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Xiao Y, Gan L, Wang J, Luo M, Luo H.
Vigabatrin versus carbamazepine monotherapy for epilepsy.
Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD008781.
DOI: [10.1002/14651858.CD008781.pub3](https://doi.org/10.1002/14651858.CD008781.pub3).

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[Intervention Review]

Vigabatrin versus carbamazepine monotherapy for epilepsy

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Editorial group: Cochrane Epilepsy Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2015.

Citation: Xiao Y, Gan L, Wang J, Luo M, Luo H. Vigabatrin versus carbamazepine monotherapy for epilepsy. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD008781. DOI: [10.1002/14651858.CD008781.pub3](https://doi.org/10.1002/14651858.CD008781.pub3).

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ABSTRACT

Background

This is an update of a Cochrane review first published in 2012 (Cochrane Database of Systematic Reviews 2012, Issue 1).

The efficacy and safety of vigabatrin (VGB) as an add-on therapy for refractory epilepsy have been well established. However, this information needs to be weighed against the risk of development of visual field defects. Whether VGB monotherapy is an effective and safe treatment compared with the standard antiepileptic drug carbamazepine (CBZ) as monotherapy for epilepsy has not been systematically reviewed.

Objectives

To investigate the efficacy and safety of VGB versus CBZ monotherapy for epilepsy in children and adults.

Search methods

For the latest update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3 of 4), MEDLINE (1948 to July 2015), EMBASE (1974 to July 2015) and the Chinese Biomedical Database (CBM) (1979 to July 2015). We searched trial registers and contacted the manufacturer of VGB and authors of included studies for additional information. We applied no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) comparing VGB versus CBZ monotherapy for epilepsy.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. The primary outcome was time to treatment withdrawal. Secondary outcomes were time to achieve six-month and 12-month remission after randomisation, time to first seizure after randomisation and adverse events. We presented results as hazard ratios (HRs) with 95% confidence intervals (CIs) (time to event data) or as risk ratios (RRs) with 95% CIs (adverse events).

Main results

Five studies involving a total of 734 participants were eligible for inclusion. We assessed only one study as good quality and the other four as poor quality. However, it was difficult to perform a meta-analysis by extracting aggregate data to synthesise the results as originally planned, mainly because not all studies reported the same outcomes as those chosen for this review. No significant differences favoured VGB or CBZ in terms of time to treatment withdrawal and time to achieve six-month remission after dose stabilisation from randomisation, but results did show a disadvantage for VGB on time to first seizure after randomisation. Compared with CBZ, VGB was associated with more

occurrences of weight gain and fewer occurrences of skin rash and drowsiness. No differences in visual field defects and visual disturbances were noted.

Authors' conclusions

Data are currently insufficient to address the risk-benefit balance of VGB versus CBZ monotherapy for epilepsy. Given the high prevalence of visual field defects reported in an existing systematic review of observational studies ([Maguire 2010](#)), VGB monotherapy should be prescribed with caution for epilepsy and should not be considered a first-line choice. If necessary, the visual field should be frequently assessed. Future research should focus on investigating the reasons for visual field defects and exploring potential prevention strategies. Moreover, future monotherapy studies of epilepsy should report results according to the recommendations of the International League Against Epilepsy (ILAE) Commission, and methodological quality should be improved.

PLAIN LANGUAGE SUMMARY

Vigabatrin versus carbamazepine monotherapy for epilepsy

Review question

This review is an update of a review previously published in the Cochrane Database of Systematic Reviews (2012, Issue 1) titled 'Vigabatrin versus carbamazepine monotherapy for epilepsy'. We reviewed the evidence on the efficacy and safety of vigabatrin versus carbamazepine (CBZ) when used as monotherapy for epilepsy. We found five studies.

Background

Epilepsy is a common neurological disorder, affecting more than 50 million people worldwide. The efficacy and safety of vigabatrin as an add-on therapy for refractory epilepsy have been well established. However, this information needs to be weighed against the risk of development of visual field defects. We wanted to know whether vigabatrin monotherapy is effective and safe compared with the standard antiepileptic drug carbamazepine as monotherapy for epilepsy.

Study characteristics

The evidence is current to July 2015. We found five trials assessing vigabatrin or carbamazepine monotherapy for newly diagnosed epilepsy, which recruited a total of 734 participants between six months and 65 years of age.

Key results

Results of this review show no significant differences between vigabatrin and carbamazepine in terms of time to treatment withdrawal and time to achieve six-month remission after dose stabilisation from randomisation, but they reveal some clinical disadvantage with vigabatrin on time to first seizure. Taking vigabatrin was more likely to result in weight gain. A safety concern was the high prevalence of visual field defects, as reported in a systematic review of observational studies ([Maguire 2010](#)).

Quality of the evidence

One study was assessed as good quality and the other four as poor quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. VGB compared with CBZ monotherapy for epilepsy

Vigabatrin (VGB) compared with carbamazepine (CBZ) monotherapy for epilepsy

Patient or population: patients with epilepsy

Settings: hospital departments

Intervention: VGB monotherapy

Comparison: CBZ monotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CBZ monotherapy	VGB				
Time to treatment withdrawal Follow-up: 52 weeks	Patients with epilepsy		HR 0.75 (0.52 to 1.1)	446 (1 study)	⊕⊕⊕⊕ Low a,b	No significant decrease in risk of withdrawal with VGB
	See comment	See comment				
Time to achieve 6-month remission after the first 6 weeks of dose stabilisation from randomisation Follow-up: 52 weeks	Patients with epilepsy		HR 1.18 (0.89 to 1.55)	404 (1 study)	⊕⊕⊕⊕ Very low a,b,c	No significant increase in clinical advantage with VGB
	See comment	See comment				
Time to first seizure after randomisation Follow-up: 52 weeks	Patients with epilepsy		HR 1.57 (1.23 to 2.02)	404 (1 study)	⊕⊕⊕⊕ Low a,b	Significant increase in clinical disadvantage with VGB
	See comment	See comment				
Adverse events Visual field defects Follow-up: 48 weeks	Patients with epilepsy		RR 5.37 (0.27 to 106.88)	54 (1 study)	⊕⊕⊕⊕ Very low d,e,f	Two participants in the VGB group experienced this adverse event
	See comment	See comment				
	Medium-risk population					
	Not estimable	Not estimable				

*The basis for **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aOne study representing 62.5% of participants contributed to this outcome analysis. The remaining 4 studies did not report outcomes chosen for this review.

