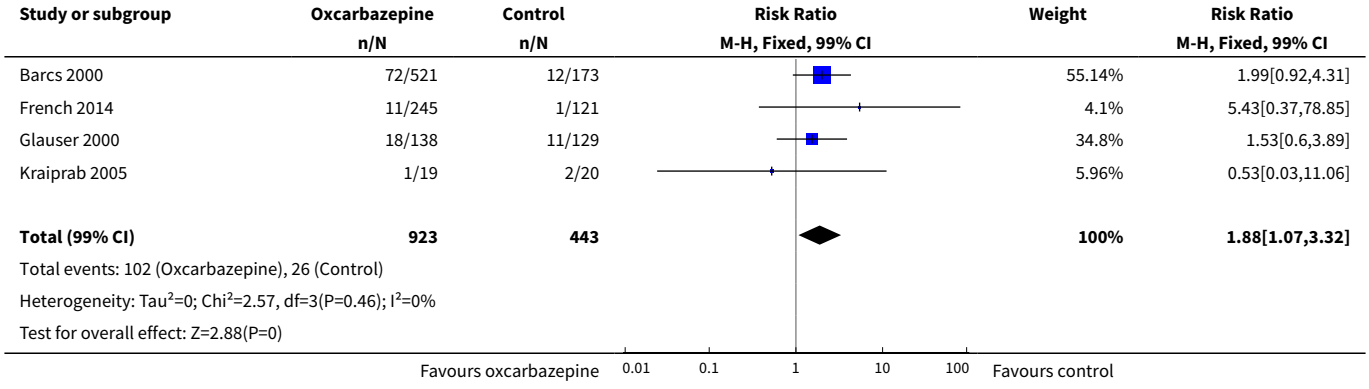
Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Random, 99% CI	Weight	Risk Ratio M-H, Random, 99% CI
Barcs 2000	103/521	9/173		32.48%	3.8[1.6,9.04]
Glauser 2000	19/138	6/129		27.86%	2.96[0.92,9.48]
Kraiprab 2005	5/19	7/20		26.38%	0.75[0.21,2.66]
NCT00975715	2/48	0/51		6.38%	5.31[0.1,277.61]
Pina-Garza 2005	5/64	0/64		6.9%	11[0.25,480.93]
Total (99% CI)	**790**	**437**		**100%**	**2.54[0.86,7.54]**
Total events: 134 (Oxcarbazepine), 22 (Control)					
Heterogeneity: Tau^2=0.44; Chi^2=9.41, df=4(P=0.05); I^2=57.51%					
Test for overall effect: Z=2.21(P=0.03)					



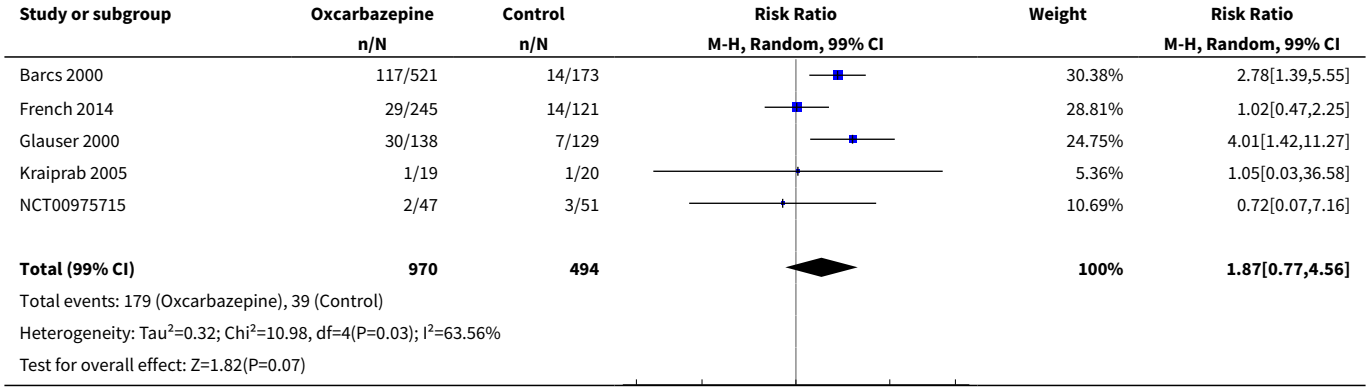
Analysis 1.3. Comparison 1 Oxcarbazepine vs. control, Outcome 3 Dizziness.



Analysis 1.4. Comparison 1 Oxcarbazepine vs. control, Outcome 4 Fatigue.

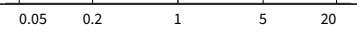


Analysis 1.5. Comparison 1 Oxcarbazepine vs. control, Outcome 5 Nausea.



Analysis 1.6. Comparison 1 Oxcarbazepine vs. control, Outcome 6 Somnolence.

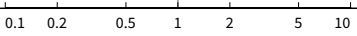
Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Random, 99% CI	Weight	Risk Ratio M-H, Random, 99% CI
Barcs 2000	137/521	20/173		22.79%	2.27[1.28,4.04]
French 2014	31/245	11/121		17.54%	1.39[0.59,3.28]
Glauser 2000	48/138	18/129		21.55%	2.49[1.32,4.72]
Kraiprab 2005	8/19	10/20		16.81%	0.84[0.34,2.07]
NCT00975715	20/48	5/51		12.79%	4.25[1.31,13.82]
Pina-Garza 2005	11/64	3/64		8.51%	3.67[0.73,18.43]
Total (99% CI)	**1035**	**558**		**100%**	**2.03[1.17,3.54]**
Total events: 255 (Oxcarbazepine), 67 (Control)					
Heterogeneity: Tau^2=0.15; Chi^2=12.29, df=5(P=0.03); I^2=59.3%					
Test for overall effect: Z=3.28(P=0)					



Favours oxcarbazepine — Favours control

Analysis 1.7. Comparison 1 Oxcarbazepine vs. control, Outcome 7 Headache.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Barcs 2000	142/521	41/173		57.53%	1.15[0.77,1.71]
French 2014	29/245	14/121		17.52%	1.02[0.47,2.25]
Glauser 2000	44/138	23/129		22.22%	1.79[1,3.2]
Kraiprab 2005	3/19	3/20		2.73%	1.05[0.15,7.28]
Total (99% CI)	**923**	**443**		**100%**	**1.27[0.94,1.71]**
Total events: 218 (Oxcarbazepine), 81 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.26, df=3(P=0.35); I^2=8.09%					
Test for overall effect: Z=2.05(P=0.04)					



Favours oxcarbazepine — Favours control

Analysis 1.8. Comparison 1 Oxcarbazepine vs. control, Outcome 8 Hyponatraemia.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Barcs 2000	2/521	0/173		39.4%	1.67[0.03,89.56]
French 2014	1/245	0/121		35.12%	1.49[0.02,98.88]
Glauser 2000	0/138	0/129			Not estimable
Kraiprab 2005	0/19	0/20			Not estimable
NCT00975715	2/48	0/51		25.49%	5.31[0.1,277.61]
Pina-Garza 2005	0/64	0/64			Not estimable
Total (99% CI)	**1035**	**558**		**100%**	**2.53[0.27,23.85]**
Total events: 5 (Oxcarbazepine), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=1.07(P=0.29)					

Favours oxcarbazepine — Favours control

Analysis 1.9. Comparison 1 Oxcarbazepine vs. control, Outcome 9 Vertigo.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Barcs 2000	55/521	4/173		92.53%	4.57[1.23,17]
NCT00975715	2/48	0/51		7.47%	5.31[0.1,277.61]
Total (99% CI)	**569**	**224**		**100%**	**4.62[1.32,16.13]**
Total events: 57 (Oxcarbazepine), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=3.15(P=0)					

Favours oxcarbazepine | Favours control

Analysis 1.10. Comparison 1 Oxcarbazepine vs. control, Outcome 10 Diplopia.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Barcs 2000	145/521	8/173		56.66%	6.02[2.43,14.92]
French 2014	28/245	5/121		31.58%	2.77[0.82,9.34]
Glauser 2000	23/138	1/129		4.88%	21.5[1.58,293.04]
Kraiprab 2005	1/19	1/20		4.6%	1.05[0.03,36.58]
NCT00975715	2/48	0/51		2.29%	5.31[0.1,277.61]
Total (99% CI)	**971**	**494**		**100%**	**5.5[2.83,10.68]**
Total events: 199 (Oxcarbazepine), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.43, df=4(P=0.25); I^2=26.35%					
Test for overall effect: Z=6.62(P<0.0001)					

