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[Intervention Review]

Felbamate add-on therapy for drug-resistant focal epilepsy

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ABSTRACT

Background

This is an updated version of the Cochrane Review previously published in 2017.

Epilepsy is a chronic and disabling neurological disorder, affecting approximately 1% of the population. Up to 30% of people with epilepsy have seizures that are resistant to currently available antiepileptic drugs and require treatment with multiple antiepileptic drugs in combination. Felbamate is a second-generation antiepileptic drug that can be used as add-on therapy to standard antiepileptic drugs.

Objectives

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

Search methods

For the latest update we searched the Cochrane Register of Studies (CRS Web), MEDLINE, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), on 18 December 2018. There were no language or time restrictions. We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies. We also contacted the manufacturers of felbamate and experts in the field for information about any unpublished or ongoing studies.

Selection criteria

We searched for randomised placebo-controlled add-on studies of people of any age with drug-resistant focal seizures. The studies could be double-blind, single-blind or unblinded and could be of parallel-group or cross-over design.

Data collection and analysis

Two review authors independently selected studies for inclusion and extracted information. In the case of disagreements, the third review author arbitrated. Review authors assessed the following outcomes: 50% or greater reduction in seizure frequency; absolute or percentage reduction in seizure frequency; treatment withdrawal; adverse effects; quality of life.

Main results

We included four randomised controlled trials, representing a total of 236 participants, in the review. Two trials had parallel-group design, the third had a two-period cross-over design, and the fourth had a three-period cross-over design. We judged all four studies to be at an unclear risk of bias overall. Bias arose from the incomplete reporting of methodological details, the incomplete and selective reporting of outcome data, and from participants having unstable drug regimens during experimental treatment in one trial. Due to significant

methodological heterogeneity, clinical heterogeneity and differences in outcome measures, it was not possible to perform a meta-analysis of the extracted data.

Only one study reported the outcome, 50% or greater reduction in seizure frequency, whilst three studies reported percentage reduction in seizure frequency compared to placebo. One study claimed an average seizure reduction of 35.8% with add-on felbamate while another study claimed a more modest reduction of 4.2%. Both studies reported that seizure frequency increased with add-on placebo and that there was a significant difference in seizure reduction between felbamate and placebo ($P = 0.0005$ and $P = 0.018$, respectively). The third study reported a 14% reduction in seizure frequency with add-on felbamate but stated that the difference between treatments was not significant. There were conflicting results regarding treatment withdrawal. One study reported a higher treatment withdrawal for placebo-randomised participants, whereas the other three studies reported higher treatment withdrawal rates for felbamate-randomised participants. Notably, the treatment withdrawal rates for felbamate treatment groups across all four studies remained reasonably low (less than 10%), suggesting that felbamate may be well tolerated. Felbamate-randomised participants most commonly withdrew from treatment due to adverse effects. The adverse effects consistently reported by all four studies were: headache, dizziness and nausea. All three adverse effects were reported by 23% to 40% of felbamate-treated participants versus 3% to 15% of placebo-treated participants.

We assessed the evidence for all outcomes using GRADE and found it as being very-low certainty, meaning that we have little confidence in the findings reported. We mainly downgraded evidence for imprecision due to the narrative synthesis conducted and the low number of events. We stress that the true effect of felbamate could likely be significantly different from that reported in this current review update.

Authors' conclusions

In view of the methodological deficiencies, the limited number of included studies and the differences in outcome measures, we have found no reliable evidence to support the use of felbamate as an add-on therapy in people with drug-resistant focal-onset epilepsy. A large-scale, randomised controlled trial conducted over a longer period of time is required to inform clinical practice.

PLAIN LANGUAGE SUMMARY

Felbamate used with other antiepileptic drugs for drug-resistant focal epilepsy

Background

Up to 30% of people with epilepsy still suffer epileptic seizures despite trying multiple antiepileptic drugs, whether separately or in combination. These people are described as having drug-resistant epilepsy. Drug-resistance is most common in people with focal epilepsy (epilepsy that initially begins in one area of the brain, but can progress to affect the whole brain). Felbamate is an antiepileptic drug that might be effective for people with drug-resistant focal epilepsy when used with other antiepileptic drugs.

Aim of the review

This review investigated whether felbamate is effective and tolerable for people with drug-resistant focal epilepsy, when used with other antiepileptic drugs (add-on therapy).

Results

After searching the available literature, we found four trials, involving 236 participants, that investigated the use of felbamate in people with drug-resistant focal epilepsy. We included the four trials in the review.

Although three of the trials reported percentage reduction in seizure frequency, they all reported very different results. One reported a 36% reduction in seizure frequency with felbamate, one reported only a 4% reduction with felbamate, and the other trial reported that there was no difference between felbamate and placebo (an inactive, dummy drug). We therefore found no clear evidence to suggest that felbamate was better than placebo at reducing seizure frequency for people with drug-resistant focal epilepsy. Additionally, there was mixed evidence about whether more people withdraw from treatment with felbamate or placebo. Notably, less than 10% of people in each trial withdrew from treatment when they were receiving felbamate, suggesting that felbamate may have good tolerability. The side effects that were reported by all four trials, suggesting that they are the most common, were headache, dizziness, and nausea.

Quality of evidence

It is important to note that the four trials in this review studied a small number of people, over a short period of time (less than 10 weeks). We are very uncertain about whether the findings of this review are accurate. It is likely that the true effect of felbamate could be very different to that reported here. More large trials, conducted over a longer period of time are necessary to improve the certainty of the findings reported by this review.

The evidence is current to 18 December 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Add-on felbamate compared to placebo for drug-resistant focal epilepsy

Add-on felbamate compared to placebo for drug-resistant focal epilepsy

Patient or population: people with drug-resistant focal epilepsy

Setting: inpatients and outpatients

Intervention: felbamate

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with felbamate				
50% or greater reduction in seizure frequency Follow-up: 8 weeks	No pooled analysis			83 (1 RCT)	⊕○○○ Very low ^{1,2}	In the one study that reported this outcome (Binelli 1999), 38% of participants who were allocated to add-on felbamate had a > 50% reduction in seizures. Of these, 11% had complete cessation of seizures. No data were reported for participants randomised to add-on placebo.
Absolute or percentage reduction in seizure frequency Follow-up (range): 8 weeks to 10 weeks	No pooled analysis			172 (3 RCTs)	⊕○○○ Very low ^{1,2,3}	One study reported a percentage reduction in seizure frequency of 35.8% for participants randomised to felbamate compared to a percentage increase of 3.3% for those randomised to placebo (Binelli 1999). Another study (Leppik 1991), reported a less striking percentage reduction in seizure frequency with add-on felbamate (4.24 ± 55.61%) but a much larger increase in seizure frequency with add-on placebo (-19.14 ± 79.70%). Notably, the direction of effect was the same for both of these studies. The third study (Theodore 1991), reported that there was no significant difference in seizure reduction between the two treatment groups.
Treatment withdrawal Follow-up (range): 2 weeks to 10 weeks	No pooled analysis			236 (4 RCTs)	⊕○○○ Very low ^{1,2,4}	Three of the studies (Bourgeois 1993; Leppik 1991; Theodore 1991), reported a higher treatment withdrawal amongst participants randomised to felbamate compared to placebo, however, one study (Binelli 1999), reported a lower treatment withdrawal rate for participants randomised to felbamate compared to placebo (4 vs 8 participants, respectively). The two cross-over studies (Bourgeois 1993; Leppik 1991), specifically reported that no partic-



				ipants withdrew from treatment during the placebo treatment period. The direction of effect is therefore unclear.
Adverse effects	No pooled analysis	236 (4 RCTs)	⊕⊕⊕⊕ Very low ^{1,2}	Amongst the adverse effects reported, headache and dizziness were both reported by all four studies whilst diplopia, nausea and vomiting were each reported by three of the included studies. Two of the studies (Bourgeois 1993 ; Leppik 1991), described the incidence of adverse effects for both treatment groups. The number of participants experiencing individual adverse effects was consistently higher amongst those randomised to felbamate compared to placebo. Other reported adverse effects included: ataxia, fatigue and blurred vision.
Follow-up (range): 2 weeks to 10 weeks				
Quality of life	No pooled analysis	64 (1 RCT)	⊕⊕⊕⊕ Very low ^{1,2}	One study (Bourgeois 1993), reported that motor skills and memory skills, as assessed by a Short Neuropsychological Test, remained the same or improved following treatment. The study did not, however, indicate whether there was any difference in outcome between the add-on felbamate and placebo treatment groups.
Follow-up: 4 weeks				

CI: confidence interval; RCT: randomised controlled trial

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.