^bFive studies were eligible for inclusion, but only 1 study contributed to this outcome analysis.

^cData were available only for time to achieve 6-month remission after the first 6 weeks of dose stabilisation from randomisation, but not since randomisation.

^dThe only study included was an open control randomised trial, did not describe the method used to generate allocation sequence and did not mention allocation concealment.

^eIncluded only 1 randomised trial of a small number of participants with short-term follow-up.

^fRandomised controlled trials often are not of optimal design for detecting unexpected adverse events; adverse events detected from observational studies were not included.

BACKGROUND

Description of the condition

Epilepsy is a common neurological disorder, affecting more than 50 million people worldwide (Banerjee 2009; De Boer 2008). About 50% to 75% of seizures are well controlled with a single antiepileptic drug (monotherapy) (Vazquez 2004). Standard drugs most commonly used as monotherapy include carbamazepine, valproate and phenytoin. Given that many patients do not achieve seizure freedom with these standard treatments, and that many of those who do achieve seizure freedom do so at the cost of adverse events, it is important to assess the efficacy and tolerability of newer antiepileptic drugs (AEDs).

Description of the intervention

During the past two decades, several newer AEDs have been investigated for epilepsy. Vigabatrin (VGB), a structural analogue of gamma-aminobutyric acid (GABA), is one of these drugs. Vigabatrin is often administered orally, has been approved by the US Food and Drug Administration to treat refractory complex partial seizures (CPS) and infantile spasms (IS) (Tolman 2009) and is currently available in more than 50 countries (Willmore 2009). A Cochrane systematic review of VGB as an add-on therapy for people with refractory partial-onset seizures found that it is effective in reducing seizure frequency, but this fact needs to be weighed against the risk of development of visual field defects (Hemming 2013). Wild 2007 reported a prospective observational study of patients with refractory partial epilepsy; using a multi-variate model, researchers estimated that 45.1% of patients taking VGB for longer than six months developed a VGB-associated visual field defect. They also found that the risk of developing a visual field deficit significantly increased with the duration of exposure and the mean dosage taken.

How the intervention might work

Vigabatrin is a relatively new AED that may exert its antiepileptic properties through several mechanisms of action. It can irreversibly inhibit the activity of GABA-transaminase, resulting in increased levels of GABA, an inhibitory neurotransmitter in the central nervous system (Petroff 1996; Wheless 2007). In animal seizure models, VGB-induced elevation of GABA levels has been associated with anticonvulsant activity (Gale 1986). Moreover, VGB may stimulate the release of GABA (Willmore 2009).

Why it is important to do this review

This review focused on the use of VGB as monotherapy for people with epilepsy, summarising evidence on efficacy and safety derived from randomised controlled trials (RCTs). This review also cross-referenced a sister systematic review of observational studies that assessed VGB add-on treatment and its effects on visual fields (Maguire 2010). This is an update of a Cochrane review first published in 2012.

OBJECTIVES

To investigate the efficacy and safety of VGB versus carbamazepine (CBZ) monotherapy for epilepsy in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished RCTs.

Types of participants

- Male and female patients of all ages with partial-onset seizures (simple partial, complex partial or secondarily generalising tonic-clonic seizures) or generalised onset tonic-clonic seizures.
- Patients treated with monotherapy.

Types of interventions

The experimental group received VGB and the control group was given CBZ as monotherapy.

Types of outcome measures

Primary outcomes

- Time to treatment withdrawal (retention time) for any reason.
 - * This global effectiveness outcome includes both efficacy and tolerability and is recommended as a primary outcome by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE) (Commission 1998).

Secondary outcomes

- Time to achieve six-month and 12-month remission after randomisation.
- Time to first seizure after randomisation.
- Numbers of participants who experienced any of the following common and important adverse events: skin rash, weight gain, dizziness, headache, fatigue, drowsiness, insomnia, depression, leucopenia (decrease in the number of white blood cells), visual field defects, visual disturbances, agitation and amnesia.

A systematic review of observational studies (Maguire 2010) assessing the risk of visual field defects was undertaken as part of the review of add-on VGB for refractory partial-onset seizures (Hemming 2013). We have presented the results of this review in the Results section and in the Discussion and Authors' conclusions sections of our review of VGB monotherapy.

Search methods for identification of studies

We conducted a systematic search to identify all relevant RCTs and applied no language restrictions.

Electronic searches

This search was run for the original review on 10 October 2011. Subsequent searches were run on 14 November 2013 and 1 July 2015. For the latest update, we searched the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3 of 4), using the strategy outlined in Appendix 1.
- MEDLINE (Ovid, 1948 to 1 July 2015), using the strategy outlined in Appendix 2.
- EMBASE (1974 to 1 July 2015), using the strategy outlined in Appendix 3.

- Chinese BioMedical Database (CBM-disc) (1980 to 1 July 2015), using the strategy outlined in [Appendix 4](#).

Previously, the Cochrane Epilepsy Group Specialised Register was also searched, but this search is no longer necessary as all Specialised Register records are now included in CENTRAL.

Searching other resources

We searched reference lists of included studies and review articles, as well as relevant journals from recent years. We contacted the pharmaceutical company Hoechst Marion Roussel, which produced VGB, to obtain relevant data, and we searched trial registers for ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (YX, LG) independently reviewed the titles and abstracts of all studies identified during the search. When we had retrieved all potentially relevant papers, each review author independently evaluated the full text of each paper for inclusion. We recorded excluded studies and the reasons for exclusion. Review authors did not disagree at any time regarding the selection of studies for inclusion.

Data extraction and management

We were unable to obtain individual patient data (IPD) from the original investigators. As planned, we performed the analysis based on the published data ([Williamson 2002](#)).

Two review authors (YX, LG) independently extracted the following information, using a data extraction form.

- Participants: seizure types, number in each group, age, gender, baseline comparability between groups, presence of neurological signs, date of randomisation, number of seizures before randomisation, electroencephalography (EEG) results.
- Methods: study design, randomisation method, allocation concealment method, stratification factors, blinding methods.
- Interventions: details of VGB or CBZ treatment, such as administration method, dosage and duration.
- Outcomes: primary and secondary outcomes, adverse events.
- Follow-up: duration of follow-up, numbers lost to follow-up, dates of and reasons for treatment withdrawals.
- Other: country and setting, publication year, sources of funding, intention-to-treat (ITT) analysis.