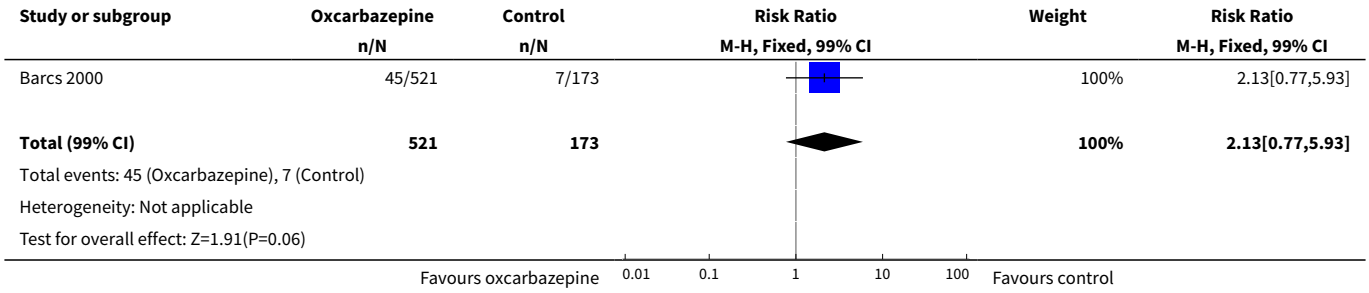
Favours oxcarbazepine | Favours control

Analysis 1.11. Comparison 1 Oxcarbazepine vs. control, Outcome 11 Rash.

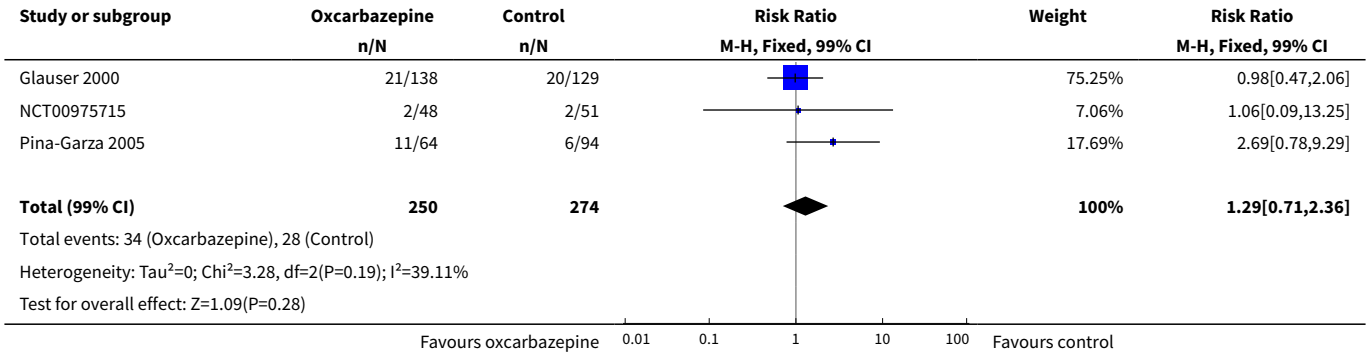
Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 99% CI	Weight	Risk Ratio M-H, Fixed, 99% CI
Glauser 2000	5/138	6/129		71.87%	0.78[0.17,3.59]
Kraiprab 2005	1/19	0/20		5.65%	3.15[0.05,195.59]
NCT00975715	4/48	2/51		22.47%	2.13[0.24,18.61]
Total (99% CI)	**205**	**200**		**100%**	**1.22[0.38,3.85]**
Total events: 10 (Oxcarbazepine), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					

Favours oxcarbazepine | Favours control

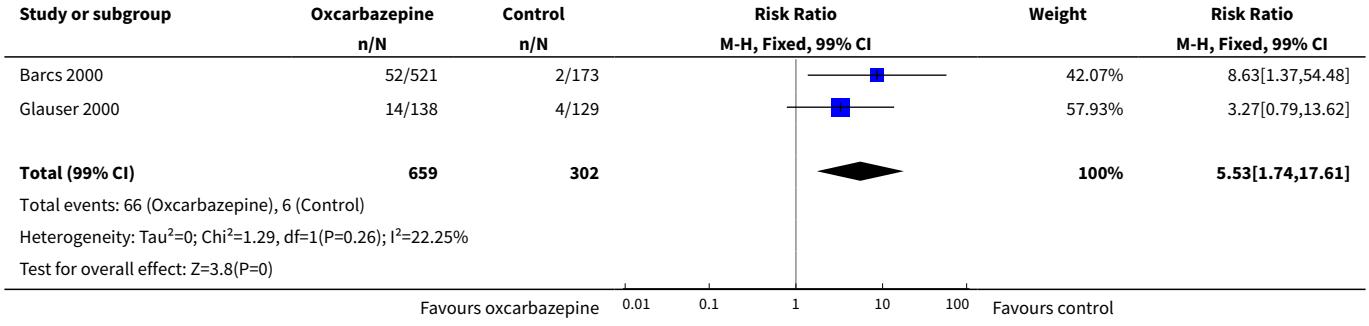
Analysis 1.12. Comparison 1 Oxcarbazepine vs. control, Outcome 12 Tremor.



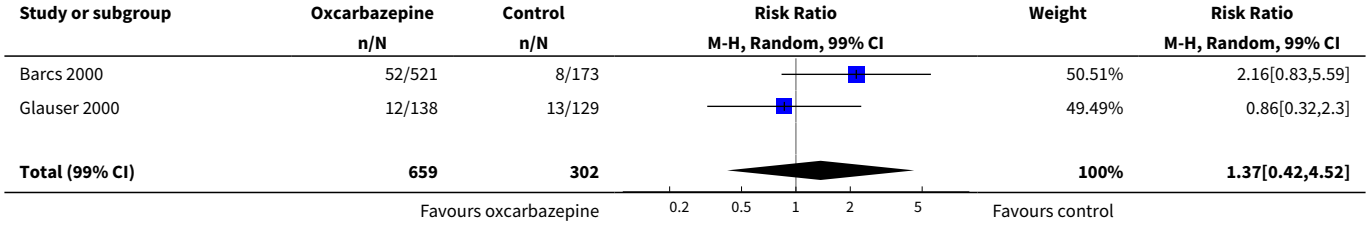
Analysis 1.13. Comparison 1 Oxcarbazepine vs. control, Outcome 13 Pyrexia.

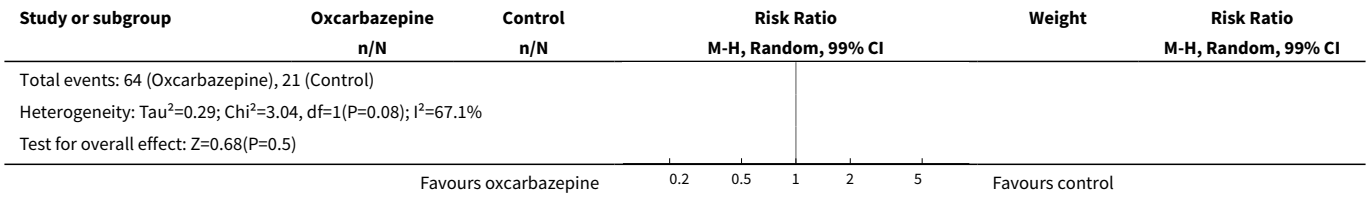


Analysis 1.14. Comparison 1 Oxcarbazepine vs. control, Outcome 14 Abnormal gait.