¹We downgraded evidence once for risk of bias due to a lack of methodological details provided, incomplete outcome data, incomplete reporting of outcomes, and other potential bias regarding the stability of participants' drug regimen.

²We downgraded evidence once for imprecision due to the narrative synthesis conducted and the absence of an estimated effect size. We downgraded evidence again for imprecision because the number of events did not satisfy the optimal information size.

³We downgraded evidence once for inconsistency because the magnitude of effect varied greatly between the three studies that reported this outcome.

⁴We downgraded evidence once for inconsistency because one of the studies reported the opposite direction of effect for this outcome.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (Issue 7, 2017), titled 'Felbamate as an add-on therapy for refractory epilepsy' (Shi 2017).

Description of the condition

Epilepsy is a chronic and disabling neurological disorder, characterised by seizures of various types and frequency. Epilepsy affects approximately 1% of the population (French 1999). Although up to two-thirds of people with epilepsy will become seizure-free on a single antiepileptic drug, up to 30% of people are considered to be drug-resistant and are not seizure-free, despite multiple medications (Granata 2009). Various criteria have been used to define drug-resistant epilepsy. The consensus definition of drug-resistant epilepsy proposed by the Task Force of the International League Against Epilepsy (ILAE) is now, "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan 2010).

Over the past 15 to 20 years, numerous second-generation antiepileptic drugs have become available, since standard drugs (e.g. carbamazepine, phenytoin, valproate) do not control all seizures in all people. Felbamate, one of these antiepileptic drugs, is the subject of this review.

Description of the intervention

Felbamate is an antiepileptic drug that can be taken orally. It is thought to be a broad-spectrum drug that is effective for a number of seizure types (Pellock 1999). The use of felbamate has been limited following reports of aplastic anaemia and hepatic failure (Pellock 1999).

How the intervention might work

The exact mechanism of action is unclear. The following possible mechanisms have been suggested: the inhibition of N-methyl-D-aspartate (NMDA) receptor-related sodium currents; the potentiation of γ -aminobutyric acid (GABA)-ergic activity; and the inhibition of voltage-gated sodium channels (Kleckner 1999; Meldrum 1996; Rho 1994).

Why it is important to do this review

Felbamate is marketed in a number of countries as an add-on treatment. A summary of data regarding its efficacy and tolerability from randomised controlled trials will help inform treatment decisions.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Studies were required to meet all of the following criteria:

1. Randomised controlled trials;

2. Parallel-group or cross-over design;
3. Double-blind, single-blind, or unblinded;
4. Placebo-controlled.

Types of participants

Participants of any age with drug-resistant focal-onset seizures (simple focal, complex focal or secondarily generalised tonic-clonic seizures).

Types of interventions

1. The active treatment group received felbamate in addition to conventional antiepileptic drug treatment.
2. The control group received matching placebo in addition to conventional antiepileptic drug treatment.

Types of outcome measures

Primary outcomes

50% or greater reduction in seizure frequency

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

Secondary outcomes

Absolute or percentage reduction in seizure frequency

Absolute reduction in seizure frequency is the seizure frequency during the baseline period minus the seizure frequency in the treatment period. Percentage reduction in seizure frequency is the absolute reduction in seizure frequency divided by the seizure frequency during the baseline period, all multiplied by 100.

Treatment withdrawal

We used the proportion of participants having treatment withdrawn during the course of the treatment period as a measure of 'global effectiveness'. The treatment may have been withdrawn due to adverse effects, lack of efficacy or a combination of both.

Adverse effects

We recorded the proportion of participants experiencing the following seven adverse effects:

1. aplastic anaemia;
2. hepatic failure;
3. ataxia;
4. dizziness;
5. fatigue;
6. nausea;
7. somnolence.

We chose aplastic anaemia and hepatic failure as they had been reported as the potential serious adverse effects of felbamate. We chose the other adverse effects as we considered them to be common and important adverse effects of all antiepileptic drugs.

We also extracted data regarding the proportion of participants experiencing the most common adverse effects (up to 10 adverse effects per study) if they were different from those listed above.

Quality of life

Since there is lack of consensus on how quality of life should be measured, we summarised data qualitatively.

Search methods for identification of studies

We ran the search for the original review on 20 May 2010 and ran subsequent searches on 24 July 2013, 4 Aug 2015, 20 October 2016, and 18 December 2018.

Electronic searches

For the latest update, we searched the following databases. There were no language and time restrictions.

1. The Cochrane Register of Studies (CRS Web, 18 December 2018) using the search strategy outlined in [Appendix 1](#). This includes the Cochrane Epilepsy Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL).
2. MEDLINE (Ovid, 1946 to December 17, 2018) using the search strategy outlined in [Appendix 2](#).
3. [ClinicalTrials.gov](#) (18 December 2018) using the search strategy shown in [Appendix 3](#).
4. [WHO International Clinical Trials Registry Platform](#) (ICTRP, 18 December 2018) using the search strategy shown in [Appendix 4](#).

Searching other resources

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

We contacted the manufacturers of felbamate and experts in the field for information about any unpublished or ongoing studies.

Data collection and analysis

Selection of studies

For the current review update, two review authors (RB and KMM) independently assessed studies for inclusion. We resolved disagreements by discussion.

For the previous review updates and the original review, two review authors (LS and JG) assessed studies for inclusion, whilst a third author (TW) arbitrated.

Data extraction and management

We extracted the relevant data from the studies supplied by the authors and the manufacturers of felbamate. During the previous review updates, as well as for the original review, two review authors (LS and JG) extracted the following information from the included studies whilst a third author (TW) arbitrated.

Methodological/trial design

1. Method of randomisation and concealment of randomisation
2. Method of blinding
3. Duration of baseline period
4. Duration of treatment period
5. Duration of 'wash-out' period in cross-over studies
6. Dose(s) of felbamate tested
7. Description of withdrawals and dropouts

Participant demographic information

1. Total number of participants allocated to each treatment group
2. Age/sex
3. Types of seizure
4. Mean baseline seizure frequency
5. Number of background drugs

Outcomes

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

Assessment of risk of bias in included studies

For the current update, two review authors (RB and KMM) independently assessed the risk of bias of the included studies using the Cochrane 'Risk of bias' tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). During previous review updates, and during the original review, two other review authors (LS and JG) independently assessed studies for bias. In total, we assessed the studies across seven 'Risk of bias' domains.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessors (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)
7. Other bias

We described supporting information for each of our judgements for each study. We resolved disagreements by discussion. If disagreements persisted, a third review author (TW) arbitrated.

Measures of treatment effect

We planned to express relative treatment effects as risk ratios with 95% confidence intervals for dichotomous data, and mean differences with 95% confidence intervals for continuous data. We would have considered a P value of less than or equal to 0.05 as statistically significant.

Unit of analysis issues

The inclusion of cross-over studies in a meta-analysis introduces unit of analysis issues. This is because the repeated measures design, utilised by cross-over studies, means that each participant contributes data to both/all treatment groups. The statistical methods of the meta-analysis require that both treatment groups remain independent of each other, an assumption that is therefore broken by the inclusion of cross-over studies ([Stedman 2011](#)).

If we had performed a meta-analysis, we would have extracted data from the first treatment period of the included cross-over studies. Essentially, we would have regarded the first treatment period as a parallel study, thus preventing data from the same participant being considered twice, whilst simultaneously avoiding any issues of carry-over effect. As we did not conduct a meta-analysis, and therefore did not require the assumption of independent groups to be met, and because the first period data was not available from the study publications, we have included all data in the narrative synthesis.

Dealing with missing data

We planned to carry out intention-to-treat analysis according to the treatment allocation, regardless of the final treatment received. We would have assumed that participants who did not complete follow-up or who had inadequate seizure data were non-responders.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between included studies (age, predominant seizure type, duration of epilepsy, number of antiepileptic drugs taken at time of randomisation). We assessed methodological heterogeneity by comparing included studies (randomisation, concealment, blinding, losses to follow-up).

Assessment of reporting biases

We planned to assess the reporting bias, according to Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2017). Specifically, we had planned to assess potential publication bias using funnel plots had we included more than nine studies in the review.

Data synthesis

We planned to analyse the data using Review Manager 5.3 (Review Manager 2014). Unfortunately, due to the nature of the included studies, we did not feel that it was appropriate to combine the data into a meta-analysis. Instead, we conducted a narrative synthesis of the data.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis according to age, seizure type, duration of epilepsy, and number of antiepileptic drugs taken at the time of randomisation. Due to insufficient data included in the review and due to narrative synthesis, these analyses were not possible.