Review authors resolved minor disagreements about data extraction by discussion.

Assessment of risk of bias in included studies

Two review authors (YX, LG) independently assessed the methodological quality of the included studies by using the quality checklist recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The quality checklist for evaluating risk of bias consists of six specific parameters: (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting and (6) other bias. For each entry, the judgement ('low risk' of bias, 'high risk' of bias or 'unclear risk' of bias) is followed by a text box that provides a description of study design, conduct or observations

that underlie the judgement ([Higgins 2011](#)). Assessment of risk of bias resulted in no disagreement between review authors.

Measures of treatment effect

We managed data by applying the ITT principle. For time-to-event outcomes, we presented results as hazard ratios (HRs) with 95% confidence intervals (CIs). For dichotomous outcomes (adverse events), we presented results as risk ratios (RRs) with 95% CIs.

Unit of analysis issues

We conducted unit of analysis issues using guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

We contacted the authors of identified studies to obtain further data. We analysed available data when further information was not received after correspondence with study authors.

Assessment of heterogeneity

We evaluated the clinical and methodological heterogeneity of included trials by comparing characteristics of participants, interventions and study designs.

We evaluated statistical heterogeneity among included studies using the Chi² test and the I² test. If the I² statistic was greater than 50% (which indicates substantial heterogeneity ([Higgins 2011](#))), we used a random-effects model to examine sources of potential clinical and methodological heterogeneity.

Assessment of reporting biases

We could not determine potential publication biases by using funnel plots, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), because too few studies were eligible for inclusion.

Data synthesis

Because of insufficient included studies and lack of uniformity in outcomes reports, we could not perform a meta-analysis and could describe only some of the results. For adverse events outcomes, as we found no significant statistical heterogeneity among the included studies, we analysed the data using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We intended to undertake the following subgroup analyses.

- Different seizure types (i.e. partial, generalised).
- Different age groups (i.e. children (younger than 17 years of age) and adults).

However, because of the limited data derived from included studies, we could not perform subgroup analyses.

Sensitivity analysis

We intended to perform the following sensitivity analyses.

- Re-analysis excluding studies without adequate allocation concealment or blinding.
- Re-analysis using a random-effects model when a fixed-effect model was used previously.

However, because of the limited data provided by included studies, we could not perform all of the planned sensitivity analyses.

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

Through the original search on 10 October 2011, we identified 339 potentially relevant articles (Cochrane Epilepsy Group Specialised

Register: 39, CENTRAL: 69, MEDLINE: 55, EMBASE: 136, CBM: 40, pharmaceutical company: 0, trial registers: 0). After reviewing the titles and abstracts, we excluded 314 articles, as they were not relevant or were obvious duplicate publications. Of the remaining 25 articles, we excluded three articles ([Edwards 1998](#); [Gobbi 1999](#); [Van Paesschen 1998](#)). Finally, we included in the review five studies ([Chadwick 1999](#); [Kalviainen 1995](#); [Sobaniec 2005](#); [Tanganelli 1996](#); [Zamponi 1999](#)) involving 22 articles (see [Figure 1](#)). We identified no ongoing trials. We performed an updated search on 1 July 2015 and found no new studies.

Figure 1. Study flow diagram.

Included studies

We included five randomised studies ([Chadwick 1999](#); [Kalviainen 1995](#); [Sobaniec 2005](#); [Tanganelli 1996](#); [Zamponi 1999](#)) investigating the efficacy and safety of VGB versus CBZ monotherapy for epilepsy. Some results from the five studies were available as abstracts in conference proceedings before the full texts were published. We contacted study authors to obtain IPD and additional information that may not have been reported in the published articles. Only Dr. David Chadwick ([Chadwick 1999](#)) quickly responded to our requests. He told us that the IPD are in the possession of the sponsoring pharmaceutical company Hoechst Marion Roussel (now known as Aventis Pharmaceuticals, Inc.). To date, we have failed to obtain raw data from the company. As planned in the review protocol, we performed the first analysis using only published data ([Williamson 2002](#)).

Study design

All five trials were RCTs. In [Chadwick 1999](#), investigators performed double-blinding and allocation concealment. In [Kalviainen 1995](#), [Sobaniec 2005](#) and [Zamponi 1999](#), researchers used an open control design, meaning that neither investigators nor participants were blinded. All three studies did not mention allocation concealment. [Tanganelli 1996](#) was a response conditional cross-over study in which only non-responders were crossed over to phase 2, then to phase 3; therefore, only phase 1 period results were eligible, and blinding and allocation concealment were not mentioned.

Participants

We included five studies involving a total of 734 participants, with 51 to 459 participants reported for each study. All included participants were newly diagnosed with epilepsy. All studies included partial seizures, except [Kalviainen 1995](#), which included both partial and generalised seizures. Participant age ranged from six months to 65 years. Two studies ([Chadwick 1999](#); [Kalviainen 1995](#)) included both children and adult participants, two studies ([Sobaniec 2005](#); [Zamponi 1999](#)) included only children younger than 17 years of age and [Tanganelli 1996](#) included only adults from 18 to 65 years of age. All studies mentioned baseline seizure frequency over the eight weeks to two years before randomisation, except [Zamponi 1999](#), which reported the number of seizures before randomisation.

Interventions

All five studies compared VGB versus CBZ monotherapy for epilepsy. The dose of VGB in [Chadwick 1999](#) and [Kalviainen 1995](#), both of which included children and adults as participants, was 2.0 g/d or 50 mg/kg/d, with treatment duration of one year. In [Sobaniec 2005](#) and [Zamponi 1999](#), both of which included only children, the dose was between 50 and 60 mg/kg/d, with treatment duration of 24 weeks or two years. In [Tanganelli 1996](#), which included only adults, the dose was 2.5 g/d, with treatment duration of 16 weeks. The dose of CBZ in [Chadwick 1999](#) and [Kalviainen 1995](#) was 600 mg/d or reached a plasma mean level of 35 µmol/L; in [Sobaniec 2005](#) and [Zamponi 1999](#), the dose was between 15 and 20 mg/kg/d; in [Tanganelli 1996](#), it was 1.0 g/d.

Outcomes

Our primary outcome - time to treatment withdrawal - was reported only in [Chadwick 1999](#).

Our secondary outcomes - time to achieve six-month and 12-month remission and time to first seizure - were reported only in [Chadwick 1999](#).