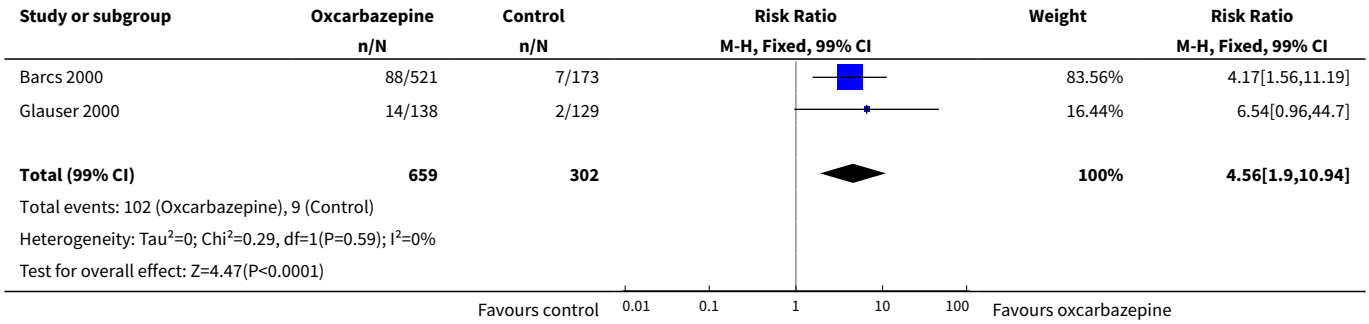


Analysis 1.15. Comparison 1 Oxcarbazepine vs. control, Outcome 15 Abdominal pain.

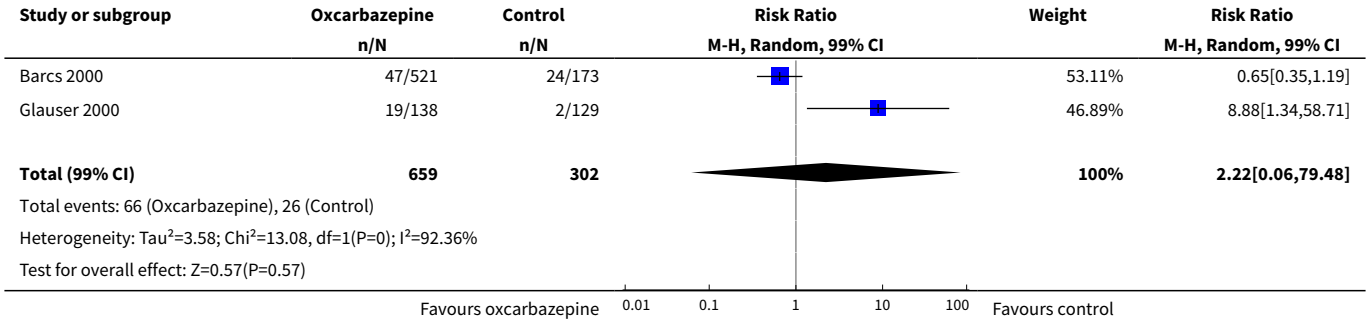




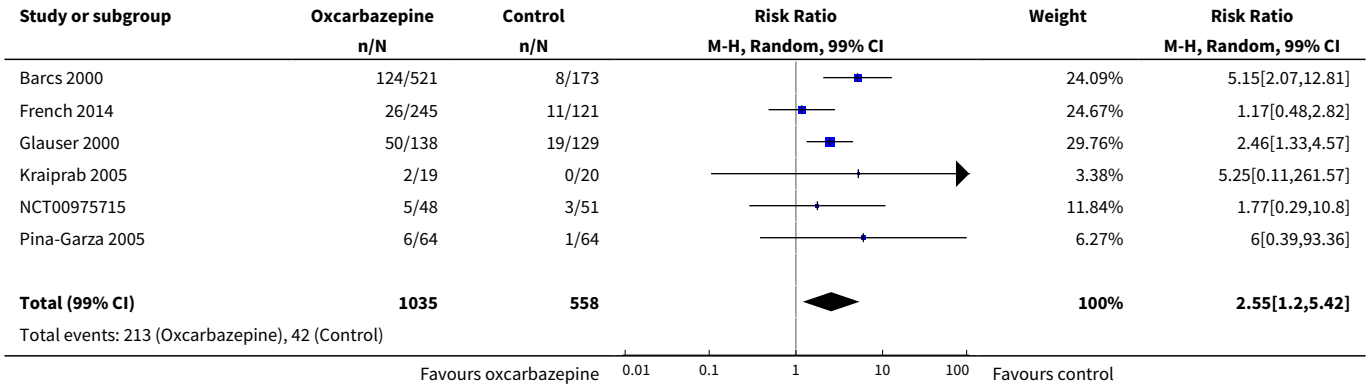
Analysis 1.16. Comparison 1 Oxcarbazepine vs. control, Outcome 16 Nystagmus.

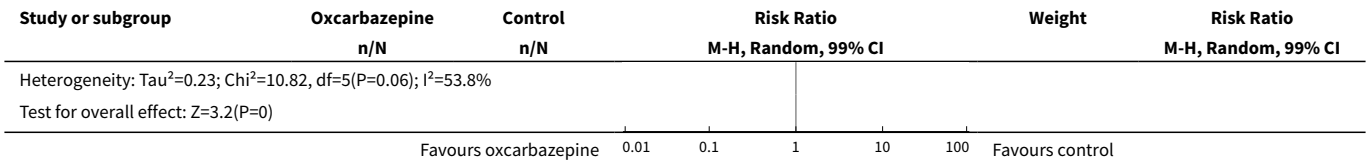


Analysis 1.17. Comparison 1 Oxcarbazepine vs. control, Outcome 17 Viral infection.

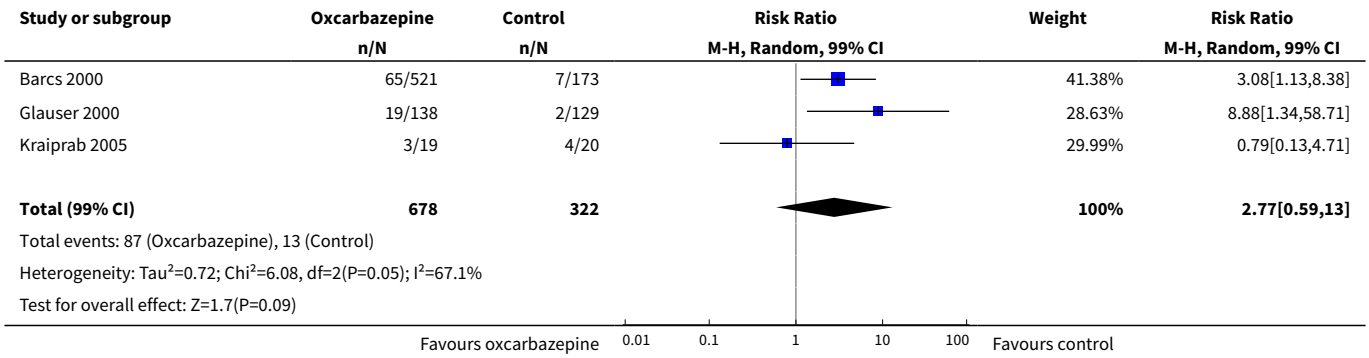


Analysis 1.18. Comparison 1 Oxcarbazepine vs. control, Outcome 18 Vomiting.