Sensitivity analysis

We planned to perform sensitivity analyses to investigate the robustness of the meta-analysis by removing the studies associated with high risk of bias, or by excluding studies with large effect size. Although we were unable to conduct the planned sensitivity analyses, we considered these factors when critically analysing the results of the review during the discussion (see [Summary of main results](#)).

Summarising and interpreting results

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to interpret findings, and GRADEpro GDT software (which imports data from Review Manager 5 software (GRADEpro 2015)), to produce a 'Summary of findings' table. We assessed all of the review outcomes using GRADE and included them in [Summary of findings for the main comparison](#). We assessed the evidence for each outcome across eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding factors, and dose-response gradient) to determine its certainty.

RESULTS

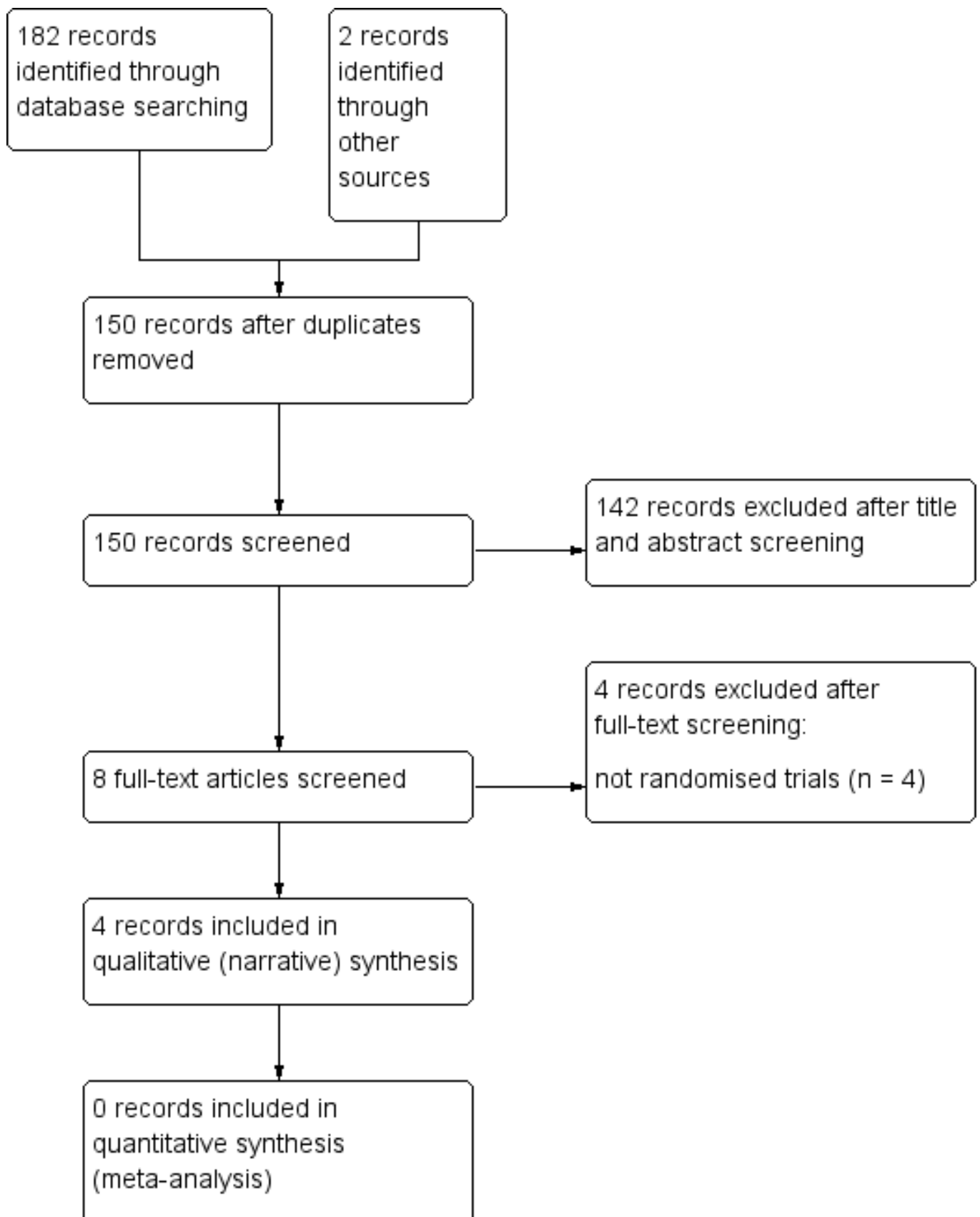
Description of studies

Results of the search

The searches yielded 184 records, of which 150 records remained after removing 34 duplicates. We assessed that eight records were potentially eligible for inclusion after title and abstract screening. Following the screening of the full-text articles of the eight remaining records, we excluded four of these records (Li 1996; Sachdeo 1990; Theodore 1990; Wilder 1991), and listed the reasons for exclusion in [Characteristics of excluded studies](#). We thus judged that the remaining four records (Binelli 1999; Bourgeois 1993; Leppik 1991; Theodore 1991), were eligible for inclusion in the review.

See [Figure 1](#) for the study flow selection diagram (Moher 2009).

Figure 1. Flow chart of study selection



Included studies

See [Characteristics of included studies](#).

Four studies met our inclusion criteria, with a total of 236 participants (Binelli 1999; Bourgeois 1993; Leppik 1991; Theodore 1991). Although all four studies were randomised, double-blind, placebo-controlled trials, they otherwise largely varied in study design. Two of the studies were parallel-group trials, one was a two-period cross-over trial, and the other was a three-period cross-over trial. They utilised varying felbamate doses, varying treatment periods, differing baseline antiepileptic drugs, and differing methodology for assessment of efficacy. Participants randomised in the four studies also had differing seizure frequency during baseline.

Binelli 1999 was a parallel-group trial including an eight-week baseline period, followed by an undefined titration period where the dose was gradually increased to the maximum tolerated dose and was then maintained over an eight-week maintenance phase. Participants were required to have at least eight seizures during the eight-week baseline period. Additionally, participants' concomitant antiepileptic therapy could be made up of no more than two of the following drugs: carbamazepine, γ -vinyl-GABA, lamotrigine, gabapentin, and benzodiazepine, however, there was no description of which drugs the felbamate group or the placebo group received. No other inclusion criteria and exclusion criteria were mentioned in the study. The study included a total of 83 participants who were randomised to one of two treatment groups, up to 3600 mg/day felbamate or placebo.

Likewise, Bourgeois 1993 was a parallel-group trial, which consisted of a four-week baseline period as well as a four-week treatment period, inclusive of a three-day titration period. Specifically, participants underwent a routine evaluation for epilepsy surgery at the end of the four-week baseline period. The treatment period immediately followed the surgical evaluation period and consisted of eight hospital days and 21 outpatient days. The study utilised strict diagnosis requiring video/electroencephalogram (EEG)-confirmed focal-onset seizures. The study publication defined both inclusion and exclusion criteria. To be eligible for inclusion, seizure frequency could not exceed an average of four complex focal-onset seizures or feature more than one secondarily generalised seizure per day, during the last three days of the surgical evaluation. Moreover, participants were also required to have a minimum average of one seizure per day for the last three days of the surgical evaluation period. Participants had to be at least 18 years of age and have a body weight of at least 40 kg. A total of 64 participants were randomised into the study by Bourgeois 1993. Participants were randomised to receive either 3600 mg/day felbamate (or their maximum tolerated dose) or placebo.

Importantly, during the surgical evaluation period, standard antiepileptic drugs were reduced or discontinued. Throughout the subsequent hospitalisation period (the first eight days of the treatment period), the participants continued with the same antiepileptic drug regimen present on the last day of the surgical evaluation period. Once participants entered the second phase of the treatment period (the 21 outpatient days), participants who were on less than the full baseline dosage of one standard antiepileptic drug(s) returned to their pre-surgical evaluation dosage of one antiepileptic drug. If participants were instead on a reduced dosage of two antiepileptic drugs, the dosage of one was restored to its pre-surgical evaluation dose. All participants in the felbamate group were

treated at the maximum dosage. Again, there was no description of which baseline antiepileptic drugs were being taken, or which participants on which antiepileptic drugs were the best responders to felbamate.