All studies reported adverse events; however, in [Tanganelli 1996](#), investigators reported only one adverse event in the CBZ group during the treatment period and provided no details. In [Zamponi 1999](#), because some participants in the VGB or CBZ group were replaced or received other AEDs as add-on therapy during treatment, real adverse events may be confounded and could not be analysed because IPD were unavailable.

Excluded studies

We excluded three trials for the following reasons: [Edwards 1998](#), a controlled study comparing polytherapy with VGB versus CBZ monotherapy for partial seizures, did not meet our inclusion criteria; [Gobbi 1999](#) was a prospective study that used a non-RCT design; and [Van Paesschen 1998](#) used magnetic resonance (MR)-based cerebral T2 relaxation time measurements to compare the neuropathological effects of VGB when compared with CBZ in participants with newly diagnosed epilepsy but provided no clinical outcomes data.

Risk of bias in included studies

See 'Overall results of all risk of bias assessments' as summarised in [Figure 2](#) and [Figure 3](#).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Chadwick 1999	+	+	+	+	+	+	+
Kalviainen 1995	?	?	+	+	?	-	-
Sobaniec 2005	?	?	+	?	?	-	-
Tanganelli 1996	?	?	-	-	?	?	?
Zamponi 1999	?	?	-	-	?	-	-

Allocation

All five studies were reported as randomised. However, only [Chadwick 1999](#) reported the method used to generate allocation sequence (random permuted blocks, stored in sequentially sealed coded envelopes) to ensure adequate allocation concealment. The remaining four studies did not describe the method used to generate allocation sequence and did not mention allocation concealment. We corresponded with the contact authors but were not able to obtain additional information; therefore, it was not possible to determine whether randomisation and allocation concealment were adequate.

Blinding

In [Chadwick 1999](#), all study personnel, participants and outcome assessors were blinded to treatment, and a matched placebo was provided for VGB or CBZ; therefore, we judged that double-blinding was adequate. [Kalviainen 1995](#), [Sobaniec 2005](#) and [Zamponi 1999](#) used an open control design, which meant that no blinding was adopted in these studies; therefore, we judged double-blinding as inadequate. The remaining study ([Tanganelli 1996](#)) did not mention whether blinding was used; therefore, we judged this as study as having unclear risk of performance bias and detection bias.

Incomplete outcome data

Both [Chadwick 1999](#) and [Kalviainen 1995](#) provided numbers of, and reasons for, withdrawals, which were balanced across groups; we judged these studies to have low risk of incomplete outcome data bias. [Tanganelli 1996](#) reported seven withdrawals due to non-compliance but provided no details and excluded them from the analysis; therefore, we judged this study to have high risk of bias in this field. Similarly, [Zamponi 1999](#) excluded from the analysis five participants in the CBZ who discontinued treatment because they received other AEDs subsequently as add-on therapy; we also judged this trial to have high risk of bias in this field. We detected no missing outcome data in [Sobaniec 2005](#); therefore, we judged this trial as having low risk of bias.

Selective reporting

We were not able to confirm whether all prespecified primary or secondary outcomes were reported, as we could not obtain protocols from any of the five included trials. Given that all favourable and unfavourable results were reported in [Chadwick 1999](#) and [Kalviainen 1995](#), we judged both studies to have low risk of selective reporting bias. Both [Sobaniec 2005](#) and [Tanganelli 1996](#) reported only favourable results. In addition, [Tanganelli 1996](#) excluded withdrawals from the final analysis; as a result, we classified [Sobaniec 2005](#) as having unclear risk of bias, and [Tanganelli 1996](#) as having high risk of bias, in this field. We also considered [Zamponi 1999](#) to have high risk of bias in this field because reasons for discontinuation of treatment by participants in the CBZ group were not well addressed.

Other potential sources of bias

[Chadwick 1999](#) was funded by the VGB manufacturer Hoechst Marion Roussel, but because many unfavourable results were reported, conflicts of interest may not exist, and we judged this trial as having low risk of other potential sources of bias. The remaining four studies did not address whether study authors or intervention drugs showed any conflicts of interest; therefore, we judged these studies as having unclear risk of other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison VGB compared with CBZ monotherapy for epilepsy](#)

See [Summary of findings for the main comparison](#).

We included five studies in the final analysis; however, the outcomes chosen for this review were not reported in all studies. As planned in our review protocol, we first performed the analysis according to the reported data.

For analysis of time-to-event outcomes, an HR greater than one indicates that an event is more likely to occur with VGB than CBZ; accordingly, for time to treatment withdrawal, or time to first seizure, an HR greater than one indicates a clinical advantage favouring CBZ, and for time to achieve six-month and 12-month remission, an HR greater than one indicates a clinical advantage favouring VGB.

Primary outcomes

Time to treatment withdrawal (retention time) for any reason

Only one study involving 459 participants representing 62.5% of participants contributed to this outcome analysis ([Chadwick 1999](#)). As a result, we did not perform a meta-analysis by extracting aggregate data to synthesise results. The reported HR with 95% CI showed no significant differences between VGB and CBZ groups in time to treatment withdrawal, with an adjusted HR of 0.75 (95% CI 0.52 to 1.10) indicating no significant decrease in risk of withdrawal with VGB.

Secondary outcomes

Time to achieve six-month and 12-month remission after randomisation

Time to achieve six-month and 12-month remission after randomisation was reported only in [Chadwick 1999](#). However, [Chadwick 1999](#) could not be included in this analysis, as the endpoints were time to achieve six-month remission after the first six weeks of dose stabilisation from randomisation, but not since randomisation. No significant differences between VGB and CBZ groups were noted, and an adjusted HR of 1.18 (95% CI 0.89 to 1.55) indicated no significant increase in clinical advantage with VGB.

Time to first seizure after randomisation

Only one study involving 459 participants contributed to this outcome analysis ([Chadwick 1999](#)). Significant differences between VGB and CBZ groups in time to first seizure were noted, with an adjusted HR of 1.57 (95% CI 1.23 to 2.02) indicating a significant increase in clinical disadvantage with VGB.

Adverse events

All five studies reported adverse events, but data from only three studies ([Chadwick 1999](#); [Kalviainen 1995](#); [Sobaniec 2005](#)) involving 599 participants and representing 81.6% of participants contributed to this outcome analysis. Data from [Tanganelli 1996](#) and [Zamponi 1999](#) were not available. No significant differences were observed in the total number of participants with adverse events (RR 0.97, 95% CI 0.90 to 1.05) (see [Analysis 1.1](#)). The test for homogeneity indicated no significant heterogeneity ($I^2 = 17\%$); therefore, we applied a fixed-effect model. When analysed according to individually listed adverse events, VGB was associated with increased rates of weight gain (RR 2.18, 95% CI 1.18 to 4.00) (see [Analysis 1.2](#)) and fewer occurrences of skin rash (RR 0.26, 95% CI 0.12 to 0.56) (see [Analysis 1.3](#)) and drowsiness (RR 0.76, 95% CI 0.59 to 0.98) (see [Analysis 1.4](#)) when compared with CBZ. In addition, no significant differences were noted in the occurrence of headache (RR 0.98, 95% CI 0.69 to 1.40) (see [Analysis 1.5](#)), dizziness (RR 0.82, 95% CI 0.54 to 1.26) (see [Analysis 1.6](#)), fatigue (RR 0.90, 95% CI 0.63 to 1.29) (see [Analysis 1.7](#)), insomnia (RR 2.00, 95% CI 0.93 to 4.31) (see [Analysis 1.8](#)), depression (RR 2.22, 95% CI 0.95 to 5.16) (see [Analysis 1.9](#)), leucopenia (RR 0.21, 95% CI 0.01 to 4.28) (see [Analysis 1.10](#)), visual field defects (RR 5.37, 95% CI 0.27 to 106.88) (see [Analysis 1.11](#)), visual disturbances (RR 15.68, 95% CI 0.92 to 266.46) (see [Analysis 1.12](#)), agitation (RR 1.24, 95% CI 0.61 to 2.51) (see [Analysis 1.13](#)) and amnesia (RR 1.00, 95% CI 0.53 to 1.92) (see [Analysis 1.14](#)). We applied a fixed-effect model. When we replaced the fixed-effect model with a random-effects model, we found no significant changes.

We excluded [Zamponi 1999](#) from this outcome analysis because some participants in the VGB or CBZ group had been replaced or had received other AEDs as add-on therapy during treatment; therefore, real adverse events may be confounded until IPD become available. In this study, in the VGB group, the most frequently reported adverse event was weight gain, which occurred in 10 participants (26.3%); the next most frequent was irritability/excitability, which occurred in six participants (15.8%). In the CBZ group, the most frequent adverse events were skin rash and excessive sedation, each of which occurred in six participants (18.8%). One participant developed skin rash, which was associated with serious leucopenia; however, the white blood cell count returned to a normal level quickly after discontinuation of CBZ. The next most frequently reported adverse event was weight gain, which occurred in only three participants. These results are consistent with outcomes of the combined analysis. We also excluded [Tanganelli 1996](#) from this outcome analysis because only one adverse event was reported in the CBZ group during the first period and no further details were provided.

[Maguire 2010](#) reported a systematic review of 32 observational studies that assessed the prevalence of visual field defects following exposure to VGB for treatment of epilepsy. Review authors indicated that visual field defects occurred in approximately one-half of adults and one-third of children, and that increasing age and exposure dose were associated with high risk of this important adverse event.

DISCUSSION

Summary of main results

Vigabatrin has been shown to have some efficacy as adjunctive treatment for refractory epilepsy ([Hemming 2013](#)). This systematic review assessed the efficacy and safety of VGB as monotherapy for epilepsy in children and adults. Five studies involving a total of 734 participants were eligible for inclusion. However, it proved difficult to perform a meta-analysis by extracting aggregate data to synthesise the results as planned, mainly because not all studies reported our chosen outcomes; therefore, we could analyse only available data. For efficacy outcomes, we failed to show significant differences favouring VGB or CBZ for time to treatment withdrawal and time to achieve six-month remission after dose stabilisation from randomisation. Results did show a disadvantage for VGB on time to first seizure after randomisation when compared with CBZ. For safety outcomes, VGB was associated with more occurrences of weight gain, fewer occurrences of skin rash and drowsiness and no differences in visual field defects and visual disturbances.

It must be noted that most of the review results analysed were based on the largest study ([Chadwick 1999](#)). Although we assessed this study to have good methodological quality, it accounted for only 62.5% of the participants included in this review. Results of the remaining four studies, representing 37.5% of participants, were not available for some outcome analyses because of lack of uniformity in reporting of outcomes. Although all four studies assessed were of poor quality, unavailable data may have had a significant impact on the results of this review. In [Sobaniec 2005](#), [Tanganelli 1996](#) and [Zamponi 1999](#), study authors revealed no significant differences in efficacies between VGB and CBZ when using different outcome measurements. In [Kalviainen 1995](#), study authors indicated that more participants taking VGB discontinued treatment and fewer were seizure free, but adverse events were

fewer than with CBZ. We are not able to combine these trials for analysis until additional data are made available for an update of this review.

Another point to note is that all reported adverse events were short-term, and the most important adverse event of VGB - visual field defects - was reported rarely in any of the five studies, especially in the largest study, [Chadwick 1999](#). Although study authors have clarified that the study was initiated before first reports described visual field defects in participants exposed to VGB, it is understandable that RCTs have reported fewer safety concerns. Randomised controlled trials often include small numbers of participants and short-term follow-up, and they can provide sufficient statistical power for testing efficacy outcomes but not for identifying harms; this would decrease the external validity of safety concerns ([Yazici 2008](#)). Another important factor is that VGB-associated visual field defects are often asymptomatic, and this would greatly decrease reporting rates. As a result, it is not surprising that in this review, only two studies reported small numbers of participants who experienced visual field defects or visual disturbances and did not show significant differences between treatments. To better understand the safety of a drug, observational studies with large number of participants are more suitable than RCTs for detecting unexpected adverse events. A systematic review of 32 observational studies ([Maguire 2010](#)) assessing risk of visual field defects has been undertaken as part of the review of add-on VGB for refractory partial-onset seizures ([Hemming 2013](#)). Results have indicated that visual field defects occurred in approximately one-half of adults and one-third of children exposed to VGB for treatment of epilepsy. Review authors also found that increasing age and exposure dose were associated with higher risk of this important adverse event ([Maguire 2010](#)).

Overall completeness and applicability of evidence

It is difficult to give any recommendations for clinical practice of VGB monotherapy in treating epilepsy. In this review, most results were based on the largest study. We were not able to use aggregate data to synthesise results from the remaining four studies, which did not report the outcomes chosen for this review. Additionally, not all outcomes, subgroup analyses or sensitivity analyses could be performed as planned because included studies were few.

Quality of the evidence

The small number and poor quality of included studies and unavailable data make the results of this review unconvincing. Only one study ([Chadwick 1999](#)) was assessed as having good quality; investigators used a double-blinding design and adequate methods of randomisation and allocation concealment. We assessed the remaining four trials ([Kalviainen 1995](#); [Sobaniec 2005](#); [Tanganelli 1996](#); [Zamponi 1999](#)) as having poor quality; three of them ([Kalviainen 1995](#); [Sobaniec 2005](#); [Zamponi 1999](#)) used an open control design, which meant that no blinding was adopted; the other study ([Tanganelli 1996](#)) did not mention blinding. In addition, all four studies reported no details of the randomisation method used, and did not provide clear information on allocation concealment. Absence of blinding and unclear methods of randomisation and allocation concealment contribute to high risk of selection, performance and detection bias, which may lead to an overestimation of intervention effects ([Boutron 2004](#); [Shulz 1995](#)). In spite of poor methodological quality and lack of uniformity in reported outcomes, of the four studies assessed

as having poor quality (Kalviainen 1995; Sobaniec 2005; Tanganelli 1996; Zamponi 1999), two contributed to the analysis of adverse events (Kalviainen 1995; Sobaniec 2005).

Other concerns included statistical power and clinical heterogeneity of included studies. Only Chadwick 1999 reported a sample size calculation and performed an ITT analysis; the other four studies (Kalviainen 1995; Sobaniec 2005; Tanganelli 1996; Zamponi 1999) carried out no sample size calculations and did not report ITT analysis. All four studies recruited relatively small numbers of participants, which may have led to inadequate statistical power; obviously neither Tanganelli 1996 nor Zamponi 1999 performed an ITT analysis because some participants were excluded from the final analysis. Clinical heterogeneity was another important concern; first, age of participants ranged from six months to 65 years, one study recruited only adults and some studies included only children; second, the reported dose and duration of VGB varied substantially among studies.

Potential biases in the review process

Potential biases from trials

Although we undertook an extensive and comprehensive search to limit bias in the review process, we could not confirm whether other studies with negative findings were not identified because trials with negative findings remain unpublished more often than trials with positive findings (Hopewell 2009). In addition, upon contacting study authors, we did not receive all additional information required.

Potential biases from review authors

Review authors introduced into the review process no potential biases. In preparing this review, two review authors independently read and screened trials retrieved for inclusion and independently extracted data and assessed the quality of included trials to

minimise potential biases. The authors of this review have reported no conflicts of interest related to the review.

Agreements and disagreements with other studies or reviews

No systematic reviews have explored the efficacy and safety of vigabatrin versus carbamazepine as monotherapy for epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is currently insufficient to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy. Given the high prevalence of visual field defects reported in a systematic review of observational studies (Maguire 2010), but not in our review, VGB monotherapy for epilepsy should be prescribed with caution and should not be considered as a first-line choice; if necessary, healthcare workers should frequently assess the visual field.

Implications for research

Future research should focus on investigating the reasons for visual field defects and exploring potential prevention strategies.

Future studies of monotherapy for epilepsy should report results according to recommendations of the ILAS Commission (Commission 1998) and should improve the quality of study methods.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Epilepsy Review Group for help in developing this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chadwick 1999

Methods	<p>Multi-centre, double-blind, randomised, parallel-group study</p> <p>Random list was generated using random permuted blocks</p> <p>Allocation sequence used sequentially sealed coded envelopes to make sure participants and investigators could not predict the assignment</p> <p>Double-blinded: All study personnel, participants and outcome assessors were blinded</p> <p>ITT analysis: yes</p>
Participants	<p>Setting: Europe</p> <p>Patients with newly diagnosed epilepsy, from 12 to 65 years of age with ≥ 2 seizures (simple or complex partial seizures with or without secondary generalisation) during the previous year were enrolled in the trial. 229 participants were randomly assigned to VGB and 230 to CBZ</p> <p>Exclusion criteria: generalised seizure</p> <p>Baseline clinical characteristics were comparable between the 2 groups</p>
Interventions	<p>Monotherapy with VGB or CBZ was provided for 52 weeks. After randomisation, participants started with VGB 1 g/d or CBZ 200 mg/d, gradually increased to maintenance of VGB 2 g/d or CBZ 600 mg/d. During maintenance treatment, increases in VGB to 4 g/d or CBZ to 600 mg/d, or decreases in VGB to 1.5 g/d or CBZ to 400 mg/d, were allowed, according to seizure control or adverse events</p>
Outcomes	<ul style="list-style-type: none"> Time to treatment failure Time to achieve 6 months of remission Time to first seizure Adverse events
Notes	<p>228 participants in VGB group and 229 participants in CBZ group were included in the ITT analysis. Both groups excluded 1 participant because of failure to take investigated drug</p> <p>When we contacted the study author, Dr. David Chadwick, he quickly responded to our requests; he told us that IPD are in the possession of the sponsoring pharmaceutical company Hoechst Marion Roussell (now known as Aventis Pharmaceuticals, Inc.). Attempts by review authors to obtain raw data from the current company have failed</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random list was generated with the use of random permuted blocks

Chadwick 1999 (Continued)

Allocation concealment (selection bias)	Low risk	Allocation sequence was determined by using sequentially sealed coded envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of and reasons for withdrawals were carefully reported and were balanced across groups
Selective reporting (reporting bias)	Low risk	All favourable and unfavourable results were reported
Other bias	Low risk	The study was funded by the manufacturer Hoechst Marion Roussel, but because many unfavourable results were reported, we judged that conflicts of interest may not exist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Dr. David Chadwick told us that outcome assessors were blinded

Kalviainen 1995

Methods	Randomised, open, controlled study Random allocation of participants was mentioned in the original article but without details; no blinding was adopted, and allocation concealment was not mentioned. We could not obtain additional information upon corresponding with study authors ITT analysis: not reported, but study authors analysed all participants enrolled since the start of the study
Participants	Setting: Finland Patients with newly diagnosed epilepsy from 15 to 64 years of age with ≥ 2 seizures (partial seizures and/or generalized tonic-clonic seizures) or with 1 seizure and distinct electroencephalographic changes indicative of epilepsy during the previous 2 years were enrolled in the trial. 50 participants were randomly assigned to VGB and 50 to CBZ Exclusion criteria: alcohol-related seizures, current alcohol or other drug abuse, progressive neurological disorders, mental retardation, severe psychiatric problems or other severe medical disorders Baseline clinical characteristics were comparable between groups
Interventions	Monotherapy with VGB or CBZ was provided for 12-month follow-up period; daily dose of VGB was increased to mean level of 50 mg/kg, and CBZ was increased to plasma mean level of 35 $\mu\text{mol/L}$ (therapeutic range, 20 to 50 $\mu\text{mol/L}$ according to efficacy and safety) during 2-month titration phase, followed by maintenance phase of the study
Outcomes	<ul style="list-style-type: none"> Seizure free Safety Cognitive function
Notes	Only adverse events were reported; primary and secondary outcomes chosen for this review were not reported

Kalviainen 1995 (Continued)

Study authors have indicated that VGB was associated with greater likelihood of discontinuation of treatment due to lack of efficacy; fewer participants were seizure free and fewer adverse events were seen than with CBZ

IPD are not available at present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of and reasons for withdrawals were carefully reported and balanced across groups
Selective reporting (reporting bias)	Low risk	Favourable and unfavourable results were reported
Other bias	Unclear risk	Conflict of interests unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study

Sobaniec 2005

Methods	<p>Randomised, open study</p> <p>Random allocation of participants was mentioned in the original article but without details, no blinding was adopted and allocation concealment was not mentioned. We could not obtain additional information by contacting study authors</p> <p>ITT analysis: not reported, but study authors analysed all participants enrolled since the start of the study</p>
Participants	<p>Setting: Poland</p> <p>Patients with newly diagnosed epilepsy from 2 to 17 years of age with ≥ 2 seizures (partial seizures with or without secondary generalisation) during the previous 6 months were enrolled in the trial. 26 participants were randomly assigned to VGB and 28 to CBZ</p>
Interventions	<p>Monotherapy with VGB or CBZ was provided for 24 weeks; mean dose of VGB was 50 mg/kg/d, and mean dose of CBZ was 18 mg/kg/d</p>
Outcomes	<ul style="list-style-type: none"> Number of seizures Percentage reduction in seizures Safety

Sobaniec 2005 (Continued)

- EEG

Notes	<p>Only adverse events were reported; primary and secondary outcomes chosen for this review were not reported</p> <p>Study authors have indicated that VGB and CBZ have similar effects in terms of total numbers of seizures, percentage reduction in seizures and adverse events</p> <p>IPD are not available at present</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description was provided
Allocation concealment (selection bias)	Unclear risk	No description was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	Only favourable results were reported
Other bias	Unclear risk	Conflicts of interest are unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study

Tanganelli 1996

Methods	<p>Randomised, response conditional cross-over study</p> <p>Random allocation of participants was mentioned in the original article but without details, and allocation concealment and blinding were not mentioned. We could not obtain additional information by contacting study authors</p> <p>ITT analysis: no; 7 enrolled participants were excluded from the analysis</p>
Participants	<p>Setting: Italy</p> <p>Patients with newly diagnosed epilepsy from 18 to 65 years of age with ≥ 2 seizures (complex partial seizures, with or without secondary generalisation) during the previous 8 weeks were enrolled in the trial. 26 participants were randomly assigned to VGB and 25 to CBZ</p> <p>Baseline clinical characteristics were comparable between groups</p>

Tanganelli 1996 (Continued)

Interventions	<p>Monotherapy with VGB or CBZ was provided for 48 weeks over 3 phases. After randomisation, participants started with VGB 1 g/d or CBZ 0.2 g/d, gradually increased to mean maintenance of VGB 2.5 g/d or CBZ 1.0 g/d</p> <p>Phase 1: randomisation period; participants were randomly allocated to VGB or CBZ group (16 weeks)</p> <p>Phase 2: cross-over period; participants with persisting seizures or intolerable adverse events in phase 1 were crossed over to the alternative drug (16 weeks)</p> <p>Phase 3: combined therapy period; participants who did not respond to either drug were enrolled (16 weeks)</p>
Outcomes	<ul style="list-style-type: none"> • Complete seizure control • Persisting seizures • Adverse events
Notes	<p>Study used a response conditional cross-over design, in which only non-responders were crossed over to phase 2, then to phase 3; therefore, only phase 1 results were eligible for inclusion</p> <p>Seven randomly assigned participants were withdrawn because of non-compliance but without details regarding treatment group assignment; they were excluded from the analysis</p> <p>Primary or secondary outcomes chosen for this review were not reported; however, 1 adverse event was recorded in CBZ group during phase 1 period but without details.</p> <p>In the phase 1 period, study authors indicated that 12 out of 26 participants (46.1%) in the VGB group and 14 of 25 participants (56%) in the CBZ group achieved complete seizure control</p> <p>IPD are not available at present</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description was provided
Allocation concealment (selection bias)	Unclear risk	No description was provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven participants were withdrawn because of non-compliance but without details regarding treatment group assignment; they were excluded from the analysis
Selective reporting (reporting bias)	High risk	All reported results were favourable. Participants withdrawn were not included in the analysis; it was not recorded to which group they belonged
Other bias	Unclear risk	Conflicts of interest were unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description was provided

Zamponi 1999

Methods	<p>Randomised, open, controlled study</p> <p>Random allocation of participants was mentioned in the original article but without details; no blinding was adopted, and allocation concealment was not mentioned. We could not obtain additional information by contacting study authors</p> <p>As the result of adverse events or lack of efficacy, some participants in the CBZ or VGB group were replaced, or they received other AEDs</p> <p>ITT analysis: no; some enrolled participants were excluded from the analysis</p>
Participants	<p>Setting: Italy</p> <p>Patients newly diagnosed with partial epilepsy, 6 months to 10 years 3 months of age in the VGB group, and 3 years to 13 years 2 months of age in the CBZ group, were enrolled in the trial. 38 participants were randomly assigned to VGB, and 32 to CBZ. In the VGB group, seizures before randomisation were fewer than 10 in 30 participants, 10 to 50 in 5 participants, and more than 50 in 3 participants; in the CBZ group, seizures before randomisation were fewer than 10 in 28 patients, and 10 to 50 in 4 participants</p>
Interventions	<p>Monotherapy with VGB or CBZ was provided with a 2-year follow-up period; mean dose of VGB was 50 to 60 mg/kg/d, and mean dose of CBZ was 15 to 20 mg/kg/d</p>
Outcomes	<ul style="list-style-type: none"> Complete seizure control Adverse events
Notes	<p>Primary and secondary outcomes chosen for this review were not reported. Also, because of adverse events or lack of efficacy, 8 participants in the VGB group were replaced and received other AEDs; in the CBZ group, 5 participants received other AEDs as add-on therapy</p> <p>Study authors have indicated that efficacy was similar between VGB and CBZ in terms of complete seizures and relapse (76.3% vs 78.1%, respectively)</p> <p>IPD are not available at present</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	High risk	Five patients discontinued in the CBZ groups were excluded from the analysis because of receiving other AEDs subsequently as add-on therapy
Selective reporting (reporting bias)	High risk	The reasons why five patients discontinued treatment in the CBZ group and received other AEDs as add-on therapy have not been addressed
Other bias	Unclear risk	Conflict of interests unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study