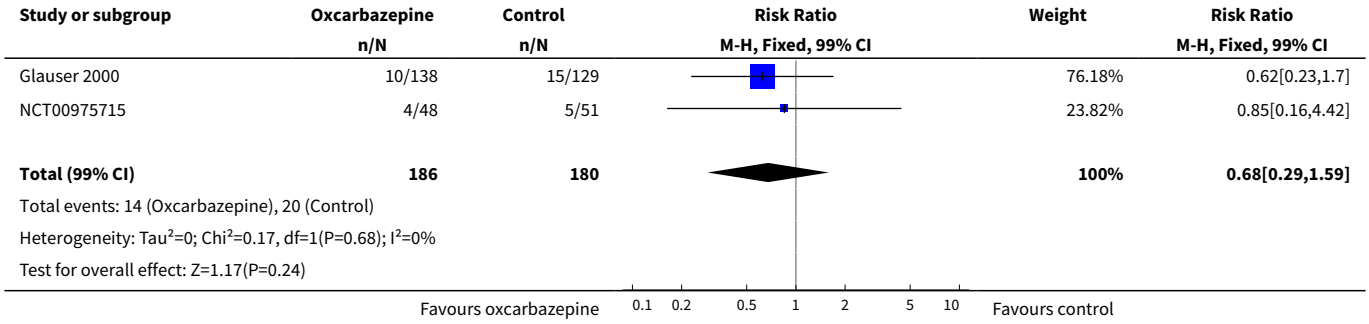




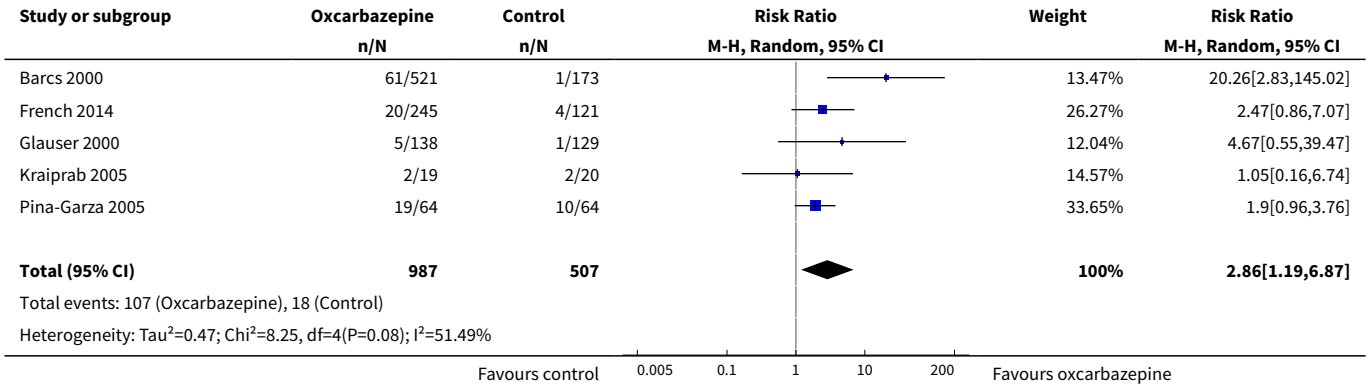
Analysis 1.19. Comparison 1 Oxcarbazepine vs. control, Outcome 19 Abnormal vision.

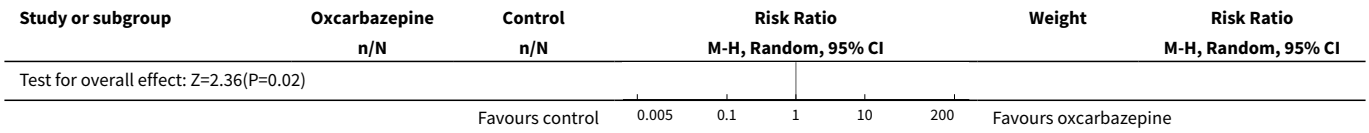


Analysis 1.20. Comparison 1 Oxcarbazepine vs. control, Outcome 20 Upper respiratory tract infection.

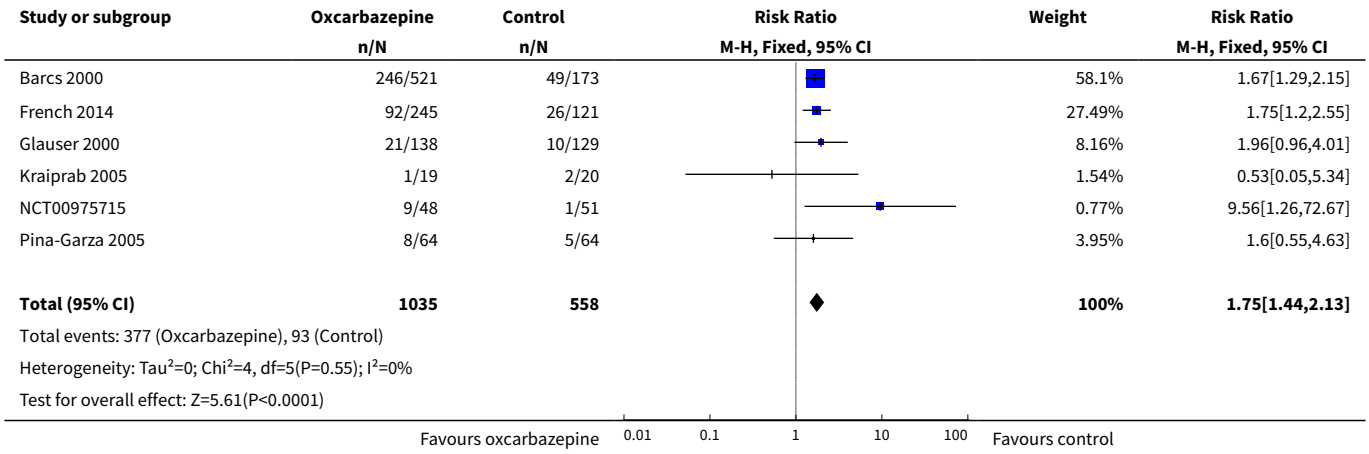


Analysis 1.21. Comparison 1 Oxcarbazepine vs. control, Outcome 21 Seizure freedom.





Analysis 1.22. Comparison 1 Oxcarbazepine vs. control, Outcome 22 Treatment withdrawal.



Comparison 2. Oxcarbazepine vs. control (Subgroup analysis - Control group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Placebo	4	1426	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.69, 2.59]
1.2 Alternate oxcarbazepine dosage	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.99, 1.86]
2 Seizure freedom	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Placebo	3	1327	Risk Ratio (M-H, Fixed, 95% CI)	6.14 [2.62, 14.41]
2.2 Alternate oxcarbazepine dosage	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.93, 3.33]
3 Treatment withdrawal	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Placebo	4	1426	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.46, 2.18]
3.2 Alternate oxcarbazepine dosage	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.51, 3.34]

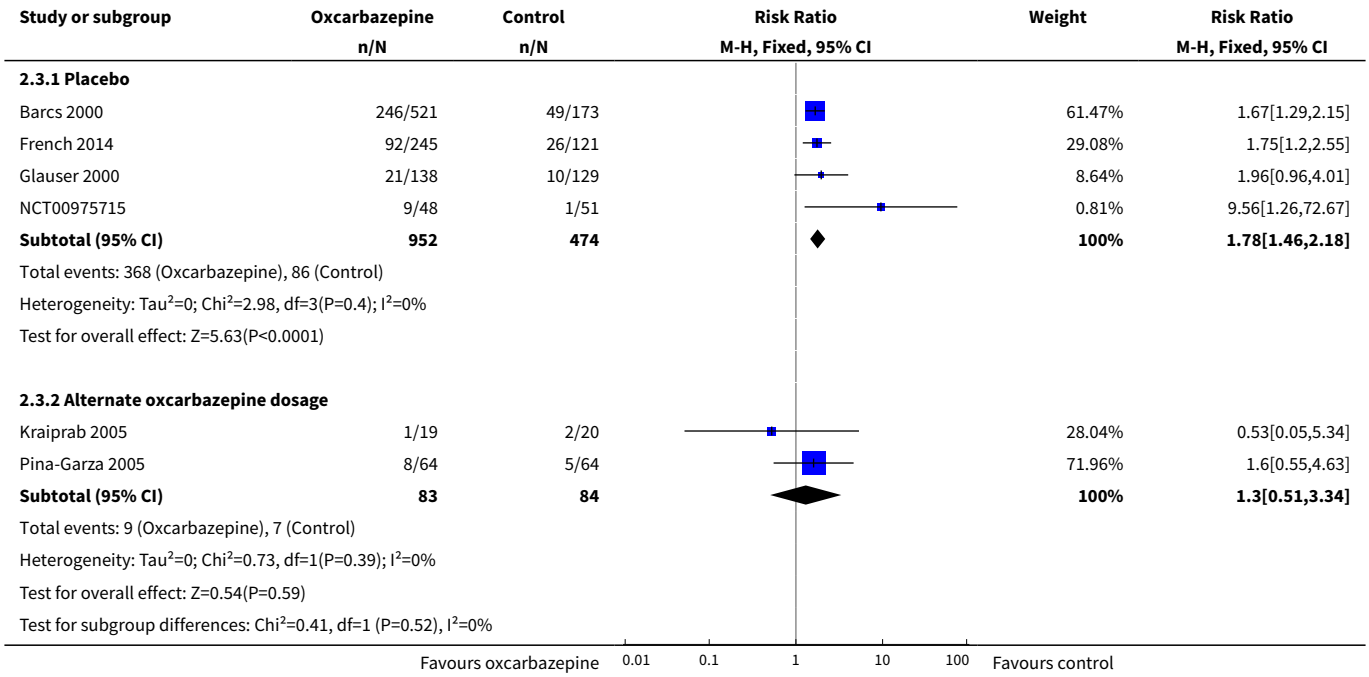
Analysis 2.1. Comparison 2 Oxcarbazepine vs. control (Subgroup analysis - Control group), Outcome 1 50% or greater reduction in seizure frequency.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Placebo					
Barcs 2000	205/521	22/173		30.18%	3.09[2.06,4.64]
French 2014	94/245	34/121		41.6%	1.37[0.99,1.89]
Glauser 2000	55/138	28/129		26.45%	1.84[1.25,2.7]
NCT00975715	11/48	2/51		1.77%	5.84[1.37,25.02]
Subtotal (95% CI)	**952**	**474**		**100%**	**2.09[1.69,2.59]**
Total events: 365 (Oxcarbazepine), 86 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.51, df=3(P=0.01); I^2=76.02%					
Test for overall effect: Z=6.81(P<0.0001)					
2.1.2 Alternate oxcarbazepine dosage					
Kraiprab 2005	9/19	8/20		22.4%	1.18[0.58,2.42]
Pina-Garza 2005	38/64	27/64		77.6%	1.41[0.99,2]
Subtotal (95% CI)	**83**	**84**		**100%**	**1.36[0.99,1.86]**
Total events: 47 (Oxcarbazepine), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=1.9(P=0.06)					
Test for subgroup differences: Chi^2=4.96, df=1 (P=0.03), I^2=79.84%					