In contrast to the two previous studies, Leppik 1991 was a two-period cross-over study. The study included an eight-week baseline period, an eight- to 10-day titration period and 10-week treatment period with an additional three-week wash-out period. Diagnosis of epilepsy was based on the observation of at least one ictal event by trained personnel and was supported by EEG. The inclusion criteria (participants required to have four or more focal seizures per month with no more than 20 subsequent seizure-free days despite stable plasma concentrations of both phenytoin and carbamazepine) and exclusion criteria (people with medical conditions other than epilepsy, non compliant or unable to accurately report seizures) were well described. The concomitant antiepileptic drugs were phenytoin and carbamazepine. The trial included a total of 59 participants who were randomised to receive either add-on felbamate (up to a maximum dose of 2600 mg/day) or placebo. Seizure data from the final eight weeks of the first and second treatment periods were used in the efficacy analyses.

Theodore 1991 was also a cross-over study but instead consisted of three treatment periods. Specifically, there were four treatment sequences to which the 30 included participants could be allocated: felbamate-placebo-felbamate; felbamate-placebo-placebo; placebo-felbamate-placebo; placebo-felbamate-felbamate. The treatments were administered across alternating titration and analysis periods, each lasting two weeks, and were preceded by a three-week baseline period. During the felbamate treatment periods, participants were titrated up to a target dose of 3000 mg/day felbamate. The diagnosis of focal epilepsy was based on clinical (the observation of focal seizures with or without secondary generalisation), EEG (onset in one cortical region), and imaging (either focal imaging abnormality or normal scan) criteria. People who had at least six seizures during the baseline period, with at least one seizure occurring per individual week, were eligible for inclusion in the trial. The exclusion criteria (acquired by contacting the first study author) specified that people with treatable causes of seizures, metastatic tumours except skin cancer, progressive neurological disorders, other serious medical or psychiatric disorders, or a history of generalised tonic-clonic status epilepticus were to be excluded from the trial.

Of note, Theodore 1991 also included a stabilisation period, prior to the baseline period. During this period, participants' antiepileptic drug regimens were altered or discontinued, such that participants were only receiving carbamazepine for the duration of the study. There was no description of mean baseline seizure frequencies. The mean seizure frequencies during baseline were not reported and were unavailable through contacting the first author of the study.

Excluded studies

See [Characteristics of excluded studies](#).

All four excluded studies (Li 1996; Sachdeo 1990; Theodore 1990; Wilder 1991), investigated the long-term use of felbamate but were not placebo-controlled, and, therefore, did not meet the inclusion criteria. Notably, two of the studies (Sachdeo 1990; Wilder 1991), also did not investigate felbamate as an add-on therapy but instead administered it as a monotherapy. Another of the excluded stud-

ies (Theodore 1990), was an open-label, long-term extension study, which we recognised was a continuation of the cross-over trial by Theodore 1991.

Risk of bias in included studies

See Figure 2 for a graph illustrating the risk of bias across all studies. See Figure 3 for a summary of the judgements made for each 'Risk of bias' domain for each individual study.

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

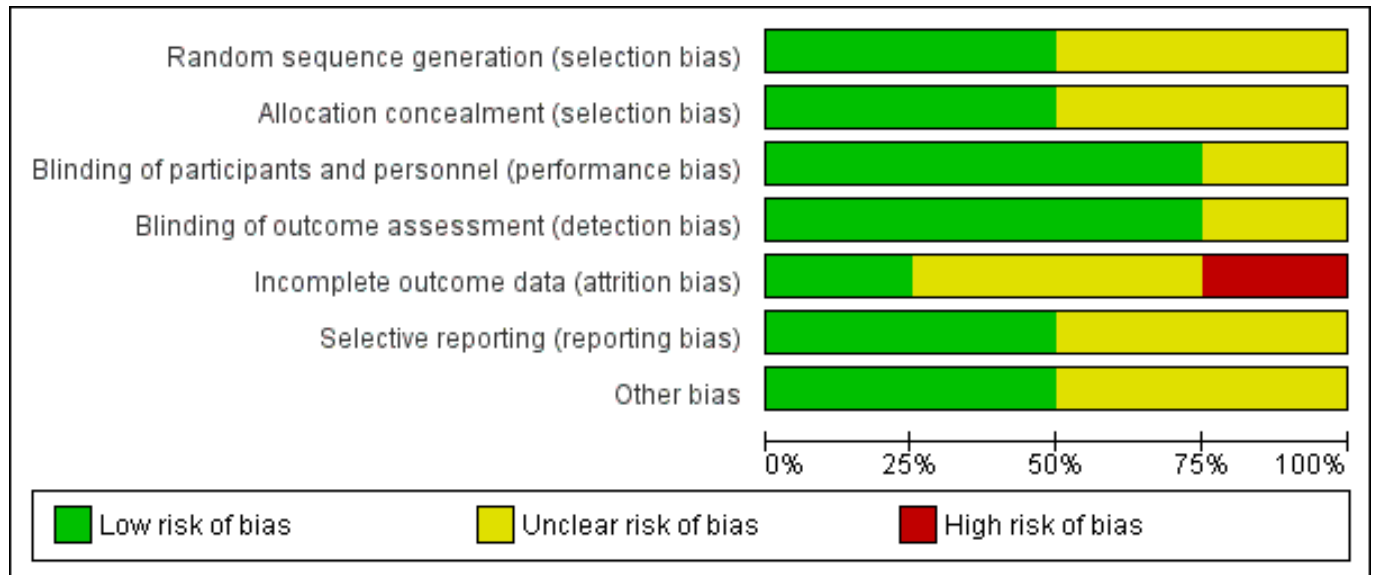


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Binelli 1999	?	?	?	?	-	?	?
Bourgeois 1993	+	+	+	+	+	+	?
Leppik 1991	?	?	+	+	?	+	+
Theodore 1991	+	+	+	+	?	?	+

The 'Risk of bias' judgement for each domain for each study are detailed in the 'Risk of bias' tables, located below the [Characteristics of included studies](#) tables.

Allocation

We awarded two of the included studies, [Binelli 1999](#) and [Leppik 1991](#), unclear risk of selection bias for both random sequence generation and allocation concealment. The two studies failed to describe the method used for either randomisation or allocation concealment. In contrast, we awarded the studies by [Bourgeois 1993](#) and [Theodore 1991](#) low risk of selection bias for both domains. The study by [Bourgeois 1993](#) most likely used a permuted block randomisation sequence and participants were allocated to their respective treatment groups by personnel who were separate from the clinical sites. In [Theodore 1991](#), a National Institutes of

Health (NIH) statistician generated randomisation schedules and the pharmacy was then responsible for subsequent treatment allocation, rather than study personnel.

Blinding

[Binelli 1999](#) was described as being double-blind, however, the study publication failed to provide specific details about how the blinding was achieved. We thus assessed that this study was at unclear risk of performance and detection bias. In contrast, correspondence with the authors of [Bourgeois 1993](#) confirmed that participants and study personnel were blinded by using identical packaging for both treatment groups. Similarly, [Leppik 1991](#) used matching placebo which would ensure the effective blinding of participants and study personnel. The study publication for [Leppik 1991](#) did, however, also state that all study medication was pre-

pared under the supervision of an unblinded pharmacist. Although this suggests that the blinding was broken, it is necessary for the pharmacist to be unblinded to ensure that study kits are correctly packaged. We therefore agreed that blinding had most likely been effectively imposed and maintained. Alternatively, [Theodore 1991](#) clarified upon personal correspondence that none of the participants, physicians, nurses, social workers, or other study personnel knew what treatment participants were being given, at any time. We therefore judged these three studies ([Bourgeois 1993](#); [Leppik 1991](#); [Theodore 1991](#)), to be at low risk of performance and detection bias.

Incomplete outcome data

Twelve out of the 83 (14.5%) randomised participants failed to complete the study by [Binelli 1999](#). The study authors did not conduct an intention-to-treat analysis to compensate for the loss of data. We therefore judged that the study was at high risk of attrition bias.

In [Leppik 1991](#), three of the 59 (5.1%) randomised participants did not complete the trial. [Theodore 1991](#) featured a similar attrition rate with only two of the 30 (6.7%) randomised participants failing to complete the trial. Again, we included only the participants who completed the trial in the analysis, thus indicating that intention-to-treat analysis was not performed. We are, however, uncertain about whether the data from a small proportion participants would affect the overall conclusions of the trial. As a result, we have awarded both studies unclear risk of attrition bias, as opposed to high risk.

Notably, [Bourgeois 1993](#) was the only included study to perform intention-to-treat analysis. In this study, three of the 64 (4.7%) randomised participants failed to complete the trial, however, their data were incorporated into subsequent statistical analyses. We thus judged that this study was associated with low risk of attrition bias.