Zamponi 1999 (Continued)

Blinding of outcome assessment (detection bias)	High risk	Open study
All outcomes		

AEDs: antiepileptic drugs.
CBZ: carbamazepine.
EEG: electroencephalogram.
IPD: individual patient data.
ITT: intention-to treat.
RCT: randomised controlled trial.
VGB: vigabatrin.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Edwards 1998	Polytherapy comparisons
Gobbi 1999	Not an RCT
Van Paesschen 1998	Outcome measure was MR-based cerebral T2 relaxation time

MR: magnetic resonance.
RCT: randomised controlled trial.

DATA AND ANALYSES
Comparison 1. Vigabatrin versus carbamazepine (adverse events)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total number of participants with adverse events	3	599	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.05]
2 Weight gain	2	511	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.18, 4.00]
3 Skin rash	2	545	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.12, 0.56]
4 Drowsiness	2	545	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.98]
5 Headache	2	545	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.69, 1.40]
6 Dizziness	3	599	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.26]
7 Fatigue	1	457	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.63, 1.29]
8 Insomnia	3	599	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.93, 4.31]
9 Depression	2	545	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [0.95, 5.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Leucopenia	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.28]
11 Visual field defects	1	54	Risk Ratio (M-H, Fixed, 95% CI)	5.37 [0.27, 106.88]
12 Visual disturbances	1	88	Risk Ratio (M-H, Fixed, 95% CI)	15.68 [0.92, 266.46]
13 Agitation	1	457	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.61, 2.51]
14 Amnesia	1	457	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.53, 1.92]

Analysis 1.1. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 1 Total number of participants with adverse events.

Analysis 1.2. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 2 Weight gain.

Analysis 1.3. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 3 Skin rash.

Analysis 1.4. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 4 Drowsiness.

Analysis 1.5. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 5 Headache.

Analysis 1.6. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 6 Dizziness.

Analysis 1.7. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 7 Fatigue.

Analysis 1.8. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 8 Insomnia.

Analysis 1.9. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 9 Depression.

Analysis 1.10. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 10 Leucopenia.

Analysis 1.11. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 11 Visual field defects.

Analysis 1.12. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 12 Visual disturbances.

Analysis 1.13. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 13 Agitation.

Analysis 1.14. Comparison 1 Vigabatrin versus carbamazepine (adverse events), Outcome 14 Amnesia.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Vigabatrin explode all trees
#2 (vigabatrin or Sabril)
#3 (#1 OR #2)
#4 MeSH descriptor Carbamazepine explode all trees
#5 (carbamazepine or Tegretol)
#6 (#4 OR #5)
#7 MeSH descriptor Epilepsy explode all trees
#8 MeSH descriptor Seizures explode all trees
#9 (epilep* or seizure* or convulsion*)
#10 (#7 OR #8 OR #9)
#11 (#3 AND #6 AND #10)

Appendix 2. MEDLINE search strategy

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

#1 randomized controlled trial.pt.
#2 controlled clinical trial.pt.
#3 randomized.ab.
#4 placebo.ab.
#5 clinical trials as topic.sh.
#6 randomly.ab.
#7 trial.ti.
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 exp animals/ not humans.sh.
#10 #8 not #9
#11 exp Epilepsy/
#12 exp Seizures/
#13 (epilep\$ OR seizure\$ OR convulsion\$).tw.
#14 #11 OR #12 OR #13
#15 exp Vigabatrin/
#16 (vigabatrin OR Sabril).tw.
#17 #15 OR #16
#18 exp Carbamazepine/
#19 carbamazepine OR Tegretol.tw.
#20 #18 OR #19
#21 #10 AND #14 AND #17 AND #20

Appendix 3. EMBASE search strategy

#1 'randomized controlled trial'/exp

```
#2 'controlled clinical trial'/exp
#3 random*:ab.
#4 placebo:ab.
#5 'clinical trial':ab.
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'epilepsy'/exp
#8 'seizure'/exp
#9 'convulsion'/exp
#10 epilep*:ab.
#11 seizure*:ab.
#12 convulsion*:ab.
#13 #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 'vigabatrin'/exp
#15 Sabril:ab.
#16 #14 OR #15
#17 'carbamazepine'/exp
#18 Tegretol:ab.
#19 #17 OR #18
#20 #6 AND #13 AND #16 AND #19
```

Appendix 4. Chinese BioMedical Database search strategy

```
#1 (MeSH)
#2 (Ti/Ab/Kw/Tx)
#3 #1 OR #2
#4 (MeSH)
#5 (Ti/Ab/Kw/Tx)
#6 #4 OR #5
#7 (MeSH)
#8 (Ti/Ab/Kw/Tx)
#9 #7 OR #8
#10 #3 AND #6 AND #9
```

WHAT'S NEW

Date	Event	Description
1 July 2015	New citation required but conclusions have not changed	No new studies were identified; conclusions remain unchanged
1 July 2015	New search has been performed	Searches were updated on 1 July 2015

CONTRIBUTIONS OF AUTHORS

All review authors listed contributed to this review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

This review was supported by the National Institute for Health Research via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias was assessed according to the recently released version of the *Cochrane Handbook for Systematic Reviews of Interventions* (5.1) ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Carbamazepine [adverse effects] [*therapeutic use]; Epilepsy [*drug therapy]; Randomized Controlled Trials as Topic; Risk Assessment; Vigabatrin [adverse effects] [*therapeutic use]

MeSH check words

Humans