Analysis 2.2. Comparison 2 Oxcarbazepine vs. control (Subgroup analysis - Control group), Outcome 2 Seizure freedom.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Placebo					
Barcs 2000	61/521	1/173		19.03%	20.26[2.83,145.02]
French 2014	20/245	4/121		67.87%	2.47[0.86,7.07]
Glauser 2000	5/138	1/129		13.1%	4.67[0.55,39.47]
Subtotal (95% CI)	**904**	**423**		**100%**	**6.14[2.62,14.41]**
Total events: 86 (Oxcarbazepine), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.36, df=2(P=0.11); I^2=54.14%					
Test for overall effect: Z=4.17(P<0.0001)					
2.2.2 Alternate oxcarbazepine dosage					
Kraiprab 2005	2/19	2/20		16.31%	1.05[0.16,6.74]
Pina-Garza 2005	19/64	10/64		83.69%	1.9[0.96,3.76]
Subtotal (95% CI)	**83**	**84**		**100%**	**1.76[0.93,3.33]**
Total events: 21 (Oxcarbazepine), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.74(P=0.08)					
Test for subgroup differences: Chi^2=5.29, df=1 (P=0.02), I^2=81.08%					

Analysis 2.3. Comparison 2 Oxcarbazepine vs. control (Subgroup analysis - Control group), Outcome 3 Treatment withdrawal.

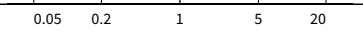


Comparison 3. Oxcarbazepine vs. control (Subgroup analysis - Age group)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	6	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.60, 2.29]
1.1 Adults	3	1099	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.58, 2.57]
1.2 Children	3	494	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.36, 2.30]
2 Seizure freedom	5	1494	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [2.07, 5.92]
2.1 Adults	3	1099	Risk Ratio (M-H, Fixed, 95% CI)	5.19 [2.29, 11.75]
2.2 Children	2	395	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [1.13, 4.14]
3 Treatment withdrawal	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Adults	3	1099	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.36, 2.06]
3.2 Children	3	494	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.32, 4.01]

Analysis 3.1. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 1 50% or greater reduction in seizure frequency.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Adults					
Barcs 2000	205/521	22/173		22.9%	3.09[2.06,4.64]
French 2014	94/245	34/121		31.56%	1.37[0.99,1.89]
Kraiprab 2005	9/19	8/20		5.4%	1.18[0.58,2.42]
Subtotal (95% CI)	**785**	**314**		**59.87%**	**2.01[1.58,2.57]**
Total events: 308 (Oxcarbazepine), 64 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.86, df=2(P=0); I^2=83.14%					
Test for overall effect: Z=5.61(P<0.0001)					
3.1.2 Children					
Glauser 2000	55/138	28/129		20.07%	1.84[1.25,2.7]
NCT00975715	11/48	2/51		1.34%	5.84[1.37,25.02]
Pina-Garza 2005	38/64	27/64		18.72%	1.41[0.99,2]
Subtotal (95% CI)	**250**	**244**		**40.13%**	**1.77[1.36,2.3]**
Total events: 104 (Oxcarbazepine), 57 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.27, df=2(P=0.12); I^2=53.11%					
Test for overall effect: Z=4.3(P<0.0001)					
Total (95% CI)	**1035**	**558**		**100%**	**1.91[1.6,2.29]**
Total events: 412 (Oxcarbazepine), 121 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.51, df=5(P=0.01); I^2=69.71%					
Test for overall effect: Z=7.06(P<0.0001)					
Test for subgroup differences: Chi^2=0.49, df=1 (P=0.49), I^2=0%					