Selective reporting

Two of the studies ([Bourgeois 1993](#); [Leppik 1991](#)), fully reported the results for all of the outcomes predefined in their respective methods sections. We thus judged that both studies were at low risk of reporting bias.

In contrast, the study publication for [Binelli 1999](#) did not describe any intended outcomes in the methods section. As a result, we could not determine whether they had reported all intended outcomes. One of the cross-over studies ([Theodore 1991](#)), did report all outcomes, however, only reported the primary efficacy outcome, seizure frequency, for the felbamate treatment periods and failed to disclose seizure frequency during the placebo-control treatment periods. Moreover, both of these studies ([Binelli 1999](#); [Theodore 1991](#)), also failed to provide details of adverse effects that occurred during treatment with add-on placebo. We consequently assessed that both studies were at unclear risk of reporting bias.

Other potential sources of bias

We were unable to determine whether there were any other potential sources of bias associated with the study by [Binelli 1999](#) because of the poor reporting of the trial and the lack of methodological details provided. We thus suspect that there could potentially be other sources of bias. We consequently awarded the study an unclear risk of other bias.

We also judged that [Bourgeois 1993](#) was at unclear risk of other bias. During the surgical evaluation period, participants' antiepileptic drug regimens were reduced or discontinued. Then, during the outpatients phase, the dose of one antiepileptic drug, taken as part of the participants' regimen, was subsequently increased to the dosage they were taking prior to the surgical evaluation. Altering the dosage of concomitant antiepileptic drugs would likely influence participants' seizure control but could also affect their responsiveness to the antiepileptic drug being trialled, felbamate. As a result, it is not clear whether the result being reported is due to the intervention or due to the alterations made to the concomitant antiepileptic drugs. Most studies require that participants must be on a stable drug regimen for at least one month prior to the study, making this study very unusual in design.

We did not detect any other potential sources of bias for the two remaining studies ([Leppik 1991](#); [Theodore 1991](#)). We thus awarded these two studies low risk of other bias.

Effects of interventions

See: [Summary of findings for the main comparison Add-on felbamate compared to placebo for drug-resistant focal epilepsy](#)

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

Due to methodological and clinical heterogeneity, it was not possible to perform a meta-analysis of the study results. We have therefore presented a narrative synthesis for our outcome measures: 50% or greater reduction in seizure frequency, absolute or percentage reduction in seizure frequency, treatment withdrawal, adverse effects and quality of life. Furthermore, because the clinical characteristics of the participants in the four included studies were heterogeneous, we were also unable to carry out our planned subgroup analysis.

50% or greater reduction in seizure frequency

Only one study, involving 83 randomised participants, reported the primary outcome. [Binelli 1999](#) reported that 38% of participants allocated to felbamate treatment experienced a 50% or greater reduction in seizure frequency. Moreover, 11% of these participants had complete cessation of seizures. The study authors did not, however, specify the number of placebo-randomised participants who attained either 50% or greater seizure reduction or complete cessation of seizures.

Absolute or percentage reduction in seizure frequency

Three of the included studies ([Binelli 1999](#); [Leppik 1991](#); [Theodore 1991](#)), consisting of 172 participants, reported this outcome.

[Binelli 1999](#) reported that participants randomised to add-on felbamate, on average, experienced a 35.8% reduction in seizure frequency during the maintenance period. In contrast, participants randomised to the placebo group experienced a 3.3% average increase in seizure frequency. The study authors did not provide any information regarding variability (i.e. standard deviation or confidence intervals) but did report that the difference in percentage seizure reduction was significant ($P = 0.0005$).

[Leppik 1991](#) reported that the mean seizure frequency during the final eight weeks of the treatment period for participants randomised to add-on felbamate was 34.4 seizures per eight weeks compared to a mean seizure frequency of 40.2 seizures per eight

weeks for those randomised to placebo. Both absolute reduction (felbamate: 4.95 ± 24.55 , placebo: -0.36 ± 27.19 , $P = 0.046$), and percentage reduction in seizure frequency (felbamate: 4.24 ± 55.61 , placebo: -19.14 ± 79.70 , $P = 0.018$) were significantly greater with add-on felbamate than with add-on placebo. [Leppik 1991](#) performed an additional analysis using the data collected across the 10 weeks of each treatment period and reported that this analysis revealed similar results.

[Theodore 1991](#) reported an average 14% reduction in seizure frequency during treatment with add-on felbamate. Although the study publication did specifically state that the percentage reduction in seizure frequency was not significantly different between the two treatments, felbamate and placebo, they did not provide the mean percentage change in seizure frequency during the placebo treatment period. As a result, the study only partially reported the outcome.

[Bourgeois 1993](#) did not report this outcome.

Treatment withdrawal

All four included studies ([Binelli 1999](#); [Bourgeois 1993](#); [Leppik 1991](#); [Theodore 1991](#)), involving all 236 randomised participants, reported treatment withdrawal. [Binelli 1999](#) reported that four participants randomised to felbamate withdrew from treatment. In two cases treatment discontinuation was caused by adverse effects (diplopia in one case, asthenia and collapse in the other). One participant died from the consequences of a seizure, whilst the fourth withdrew consent. Eight of the participants randomised to add-on placebo did not complete the study, however, the study authors did not provide any reasons.

[Bourgeois 1993](#) reported that two participants in the felbamate group withdrew from treatment due to adverse effects. One participant in the placebo group withdrew consent.

[Leppik 1991](#) reported that three participants withdrew from treatment during the felbamate period because of diplopia, nausea and vomiting, and fever with malaise, respectively. [Theodore 1991](#) reported that two participants left the study during the felbamate period, one owing to seizure exacerbation and the other due to hyponatraemia, which might specifically relate to the use of carbamazepine. Notably, no participants withdrew from treatment during the placebo period during either study.

Overall, only one of the four included studies ([Binelli 1999](#)), reported a higher treatment withdrawal rate amongst participants receiving placebo. The other three studies all reported a higher treatment withdrawal rate for participants receiving add-on felbamate. Of note, the treatment withdrawal rate for participants randomised to felbamate remained below 10% in all four studies. The most common reason for treatment withdrawal amongst participants receiving add-on felbamate was due to adverse effects.

Adverse effects

All four included studies ([Binelli 1999](#); [Bourgeois 1993](#); [Leppik 1991](#); [Theodore 1991](#)), involving all 236 randomised participants, reported adverse effects.

[Binelli 1999](#) reported 26 adverse effects in the group of participants treated with felbamate. The adverse effects were central nervous system events such as headache, dizziness, ataxia, diplopia, con-

fusion, depression, sedation, and paraesthesia, and gastrointestinal tract events such as stomach pain, nausea, vomiting and loss of appetite. Only 4.9% (2/41) discontinued the treatment due to the occurrence of adverse effects. In the group of participants treated with felbamate, significant weight loss occurred (mean reduction from 72.9 kg to 71.4 kg). In 19.5% (8/41) of participants, the decrease in weight was between 5 kg to 7 kg. This weight loss was justifiable in two cases because of gastrointestinal adverse effects. Of the participants treated with felbamate, 2.4% (1/41) suffered a modest and transient reduction in the value of leukocytes. There was no description of adverse effects in the group of participants treated with placebo.

[Bourgeois 1993](#) reported that the most commonly occurring adverse effect in both treatment groups was headache (40% (12/30) felbamate and 12% (4/34) placebo). Other commonly occurring adverse effects in the felbamate group were insomnia (37% (11/30)), nausea (37% (11/30)), dizziness (23% (7/30)), fatigue (20% (6/30)), constipation (20% (6/30)), anorexia (20% (6/30)), dyspepsia (17% (5/30)), anxiety (13% (4/30)), and vomiting (13% (4/30)). The most common adverse effects in the placebo group were dizziness (15% (5/34)), dyspepsia (9% (3/34)), somnolence (9% (3/34)), insomnia (6% (2/34)), fatigue (6% (2/34)), anxiety (6% (2/34)), nausea (3% (1/34)), constipation (3% (1/34)), and vomiting (3% (1/34)). Only one participant in the felbamate group had a severe adverse effect: stupor and confusion (3% (1/30)). Two participants in the felbamate group (7% (2/30)) failed to complete the trial due to adverse effects.

[Leppik 1991](#) reported that the most frequent adverse effects were in the central nervous system and gastrointestinal tract, of which headache (36% (21/59) felbamate and 3% (2/59) placebo), dizziness (36% felbamate (21/59) and 5% (3/59) placebo), diplopia (36% (21/59) felbamate and 2% (1/59) placebo), blurred vision (22% (13/59) felbamate and 5% (3/59) placebo), ataxia (32% (19/59) felbamate and 2% (1/59) placebo), nausea (39% (23/59) felbamate and 7% (4/59) placebo), and vomiting (25% (15/59) felbamate and 3% (2/59) placebo) were noted.