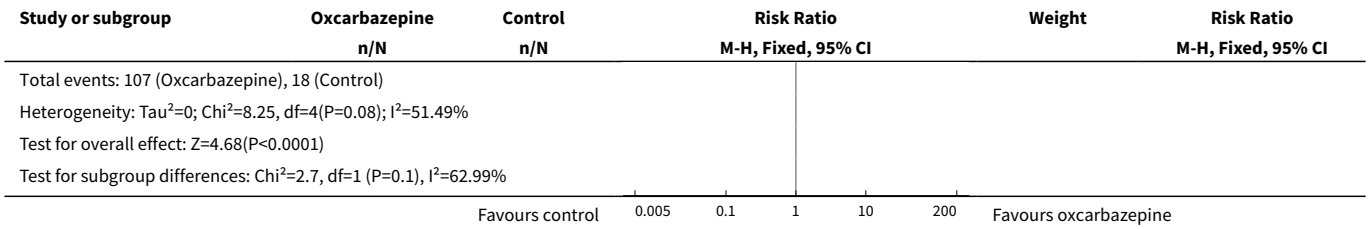


Favours control — Favours oxcarbazepine

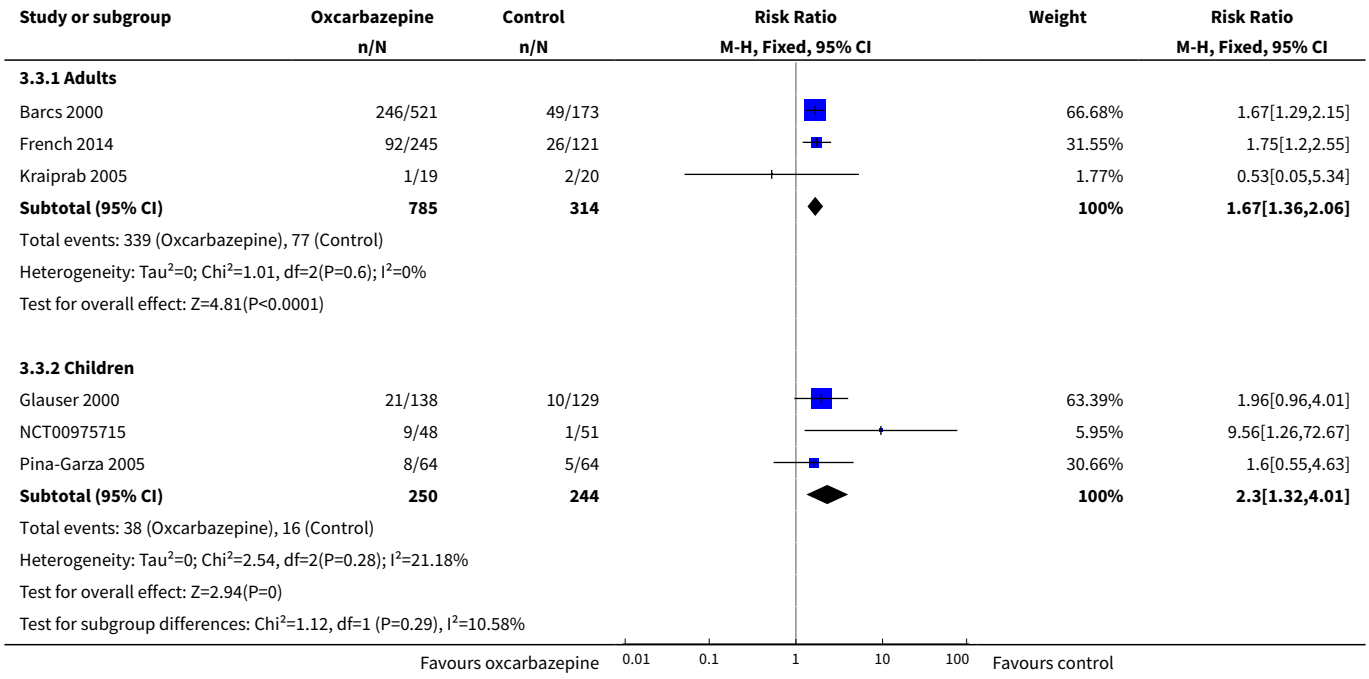
Analysis 3.2. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 2 Seizure freedom.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Adults					
Barcs 2000	61/521	1/173		7.57%	20.26[2.83,145.02]
French 2014	20/245	4/121		26.99%	2.47[0.86,7.07]
Kraiprab 2005	2/19	2/20		9.82%	1.05[0.16,6.74]
Subtotal (95% CI)	**785**	**314**		**44.38%**	**5.19[2.29,11.75]**
Total events: 83 (Oxcarbazepine), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.59, df=2(P=0.04); I^2=69.66%					
Test for overall effect: Z=3.95(P<0.0001)					
3.2.2 Children					
Glauser 2000	5/138	1/129		5.21%	4.67[0.55,39.47]
Pina-Garza 2005	19/64	10/64		50.41%	1.9[0.96,3.76]
Subtotal (95% CI)	**202**	**193**		**55.62%**	**2.16[1.13,4.14]**
Total events: 24 (Oxcarbazepine), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=2.32(P=0.02)					
Total (95% CI)	**987**	**507**		**100%**	**3.5[2.07,5.92]**

Favours control — Favours oxcarbazepine



Analysis 3.3. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 3 Treatment withdrawal.



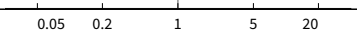
Comparison 4. Oxcarbazepine vs. control (Subgroup analysis - Duration of treatment)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 8 weeks or less	2	227	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.20, 2.41]
1.2 16 weeks	3	672	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.20, 1.92]
1.3 26 weeks	1	694	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [2.06, 4.64]
2 Seizure freedom	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 8 weeks or less	1	128	Risk Ratio (M-H, Fixed, 95% CI)	1.9 [0.96, 3.76]
2.2 16 weeks	3	672	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.05, 5.52]
2.3 26 weeks	1	694	Risk Ratio (M-H, Fixed, 95% CI)	20.26 [2.83, 145.02]
3 Treatment withdrawal	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 8 weeks or less	2	227	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.19, 7.06]
3.2 16 weeks	3	672	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.26, 2.42]
3.3 26 weeks	1	694	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.29, 2.15]

Analysis 4.1. Comparison 4 Oxcarbazepine vs. control (Subgroup analysis - Duration of treatment), Outcome 1 50% or greater reduction in seizure frequency.

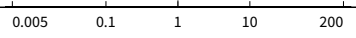
Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 8 weeks or less					
NCT00975715	11/48	2/51		6.7%	5.84[1.37,25.02]
Pina-Garza 2005	38/64	27/64		93.3%	1.41[0.99,2]
Subtotal (95% CI)	**112**	**115**		**100%**	**1.7[1.2,2.41]**
Total events: 49 (Oxcarbazepine), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.9, df=1(P=0.05); I^2=74.37%					
Test for overall effect: Z=3(P=0)					
4.1.2 16 weeks					
French 2014	94/245	34/121		55.34%	1.37[0.99,1.89]
Glauser 2000	55/138	28/129		35.19%	1.84[1.25,2.7]
Kraiprab 2005	9/19	8/20		9.48%	1.18[0.58,2.42]
Subtotal (95% CI)	**402**	**270**		**100%**	**1.51[1.2,1.92]**
Total events: 158 (Oxcarbazepine), 70 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.79, df=2(P=0.41); I^2=0%					
Test for overall effect: Z=3.45(P=0)					
4.1.3 26 weeks					
Barcs 2000	205/521	22/173		100%	3.09[2.06,4.64]
Subtotal (95% CI)	**521**	**173**		**100%**	**3.09[2.06,4.64]**
Total events: 205 (Oxcarbazepine), 22 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.47(P<0.0001)					
Test for subgroup differences: Chi^2=9.05, df=1 (P=0.01), I^2=77.89%					



Favours control — Favours oxcarbazepine

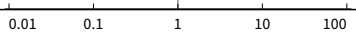
Analysis 4.2. Comparison 4 Oxcarbazepine vs. control (Subgroup analysis - Duration of treatment), Outcome 2 Seizure freedom.

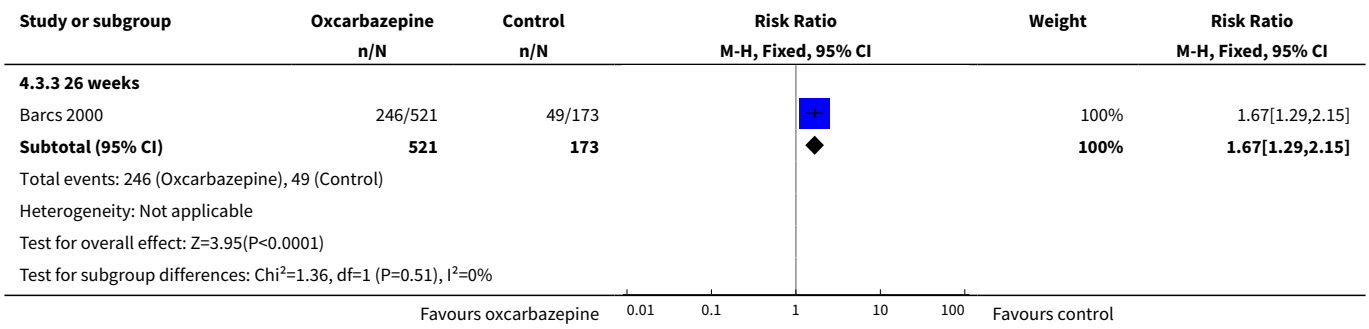
Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 8 weeks or less					
Pina-Garza 2005	19/64	10/64		100%	1.9[0.96,3.76]
Subtotal (95% CI)	**64**	**64**		**100%**	**1.9[0.96,3.76]**
Total events: 19 (Oxcarbazepine), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.84(P=0.07)					
4.2.2 16 weeks					
French 2014	20/245	4/121		64.23%	2.47[0.86,7.07]
Glauser 2000	5/138	1/129		12.4%	4.67[0.55,39.47]
Kraiprab 2005	2/19	2/20		23.37%	1.05[0.16,6.74]
Subtotal (95% CI)	**402**	**270**		**100%**	**2.41[1.05,5.52]**
Total events: 27 (Oxcarbazepine), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
4.2.3 26 weeks					
Barcs 2000	61/521	1/173		100%	20.26[2.83,145.02]
Subtotal (95% CI)	**521**	**173**		**100%**	**20.26[2.83,145.02]**
Total events: 61 (Oxcarbazepine), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3(P=0)					
Test for subgroup differences: Chi^2=4.96, df=1 (P=0.08), I^2=59.65%					



Analysis 4.3. Comparison 4 Oxcarbazepine vs. control (Subgroup analysis - Duration of treatment), Outcome 3 Treatment withdrawal.