According to [Theodore 1991](#), adverse effects experienced by participants included headache (87% (26/30)), nausea (57% (17/30)), dizziness (50% (15/30)), diplopia (33% (10/30)), vomiting (33% (10/30)), blurred vision (30% (9/30)), fatigue (17% (5/30)), and poor balance (10% (3/30)). Notably, the adverse effects listed account for all participants and do not differentiate between felbamate and placebo cross-over periods. The study did, however, state that adverse effects were reported more during treatment periods when felbamate dosage was either steady or was being increased compared to periods of either no felbamate or when felbamate dosage was being tapered. Only nausea, double vision and blurred vision were significantly associated with periods during which felbamate was administered. Importantly, felbamate led to a significant decrease in both blood urea nitrogen and white blood count.

Quality of life

[Bourgeois 1993](#) was the only study to describe quality of life. During the four-week outpatient baseline period the study authors obtained each participant's vital signs and administered the Short Neuropsychological Test. For those who had the Short Neuropsychological Test and completed the treatment period, motor skills and memory skills remained the same or were improved. The study did not, however, provide any detailed data for the Short Neuropsychological Test.

chological Test, or specify whether there was any significant difference in outcome between the two treatment groups.

DISCUSSION

Summary of main results

Four studies, representing 236 randomised participants, met the inclusion criteria for this review (Binelli 1999; Bourgeois 1993; Leppik 1991; Theodore 1991). All four studies were randomised, double-blind, placebo-controlled trials. Among them, however, two were parallel-group design trials, one was a two-period cross-over trial, and the fourth was a three-period cross-over trial.

All four included studies (Binelli 1999; Bourgeois 1993; Leppik 1991; Theodore 1991), were at unclear risk of bias. The reporting of important methodological factors, such as the method of randomisation, allocation concealment, and blinding was poor in Binelli 1999 and Leppik 1991. Additionally, there was also bias related to incomplete outcome data associated with both of these studies. For Bourgeois 1993 there was an issue regarding the unstable drug regimens of participants throughout the trial, and for Theodore 1991, the incomplete outcome data and selective reporting of outcomes, specifically only for the intervention group, were of concern. Due to the differences in study methodology, choice of outcomes and the inadequate reporting of outcome data, it was not possible to summarise data in a meta-analysis. We, therefore, narratively summarised the data from the studies included in the review.

With regard to efficacy, two studies demonstrated a significant reduction in seizure frequency with add-on felbamate compared to placebo. The size of the effect was, however, notably very different between the two studies. Specifically, one study (Leppik 1991), reported a much smaller effect with considerable inter-participant variability, as demonstrated by the large standard deviation value. In contrast, the other study (Binelli 1999), reported a much greater effect, but failed to disclose any measure of variability. One study (Theodore 1991), however, described that there was no significant difference between add-on felbamate and placebo for seizure reduction.

Similarly, there were contrasting reports for treatment withdrawal. One study (Binelli 1999), reported a higher treatment withdrawal rate amongst participants randomised to placebo, whereas the three other studies (Bourgeois 1993; Leppik 1991; Theodore 1991), firstly reported fewer treatment withdrawals overall, and secondly, consistently observed a higher incidence of treatment withdrawal for participants receiving felbamate. Overall, the treatment withdrawal rates for felbamate-treated groups across all four included studies remained below 10%, suggesting that felbamate may be well tolerated. Headache, dizziness and nausea were the adverse effects that were consistently reported by all four included studies, whilst diplopia and vomiting were each reported by three of the studies. We could not adequately assess the impact of felbamate on quality of life in the review as only one study (Bourgeois 1993), partially reported this outcome.

Notably, in both of the analyses that demonstrated conflicting results (percentage reduction in seizure frequency and treatment withdrawal), it was Binelli 1999 that contrasted the findings of the other studies and reported data that massively favoured felbamate as an efficacious add-on therapy (i.e. a substantial reduction in seizure frequency and low treatment withdrawal rate). Moreover, it

was also Binelli 1999 that was associated with either unclear or high risk of bias across all 'Risk of bias' domains. Caution must therefore be taken when considering the findings of Binelli 1999. Importantly, if this study were to be excluded from the narrative synthesis, similar to when conducting a sensitivity analysis, this review would be much less encouraging of the use of felbamate as an add-on therapy.

Although the current data suggest that felbamate may possibly reduce seizure frequency, we must emphasise that we are very uncertain about both whether felbamate does demonstrate a therapeutic effect, and, furthermore, whether the size of the effect is of any clinical significance or relevance. Overall, the current data do not provide convincing evidence to support the use of add-on felbamate in people with drug-resistant focal-onset epilepsy.

Overall completeness and applicability of evidence

Among the included studies, the felbamate doses (target doses ranged from 2600 mg/day to 3600 mg/day) and the length of the treatment periods (2 to 10 weeks in duration) were variable, as summarised in the [Characteristics of included studies](#) table. Consequently, we were unable to combine the data into a meta-analysis. Instead, we were limited to conducting a narrative synthesis with the data collected. The variability in study quality and the inconsistency of results between studies also had an impact on our ability to report accurate findings. Using GRADE, we judged the majority of the included outcomes as being from very low-certainty evidence, meaning that we have very little confidence that the effect reported is accurate. It also means that it is possible that the true effect could be substantially different from that reported here.

Of further note, we suspected that all four studies consisted of solely adult study populations. Binelli 1999 did not state the inclusion age for participants, however, the mean age of 33.5 years implies that they studied an adult population. Consequently, any findings of this review are potentially only applicable to adults with drug-resistant focal epilepsy and cannot inform readers about the effects of felbamate in children or adolescents. Similarly, we specifically searched for studies that only included people with drug-resistant focal epilepsy, opposed to generalised epilepsy or other epilepsy types. As a result, the review findings cannot be extrapolated to other seizure types.

Quality of the evidence

Out of the included studies, Binelli 1999 was associated with the greatest risk of bias. This was largely due to the very poor reporting of methodological details. Additionally, the study also featured a high attrition rate with more 14% of participants withdrawing from the study overall. The study authors did not conduct an intention-to-treat analysis to compensate for the loss of data from the withdrawn participants. Leppik 1991 also had missing methodological details. For example, they did not describe the methods used for random sequence generation and allocation concealment. Separately, one of the remaining studies was associated with other bias due to alterations made to participants' concomitant drugs at multiple time points throughout the trial (Bourgeois 1993), whilst the other study (Theodore 1991), featured incomplete and selective reporting of outcome data.

As a result of the risk of bias detected across the included studies, specifically with regard to Binelli 1999 and Leppik 1991, we down-

graded the evidence for all of the GRADE-assessed outcomes once. We then downgraded the evidence for all outcomes twice again for imprecision. It was firstly necessary to downgrade for imprecision because of the narrative synthesis employed. During a narrative synthesis, the effect size is subjectively described, whilst, during a meta-analysis, an estimated effect size is statistically calculated. The findings reported from a narrative synthesis are therefore automatically considered to be imprecise. Secondly, we downgraded for imprecision because of the low number of events. Notably, the total number of participants, when considering all studies, was 236 participants. The number of events, therefore, could not satisfy the optimal information size (normally considered to be more than 400 events; [Guyatt 2011](#)). We downgraded the evidence once for inconsistency for two of the outcomes, absolute or percentage reduction in seizure frequency and treatment withdrawal, because of disparity in either the effect size described or the direction of the effect reported between the studies.

Overall, our GRADE assessment showed that all five outcomes were derived from very low certainty-evidence. As a result, we have very little confidence in the accuracy of the review findings that we have reported. It is important to acknowledge that the true effect of felbamate is likely to be significantly different to that reported in this review.

Potential biases in the review process

We are not aware of any potential bias within our search strategies. We do, however, acknowledge that there are potential issues for bias within our data extraction. For many of the details regarding methodology, we were forced to rely upon correspondence with the study authors because they did not provide details in the original study publication. This is specifically in reference to [Bourgeois 1993](#) and [Theodore 1991](#). For example, the [Bourgeois 1993](#) corresponding author reported, "I think that randomisation was by permuted block, but I do not remember for sure". Although we have accepted that randomisation was by random permuted blocks, it is possible that the study author is remembering incorrectly. Consequently, [Bourgeois 1993](#) and [Theodore 1991](#) could potentially be associated with more risk of bias than we have awarded here, as we are relying on the ability of study authors to correctly recall details retrospectively.