Study or subgroup	Oxcarbazepine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 8 weeks or less					
NCT00975715	9/48	1/51		16.24%	9.56[1.26,72.67]
Pina-Garza 2005	8/64	5/64		83.76%	1.6[0.55,4.63]
Subtotal (95% CI)	**112**	**115**		**100%**	**2.89[1.19,7.06]**
Total events: 17 (Oxcarbazepine), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.53, df=1(P=0.11); I^2=60.47%					
Test for overall effect: Z=2.33(P=0.02)					
4.3.2 16 weeks					
French 2014	92/245	26/121		73.91%	1.75[1.2,2.55]
Glauser 2000	21/138	10/129		21.95%	1.96[0.96,4.01]
Kraiprab 2005	1/19	2/20		4.14%	0.53[0.05,5.34]
Subtotal (95% CI)	**402**	**270**		**100%**	**1.74[1.26,2.42]**
Total events: 114 (Oxcarbazepine), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.13, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=3.32(P=0)					

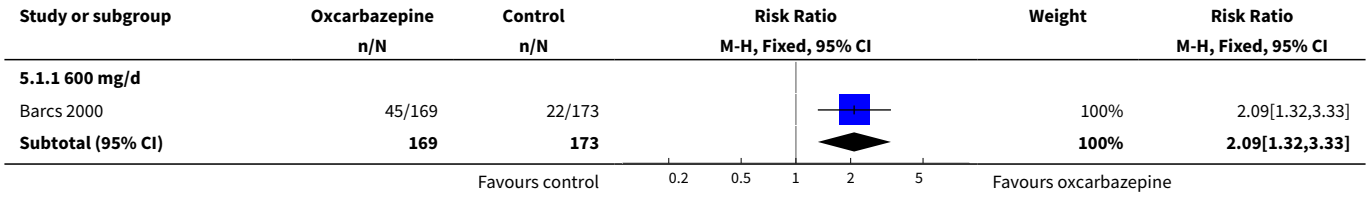


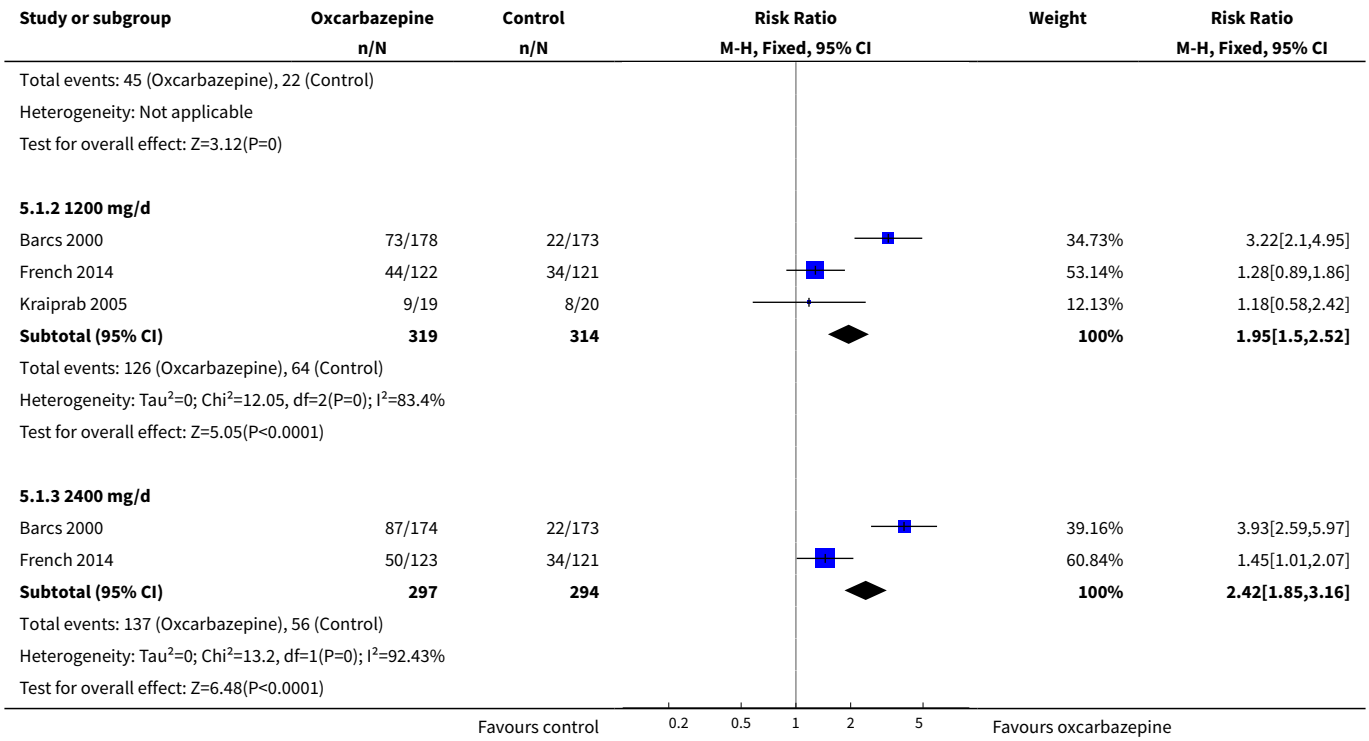


Comparison 5. Oxcarbazepine vs. control (Subgroup analysis - Experimental dose)

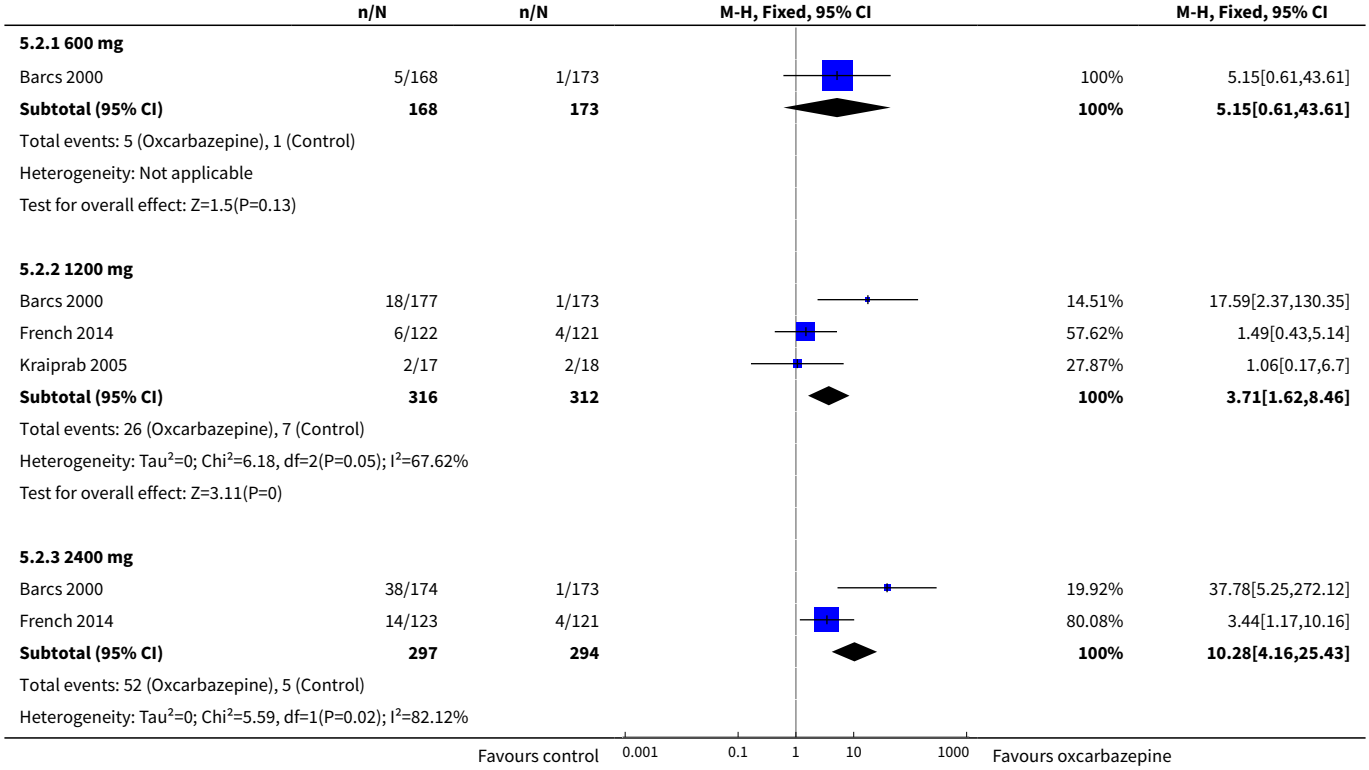
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 600 mg/d	1	342	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.32, 3.33]
1.2 1200 mg/d	3	633	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.50, 2.52]
1.3 2400 mg/d	2	591	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [1.85, 3.16]
2 Seizure freedom	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mg	1	341	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [0.61, 43.61]
2.2 1200 mg	3	628	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [1.62, 8.46]
2.3 2400 mg	2	591	Risk Ratio (M-H, Fixed, 95% CI)	10.28 [4.16, 25.43]
3 Treatment withdrawal	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mg	1	342	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.55, 1.15]
3.2 1200 mg	3	633	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.21, 1.95]
3.3 2400 mg	2	591	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.92, 2.94]