Agreements and disagreements with other studies or reviews

Our review found that adverse effects were more commonly reported during the felbamate period than the placebo period, particularly headache, nausea and dizziness. Whilst the studies in this review reported adverse effects that were largely either mild to moderate in severity, a literature review by [Pellock 1999](#) reported serious adverse effects, namely aplastic anaemia and hepatic failure. Neither of these serious adverse effects were reported by any of the four studies included in this review.

One reason for this might be that these two severe adverse effects are small-probability events. The likely incidence of felbamate-associated aplastic anaemia is 127 per one million people ([Pellock 1999](#)). A total of 18 cases of hepatic failure had been reported in people receiving felbamate ([Pellock 1999](#)), the rate of which was lower than the incidence of aplastic anaemia. Another reason might be that the duration of the four included trials was not long enough for the occurrence of the two severe adverse effects (the

longest exposure time in felbamate was 10 weeks in [Leppik 1991](#)). All cases of aplastic anaemia presented after two and a half to six months of felbamate therapy ([Pennell 1995](#)), whilst the mean time to hepatic failure presentation was 217 days (range 25 to 939 days) ([Pellock 1999](#)). As of 2006, despite approximately 10,000 to 13,000 patients annually being treated with felbamate, only one additional patient had suffered aplastic anaemia since the first reports of the event in 1993 and 1994 ([Pellock 2006](#)). This thus emphasises that the serious adverse effects reported are exceptionally rare.

Notably, the reports of these serious adverse effects surfaced within a year of felbamate receiving US Food and Drug Administration (FDA) approval ([French 1999](#)). Subsequently, the majority of patients were discontinued from treatment with felbamate and were diverted to treatment with other antiepileptic drugs. The fears and concerns regarding felbamate likely resulted in diminished pharmaceutical interest in the drug. Hence explaining why we were only able to identify one clinical trial that investigated the add-on use of felbamate, conducted after 1994.

Despite the reports of serious adverse effects, a later review by [Pellock 2006](#), stated that felbamate, when used as an add-on therapy, offers, "small, but encouraging, improvements in seizure control" and should still be regarded as a useful add-on for some individuals with drug-resistant epilepsy. The review ([Pellock 2006](#)), bases this finding on the observations of studies by [Leppik 1991](#) and [Theodore 1991](#), both of which are included studies in our current review. Notably, in this review, our narrative synthesis for the outcome, absolute or percentage reduction in seizure frequency, was based on data derived from three studies, [Binelli 1999](#), [Leppik 1991](#) and [Theodore 1991](#). [Leppik 1991](#) described a much more modest percentage reduction for participants receiving felbamate, compared to [Binelli 1999](#) (4.2% versus 35.8%, respectively). [Theodore 1991](#) meanwhile demonstrated that there was no significant difference in seizure reduction between the two treatment groups, felbamate and placebo. Consequently, the results of neither [Leppik 1991](#) nor [Theodore 1991](#) support the statement made by [Pellock 2006](#). Instead, the findings of our current review suggest that there is not a clinically relevant reduction in seizure frequency to justify the risk of serious adverse effects.

AUTHORS' CONCLUSIONS

Implications for practice

We have not identified any additional studies since the previous update of this review ([Shi 2017](#)). The quality of existing data is poor and, consequently, it is not possible to ascertain whether there is a treatment effect, or to define the size of any potential treatment effect. There is currently no convincing evidence to suggest that felbamate, when used as an add-on therapy, reduces seizure frequency for people with drug-resistant focal epilepsy. The most commonly reported adverse effects in the included short-term studies were headache, nausea and dizziness. None of the studies reported aplastic anaemia or hepatic failure. Evidence for the use of felbamate as an antiepileptic drug remains insufficient.

Implications for research

A large-scale, randomised controlled trial conducted over a longer period of time (at least one year) is required to inform clinical practice. The trial should recruit a heterogeneous population with well-defined seizure and epilepsy types. This will allow the identification

of patient factors, pathology, seizure types and baseline antiepileptic drugs associated with the greatest benefit or harm. In addition, research is increasingly being undertaken into epilepsy genetics, with regard to the factors contributing to drug-resistant epilepsy, to identify the people in which antiepileptic drugs will achieve the greatest efficacy. Such investigation should be incorporated into future research investigating the use of add-on felbamate.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Binelli 1999

Methods	Randomised, double-blind, placebo-controlled, multicenter study 8-week baseline period, a period of gradual increase of the drug to the maximum tolerated dose, and 8-week maintenance phase
Participants	83 participants (mean age 33.5 years) were enrolled and randomised, 45 to felbamate and 38 to placebo The average monthly seizure frequency in baseline period: 1. felbamate: 15.3 ± 22.1 2. placebo: 12.3 ± 6.4 41 participants taking felbamate and 30 participants taking placebo completed the maintenance period.
Interventions	Add-on felbamate or placebo

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

Binelli 1999 (Continued)

A period of gradual increase of the drug to the maximum tolerated dose, but not higher than 3600 mg/d, and then an 8-week maintenance phase

Outcomes	<ol style="list-style-type: none"> 1. Reduction of seizures 2. Greater than 50% reduction of seizures 3. Treatment withdrawal 4. Adverse effects
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no details were provided regarding random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no details were provided regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no details were provided regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no details were provided regarding blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 12 participants did not complete the maintenance period. Study did not use ITT analysis
Selective reporting (reporting bias)	Unclear risk	Comment: no details were provided regarding intended outcomes
Other bias	Unclear risk	Comment: lack of methodological details and poor reporting of the trial means that we are unable to determine whether there are other potential sources of bias.

Bourgeois 1993

Methods	<p>Randomised, double-blind, placebo-controlled, parallel-group, multicenter study</p> <p>4-week baseline period, 4-week treatment period (including 3-day titration period)</p>
Participants	<p>64 participants were randomised (38 male), aged 17-51 years. 30 participants were randomised to felbamate and 34 to placebo.</p> <p>Mean 4-weekly baseline seizure frequency</p> <ol style="list-style-type: none"> 1. felbamate group: simple focal seizure = 4.9, complex focal seizure = 14.1, focal-onset seizures with generalisation = 0.4 2. placebo group: simple focal seizure = 5.9, complex focal seizure = 7.6, focal-onset seizures with generalisation = 0.3

Bourgeois 1993 (Continued)

Number of other AEDs: felbamate group = 3-9; placebo group = 2-9

Interventions	Add-on felbamate or placebo Felbamate was titrated from 1600 mg/d-3600 mg/d over a period of 3 d and maintained on 3600 mg/d or the maximum tolerated dose, not to exceed 3600 mg/d
Outcomes	1. Mean rank of seizure frequency 2. Time to 4th seizure 3. Adverse effects
Notes	Trial sponsored by Carter-Wallace Laboratories, Inc., the manufacturer of felbamate at the time of conduct.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "they were randomised to the felbamate or placebo treatment groups" Comment: we contacted the study author and the reply was as follows, "I think that randomisation was by permuted block, but I do not remember for sure".
Allocation concealment (selection bias)	Low risk	We contacted the study author and the reply was as follows, "The randomisation was done at Wallace Laboratories and no one at the clinical sites was involved in the allocation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We contacted the study author and the reply was as follows, "Medication (or placebo) was provided by Wallace Laboratories to the clinical sites in identical packages. The study was double-blind. The patients as well as the doctors and nurses did not know whether the treatment was felbamate or placebo."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind", "...the doctors and nurses did not know whether the treatment was felbamate or placebo." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3/64 randomised participants failed to complete the study. The 3 participants could not be included in the analysis of mean rank of seizure frequency, however, all 64 participants were included in all other analyses, compliant with ITT
Selective reporting (reporting bias)	Low risk	Comment: the outcomes mentioned in the methods were reported.
Other bias	Unclear risk	Comment: participants were not on stable drug regimens for the duration of the study. This would most likely influence participants' responsiveness to the intervention being investigated.