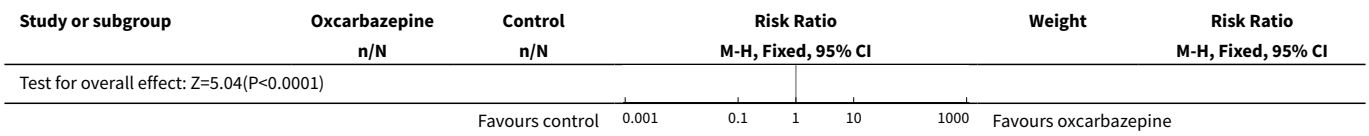
Analysis 5.1. Comparison 5 Oxcarbazepine vs. control (Subgroup analysis - Experimental dose), Outcome 1 50% or greater reduction in seizure frequency.



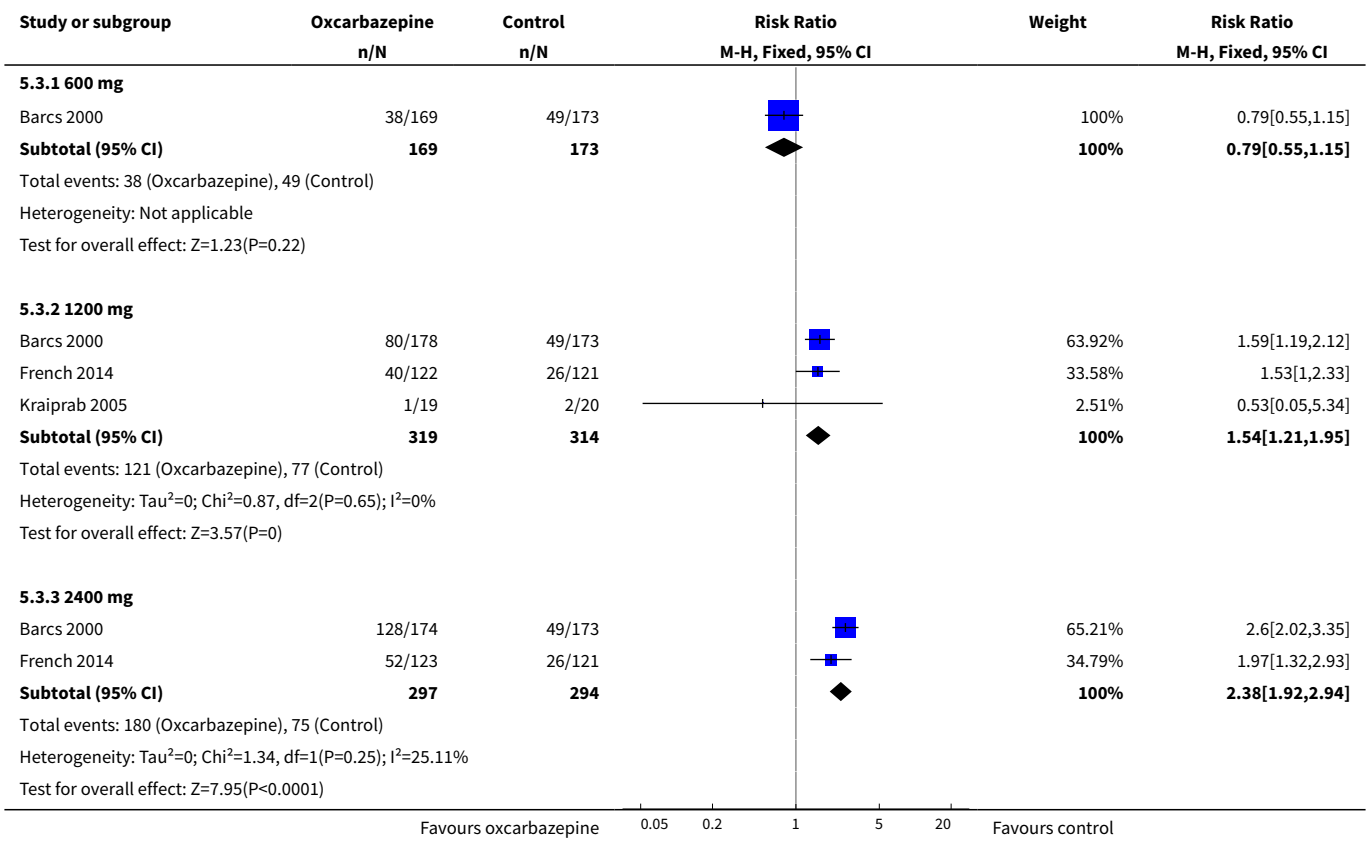


Analysis 5.2. Comparison 5 Oxcarbazepine vs. control (Subgroup analysis - Experimental dose), Outcome 2 Seizure freedom.





Analysis 5.3. Comparison 5 Oxcarbazepine vs. control (Subgroup analysis - Experimental dose), Outcome 3 Treatment withdrawal.



APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web) search strategy

1. actinium or barzepin or carbox or deprectal or "gp 47680" or lonazet or ocbz or oxalepsy or oxcarbamazepin* or oxcarbazepin* or oxetol or oxpin or oxrate or "oxtellar xr" or oxypine or pharozepine or prolepsi or timox or trexapin or trileptal or trileptin AND CENTRAL:TARGET

2. MESH DESCRIPTOR Epilepsies, Partial EXPLODE ALL AND CENTRAL:TARGET

3. ((partial or focal) and (seizure* or epilep*)):AB,KW,MC,MH,TI AND CENTRAL:TARGET

4. #2 OR #3 AND CENTRAL:TARGET

5. #1 AND #4

6. (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND CENTRAL:TARGET

#5 NOT #6

Appendix 2. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011).

1. (actinium or barzepin or carbox or deprectal or "gp 47680" or lonazet or ocbz or oxalepsy or oxcarbamazepin$ or oxcarbazepin$ or oxetol or oxpin or oxrate or "oxtellar xr" or oxypine or pharozepine or prolepsi or timox or trexapin or trileptal or trileptin).tw.

2. exp Epilepsies, Partial/

3. ((partial or focal) and (seizure$ or epilep$)).tw.

4. 2 or 3

5. 1 and 4

6. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.

7. 5 not 6

8. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. 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. 7 and 13

15. remove duplicates from 14

Appendix 3. ClinicalTrials.gov search strategy

Interventional Studies | Epilepsies, Partial | Oxcarbazepine

Appendix 4. ICTRP search strategy

Condition: partial AND epilepsy OR focal AND epilepsy OR partial AND seizure OR focal AND seizure

Intervention: oxcarbazepine

Recruitment status: all

Phases: all

CONTRIBUTIONS OF AUTHORS

RB: primarily responsible for the conduct of the review.

MO: provided support for this review and contributed to the writing of the review.

AGM: supervised the review process and provided expert opinion and feedback.

DECLARATIONS OF INTEREST

RB: none known.

MO: none known.

AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by the Applied Research Collaboration North West Coast (ARC NWC).

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have reported the proportion of participants who experienced each individual adverse effect as risk ratios (RR) with 99% confidence intervals (CI) rather than as RR with 95% CI, as specified in the review protocol, to compensate for multiple outcome testing.

We were unable to conduct a subgroup analysis stratified by the number of concomitant AEDs because the studies included in the review did not report outcome data stratified by number of concomitant AEDs.

The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).