Leppik 1991

Methods	Randomised, double-blind, placebo-controlled, multicenter, cross-over study conducted across two sites (University of Minnesota and University of Virginia Health Services Center) 2 treatment sequences: felbamate-placebo and placebo-felbamate
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Leppik 1991 (Continued)

8-week baseline period, 8-10-d titration period and 10-week treatment period with 3-week wash-out period

Participants	<p>59 participants were randomised, aged 18-55 years. 56 participants (32 male) completed the trial. 31 participants were randomised to the felbamate-placebo sequence and 28 to the placebo-felbamate</p> <p>Mean 8-weekly baseline seizure frequencies of the 56 participants who completed the trial</p> <ol style="list-style-type: none"> 1. University of Minnesota site: felbamate-placebo group = 43.6 (16 participants), placebo-felbamate group = 42.8 (15 participants) 2. University of Virginia site: felbamate-placebo group = 28.9 (14 participants), placebo-felbamate group = 44.0 (11 participants) <p>Other AEDs were phenytoin and carbamazepine</p> <p>Simple focal seizures, complex focal seizures, secondary generalised seizures</p>
Interventions	<p>Add-on placebo or felbamate</p> <p>In the initial 8-10-d treatment, the dosage was increased daily to 3000 mg/d. Due to reports of nausea and vomiting, the maximum dosage was reduced to 2600 mg/d. The mean felbamate dosage was 2300 mg/d.</p>
Outcomes	<ol style="list-style-type: none"> 1. Seizure frequency reduction 2. Seizure frequency percentage reduction 3. Truncated seizure frequency percentage reduction 4. Adverse effects
Notes	Trial was funded by a grant from the National Institute of Neurological Disorders and Stroke (NINDS)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "...randomised ... clinical trial. Table 1 summarizes the baseline characteristics of these 56 patients by center and randomised treatment sequence."</p> <p>Comment: no details were provided for how the randomisation sequence was generated</p>
Allocation concealment (selection bias)	Unclear risk	Comment: no details were provided regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "matching PLB [placebo] capsules...All medications were pre-packed under the supervision of the unblinded pharmacist."</p> <p>Comment: matching placebo ensures effective blinding. Pharmacists cannot be blinded to treatment as they are responsible for preparing the study kits. As long as they are not otherwise involved in the study then this is acceptable.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 3 participants did not complete the trial and, subsequently, were not included in any statistical analyses. ITT was therefore not conducted. We, however, judge that the inclusion of data from 3 additional participants is unlikely to influence the findings of the trial.

Leppik 1991 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: the outcomes mentioned in the methods were reported
Other bias	Low risk	Comment: no other sources of bias detected

Theodore 1991

Methods	<p>Randomised, double-blinded, 3-period cross-over study</p> <p>4-treatment sequence:</p> <ol style="list-style-type: none"> 1. felbamate-placebo-felbamate 2. felbamate-placebo-placebo 3. placebo-felbamate-placebo 4. placebo-felbamate-felbamate <p>3-week baseline period, treatments were administered over alternating titration and analysis periods, each lasting 2 weeks (participants were observed in the hospital for the entire trial period).</p>
Participants	<p>30 participants were randomised (10 male), aged 19-50 years.</p> <ol style="list-style-type: none"> 1. 8 participants were randomised to felbamate-placebo-felbamate sequence 2. 8 participants were randomised to felbamate-placebo-placebo sequence 3. 7 participants were randomised to placebo-felbamate-placebo sequence 4. 7 participants were randomised to placebo-felbamate-felbamate sequence <p>Simple focal seizures, complex focal seizures, generalised tonic-clonic seizures</p> <p>Mean baseline seizure frequencies of the participants were unavailable</p> <p>The other AED was carbamazepine</p>
Interventions	<p>Add-on placebo or felbamate</p> <p>28 participants who completed the study received felbamate dosage of 3000 mg/d. The 2 exceptions who left the study received felbamate dosage of 2400 mg/d</p>
Outcomes	<ol style="list-style-type: none"> 1. The number of seizures experienced by each participant during each of the 3 analysis periods 2. Adverse effects
Notes	<p>Received support from the National Institute of Neurological Disorders and Stroke (NINDs) nursing service, the NIH and Carter-Wallace, Inc. It was not clear from the publication whether this support was financial, methodological, or both.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We contacted the study author and the reply was as follows, "The randomisation schedule was generated by the NIH statistician and administered by the pharmacy."
Allocation concealment (selection bias)	Low risk	We contacted the study author and the reply was as follows, "The randomisation schedule was generated by the NIH statistician and administered by the pharmacy."

Theodore 1991 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	We contacted the study author and the reply was as follows, "None of the physicians or nurses or patients knew what drug they were being given, felbamate or placebo, at any time."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "47 individuals were enrolled, 17 were not randomised, 2 of the 30 randomisation left the study after randomisation." Comment: the 2 participants were not included in the statistical analyses therefore ITT was not conducted. However, the inclusion of data from 2 additional participants is unlikely to influence the findings of the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: the outcomes mentioned in the methods were reported, however, the study authors did not report seizure frequency during the placebo treatment period
Other bias	Low risk	Comment: no other sources of bias detected

AED: antiepileptic drug; **d:** day; **ITT:** intention-to-treat; **NIH:** National Institutes of Health

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Li 1996	Open-label, add-on study, but not a RCT
Sachdeo 1990	Open-label study, but not a RCT. Felbamate was also used as a monotherapy.
Theodore 1990	Open-label, long-term extension study, but not a RCT.
Wilder 1991	Open-label add-on study, but not a RCT. Felbamate was also used as a monotherapy.

RCT: randomised controlled trial

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

1. (felba* or taloxa):AB,KW,MC,MH,TI AND CENTRAL:TARGET
2. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET
3. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET
4. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
5. #2 OR #3 OR #4 AND CENTRAL:TARGET
6. #1 AND #5 AND CENTRAL:TARGET
7. #6 AND >20/10/2016:CRSCREATED

Appendix 2. MEDLINE search strategy

This strategy was based on the Cochrane highly sensitive search strategy for identifying randomised trials (Lefebvre 2011).

1. felbamate.nm. or (felba* or taloxa or "ADD-03055" or "W-554" or "ADD 03055" or "W 554").tw.
2. exp Epilepsy/
3. exp Seizures/
4. (epilep\$ or seizure\$ or convuls\$).tw.
5. 2 or 3 or 4
6. exp *Pre-Eclampsia/ or exp *Eclampsia/
7. 5 not 6
8. (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. 1 and 7 and 13
15. (monotherap\$ not (adjunct\$ or "add-on" or "add on" or adjuvant\$ or combination\$ or polytherap\$)).ti.
16. 14 not 15
17. remove duplicates from 16
18. limit 17 to ed=20161020-20181218
19. 17 not (1\$ or 2\$).ed.
20. 19 and (2016\$ or 2017\$ or 2018\$).dt.
21. 18 or 20

Appendix 3. ClinicalTrials.gov search strategy

Interventional Studies | Epilepsy | Felbamate | First posted on or after 10/20/2016

Appendix 4. ICTRP search strategy

Condition: epilepsy

Intervention: felbamate

Recruitment status: all

Date of registration between 20/10/2016 and 18/12/2018

WHAT'S NEW

Date	Event	Description
2 August 2019	Amended	Minor copyedits carried out

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 1, 2011

Date	Event	Description
18 December 2018	New citation required but conclusions have not changed	The conclusions are unchanged. 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).
18 December 2018	New search has been performed	Searches updated 18 December 2018; no new studies identified.
20 October 2016	New search has been performed	Searches updated 20 October 2016; one new study (Binelli 1999) has been included.
20 October 2016	New citation required but conclusions have not changed	The conclusions are unchanged.

CONTRIBUTIONS OF AUTHORS

Li Li Shi: drafted protocol, all author correspondence, primarily responsible for the conduct of previous review versions

Rebecca Bresnahan: primarily responsible for current review update

Kirsty Martin-McGill: author support for current review update

JianCheng Dong: conduct of previous review versions

HengJian Ni: obtained trial reports for previous review versions

JinSong Geng: conduct of previous review versions

DECLARATIONS OF INTEREST

Li Li Shi: no conflicts of interest

Rebecca Bresnahan: no conflicts of interest

Kirsty Martin-McGill: no conflicts of interest

JianCheng Dong: no conflicts of interest

HengJian Ni: no conflicts of interest

JinSong Geng: no conflicts of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. In the protocol, we defined drug-resistant epilepsy as "continued seizures despite antiepileptic drug treatment" (French 2006), and in the review, we used the definition proposed by the Task Force of the International League Against Epilepsy (ILAE) "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan 2010).

2. In the protocol, we planned to summarise data in a meta-analysis, assess the reporting biases, and do sensitivity analyses. In the review, due to the clinical and methodological heterogeneity in the four included trials, we summarised data narratively.
3. In the protocol, we did not consider unit of analysis issues. We have therefore amended the methods to describe how we would deal with unit of analysis issues in this current review update and in future review updates.
4. 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](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Drug Resistance; Epilepsies, Partial [*drug therapy]; Felbamate; Phenylcarbamates [adverse effects] [*therapeutic use]; Propylene Glycols [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans