Cochrane Library

Cochrane Database of Systematic Reviews

Brivaracetam add-on therapy for drug-resistant epilepsy (Review)

Bresnahan R, Panebianco M, Marson AG

Bresnahan R, Panebianco M, Marson AG.
Brivaracetam add-on therapy for drug-resistant epilepsy.
Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD011501.
DOI: 10.1002/14651858.CD011501.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Brivaracetam add-on therapy for drug-resistant epilepsy

Rebecca Bresnahan[1,2], Mariangela Panebianco[2], Anthony G Marson[2,3,4]

[1]Liverpool Reviews and Implementation Group, Institute of Population Health, University of Liverpool, Liverpool, UK. [2]Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK. [3]The Walton Centre NHS Foundation Trust, Liverpool, UK. [4]Liverpool Health Partners, Liverpool, UK

Contact: Rebecca Bresnahan, rebecca.bresnahan@liverpool.ac.uk.

Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2022.

Citation: Bresnahan R, Panebianco M, Marson AG.Brivaracetam add-on therapy for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews* 2022, Issue 3. Art. No.: CD011501. DOI: 10.1002/14651858.CD011501.pub3.

ABSTRACT

Background

This is an updated version of the Cochrane Review previously published in 2019.

Epilepsy is one of the most common neurological disorders. It is estimated that up to 30% of individuals with epilepsy continue to have epileptic seizures despite treatment with an antiepileptic drug. These patients are classified as drug-resistant and require treatment with a combination of multiple antiepileptic drugs. Brivaracetam is a third-generation antiepileptic drug that is a high-affinity ligand for synaptic vesicle protein 2A. In this review we investigated the use of brivaracetam as add-on therapy for epilepsy.

Objectives

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

Search methods

For the latest update we searched the following databases on 7 September 2021: the Cochrane Register of Studies (CRS Web); MEDLINE (Ovid) 1946 to 3 September 2021. CRS Web includes randomised controlled trials (RCTs) and quasi-RCTs from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including Cochrane Epilepsy.

Selection criteria

We searched for parallel-group RCTs that recruited people of any age with drug-resistant epilepsy. We accepted studies with any level of blinding (double-blind, single-blind, or unblinded).

Data collection and analysis

In accordance with standard Cochrane methodological procedures, two review authors independently assessed trials for inclusion before evaluating trial quality and extracting relevant data. The primary outcome to be assessed was 50% or greater reduction in seizure frequency. Secondary outcomes were: seizure freedom, treatment withdrawal for any reason, treatment withdrawal due to adverse events, the proportion of participants who experienced any adverse events, and drug interactions. We used an intention-to-treat population for all primary analyses, and presented results as risk ratios (RRs) with 95% confidence intervals (CIs).

Main results

We did not identify any new studies for this update, therefore the results and conclusions of the review are unchanged.

The previous review included six studies involving a total of 2411 participants. Only one study included participants with both focal and generalised onset seizures; the other five trials included participants with focal onset seizures only. Study participants were aged 16 to 80 years. Treatment periods ranged from 7 to 16 weeks. We judged two studies to have low risk of bias and four to have unclear risk of bias. Details on the method used for allocation concealment and how blinding was maintained were insufficient in one study each. One study did not report all outcomes prespecified in the trial protocol, and there were discrepancies in reporting in a further study.

Participants receiving brivaracetam add-on were more likely to experience a 50% or greater reduction in seizure frequency than those receiving placebo (RR 1.81, 95% CI 1.53 to 2.14; 6 studies; moderate-certainty evidence). Participants receiving brivaracetam were more likely to attain seizure freedom; however, the evidence is of low certainty (RR 5.89, 95% CI 2.30 to 15.13; 6 studies). The incidence of treatment withdrawal for any reason was slightly greater for participants receiving brivaracetam compared to those receiving placebo (RR 1.27, 95% CI 0.94 to 1.74; 6 studies; low-certainty evidence). The risk of participants experiencing one or more adverse events did not differ significantly following treatment with brivaracetam compared to placebo (RR 1.08, 95% CI 1.00 to 1.17; 5 studies; moderate-certainty evidence). However, participants receiving brivaracetam did appear to be more likely to withdraw from treatment due to adverse events compared with those receiving placebo (RR 1.54, 95% CI 1.02 to 2.33; 6 studies; low-certainty evidence).

Authors' conclusions

When used as add-on therapy for individuals with drug-resistant epilepsy, brivaracetam may be effective in reducing seizure frequency and may aid patients in achieving seizure freedom. However, add-on brivaracetam is probably associated with a greater proportion of treatment withdrawals due to adverse events compared with placebo. It is important to note that only one of the eligible studies included participants with generalised epilepsy. None of the included studies involved participants under the age of 16, and all studies were of short duration. Consequently, the findings of this review are mainly applicable to adult patients with drug-resistant focal epilepsy. Future research should focus on investigating the tolerability and efficacy of brivaracetam during longer-term follow-up, as well as assess the efficacy and tolerability of add-on brivaracetam in managing other types of seizures and in other age groups.

PLAIN LANGUAGE SUMMARY

Brivaracetam add-on therapy for drug-resistant epilepsy

Background

Epilepsy is a disorder characterised by multiple seizures. Most people can control their epilepsy with a single antiepileptic drug; however, some people require multiple antiepileptic drugs. These people are said to have drug-resistant epilepsy. Brivaracetam is an antiepileptic drug that can be taken with another antiepileptic medication to try to manage drug-resistant epilepsy.

Aim of the review

We aimed to determine whether brivaracetam is effective and tolerable when used as add-on treatment for people with drug-resistant epilepsy. For this update, we did not identify any new studies to add, therefore our conclusions remain unchanged.

Results

We identified six studies (2411 participants) that investigated brivaracetam as add-on treatment for drug-resistant epilepsy. Study participants were aged 16 to 80, and most had focal epilepsy (i.e. epilepsy that originates in one area of the brain). People who received brivaracetam in addition to their normal antiepileptic medication were almost twice as likely to experience a 50% or greater reduction in the frequency of their seizures compared to people who were given placebo (i.e. a fake, inactive drug that should not affect epilepsy). People who received brivaracetam were also nearly six times more likely to achieve freedom from all seizures than those receiving placebo. People who received brivaracetam were not more likely to experience side effects compared to people receiving placebo; however, they were more likely to withdraw from study due to side effects.

Certainty of the evidence

The evidence for freedom from all seizures was of low certainty and the evidence for 50% or greater reduction in the seizure frequency was of moderate certainty. This means that when brivaracetam is used as an add-on for adults with drug-resistant focal epilepsy, people may be more likely to become free from all seizures than people given placebo and that brivaracetam is probably effective at reducing seizure frequency. The evidence for the proportion of people who experienced any side effects was of moderate certainty so is likely to be accurate. We did not investigate the number of people who experienced individual adverse events. This should be investigated in future reviews.

The evidence for this review was taken from randomised controlled trials that only studied adults and mainly studied people with drug-resistant focal epilepsy, and not with generalised epilepsy.

This review shows that overall brivaracetam is a fairly tolerable and effective drug for use specifically in adults with drug-resistant focal epilepsy. All study participants were adults, and most had focal epilepsy. Therefore, we do not know the effectiveness of brivaracetam in children or in people with other types of epilepsy, such as generalised epilepsy (i.e. epilepsy that involves the whole brain).

The evidence is current to 7 September 2021.

Summary of findings 1. Brivaracetam compared to placebo as add-on therapy for focal epilepsy

Brivaracetam compared to placebo as add-on therapy for focal epilepsy

Patient or population: people with drug-resistant focal epilepsy
Setting: outpatients
Intervention: brivaracetam (all doses)
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 brivaracetam				
50% or greater reduction in seizure frequency (responder rate) Follow-up (range): 7 to 16 weeks	**Study population**		**RR 1.81** (1.53 to 2.14)	2411 (6 RCTs)	⊕⊕⊕⊖ **MODERATE**[a]	Brivaracetam likely increases the 50% responder rate.
	189 per 1000	342 per 1000 (289 to 404)				
Seizure freedom Follow-up (range): 7 to 16 weeks	**Study population**		**RR 5.89** (2.30 to 15.13)	2411 (6 RCTs)	⊕⊕⊖⊖ **LOW**[a,b,]	Brivaracetam may result in a large increase in the number of participants achieving seizure freedom.
	4 per 1000	26 per 1000 (10 to 66)				
Treatment withdrawal Follow-up (range): 7 to 16 weeks	**Study population**		**RR 1.27** (0.94 to 1.74)	2411 (6 RCTs)	⊕⊕⊖⊖ **LOW**[a,b]	Brivaracetam may increase treatment withdrawal slightly.
	71 per 1000	90 per 1000 (67 to 124)				
Proportion of participants who experienced adverse events leading to treatment withdrawal Follow-up (range): 7 to 16 weeks	**Study population**		**RR 1.54** (1.02 to 2.33)	2411 (6 RCTs)	⊕⊕⊖⊖ **LOW**[a,b]	Brivaracetam may increase the proportion of participants who experience adverse events leading to treatment withdrawal.
	39 per 1000	60 per 1000 (40 to 91)				
Proportion of participants who experienced any adverse events	**Study population**		**RR 1.08** (1.00 to 1.17)	2011 (5 RCTs)	⊕⊕⊕⊖ **MODERATE**[a]	Brivaracetam probably does not affect the proportion of participants who experience any adverse events.
	598 per 1000	646 per 1000 (598 to 700)				

Follow-up (range): 7 to 16 weeks

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for risk of bias: all studies were pharmaceutical sponsored, and some included studies had incomplete methodological information.
[b]Downgraded once for imprecision: number of events does not suffice for optimal information size.

BACKGROUND

This is an update of a Cochrane Review first published in 2019 (Bresnahan 2019); no new studies have been added, thus the conclusions remain unchanged.

Description of the condition

Epilepsy is a chronic neurological disorder that is characterised by recurrent seizures. These seizures are caused by sudden, usually brief, excessive electrical discharges within a group of neurons. More than 50 million people in the world today have received a diagnosis of epilepsy, and approximately 2.4 million new cases occur each year, worldwide (WHO 2013). Antiepileptic drug monotherapy is generally accepted as the preferred initial management approach in epilepsy care. However, up to 30% of individuals with epilepsy do not respond adequately to conventional antiepileptic drug treatment, either due to recurrent seizures despite optimised antiepileptic drug therapy, or adverse effects (van Paesschen 2013). Many of these people will use add-on therapies. Consequently, there is a need for antiepileptic drugs that can control the seizures of those who do not respond to conventional drug treatment. As dozens of novel antiepileptic drugs have been marketed in the past two decades, it is important that researchers assess the efficacy and tolerability of these new antiepileptic drugs.

Description of the intervention

Brivaracetam is a novel antiepileptic drug that has been investigated as add-on therapy for epilepsy. Brivaracetam is a third-generation antiepileptic agent that shares a similar chemical structure with levetiracetam and piracetam. Brivaracetam has been shown to have a wider antiepileptic spectrum and higher efficacy than levetiracetam in several animal models of structural and genetic epilepsy (Schulze-Bonhage 2011). In 2005, the European Commission approved brivaracetam as an orphan drug for the treatment of progressive myoclonus epilepsies (Chu-Shore 2010). In the same year, the US Food and Drug Administration (FDA) also approved brivaracetam as a treatment for symptomatic myoclonus (Johannessen Landmark 2008). Brivaracetam has been shown to suppress generalised photoparoxysmal electroencephalography (EEG) responses in a photosensitivity model as proof-of-principle of its efficacy in individuals with epilepsy (Kasteleijn-Nolst Trenité 2007). Brivaracetam was well tolerated as add-on therapy in adults with drug-resistant focal-onset seizures, but failed to show consistent efficacy in decreasing the frequency of seizures in phase IIb and phase III randomised controlled trials (French 2010; van Paesschen 2013; Werhahn 2010).

Brivaracetam exhibits linear pharmacokinetics across a wide dose range (10 mg to 600 mg) when administrated as a single oral dose to healthy participants. It is rapidly and completely absorbed and is weakly bound to plasma proteins (≤ 20%), with an elimination half-life of seven to eight hours after oral administration (Schulze-Bonhage 2011). Brivaracetam is metabolised primarily via hepatic hydrolysis of the acetamide group, and secondarily through hydroxylation mediated by cytochrome P450 (CYP) 2C19 (Nicolas 2012). It is extensively eliminated renally within 72 hours of ingestion (> 95%). In individuals with hepatic impairment, total body clearance of brivaracetam is reduced, and plasma half-life is accordingly prolonged. However, the pharmacokinetic profile of brivaracetam in individuals with renal impairment is similar to that in healthy participants (von Rosenstiel 2007). Researchers observed a slight decrease in plasma carbamazepine levels and a 2.5-fold increase in plasma carbamazepine-epoxide levels when brivaracetam was applied with other antiepileptic drugs at 400 mg per day. In addition, peak concentrations of a single dose of 600 mg phenytoin were decreased slightly when co-administered with brivaracetam (Schulze-Bonhage 2011). The manufacturers of brivaracetam claim that evidence from phase II/III trials has shown that no dose adjustment is required when brivaracetam is used as add-on therapy with other antiepileptic drugs (Bialer 2010).

How the intervention might work

Brivaracetam is a high-affinity synaptic vesicle protein SV2A ligand that is involved in presynaptic transmitter release. It shows inhibition of neuronal voltage-dependent sodium (Na+) channels (French 2010; Schulze-Bonhage 2011; van Paesschen 2013).

Why it is important to do this review

To our knowledge, this is the first systematic review to focus on the use of brivaracetam as add-on therapy for epilepsy. In this review, we have summarised the available evidence on the efficacy and tolerability of brivaracetam as derived form randomised controlled trials.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We required that trials meet all of the following criteria.

1. Randomised controlled trials (RCTs) using an adequate method of concealment of randomisation (e.g. allocation of sequentially numbered, sealed packages of medication; sealed, opaque envelopes; telephone randomisation). We excluded quasi-RCTs where treatment allocation was decided through such methods as alternate days of the week.
2. Double-blind, single-blind, or unblinded.
3. Placebo- or active-controlled.
4. Parallel-group design.

Types of participants

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

Types of interventions

1. The experimental group consisted of participants who received had brivaracetam in addition to an existing antiepileptic drug regimen taken at the time of randomisation.
2. The control group consisted of participants who had received a matched placebo or active comparator in addition to an existing antiepileptic drug regimen taken at the time of randomisation.

Types of outcome measures

Primary outcomes

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

Our primary outcome was the proportion of individuals with a 50% or greater reduction in seizure frequency during the treatment period compared with the pre-randomisation baseline period.

Secondary outcomes

1. **Seizure freedom:** the proportion of participants with complete cessation of seizures at the end of the follow-up period.
2. **Treatment withdrawal:** the proportion of participants for whom treatment was withdrawn, for any reason, during the course of the treatment period. This provides a measure of global effectiveness. Treatment is likely to be withdrawn due to adverse effects, lack of efficacy, or a combination of both. This is an outcome to which the individual makes a direct contribution. In trials of short duration, the most common reason for withdrawal is likely to be adverse effects.
3. **Adverse events:**
   a. The proportion of participants who experienced adverse events leading to treatment withdrawal.
   b. The proportion of participants who experienced any adverse events.
4. **Drug interactions:** any drug interactions reported in the included studies.

Search methods for identification of studies

Electronic searches

We first ran searches for this review in April 2013, and ran subsequent searches in March 2015, March 2017, and October 2018. For the current update, we searched the following databases on 7 September 2021, with no language restrictions:

1. Cochrane Register of Studies (CRS Web), using the search strategy in Appendix 1;
2. MEDLINE (Ovid), 1946 to 3 September 2021, using the search strategy in Appendix 2.

CRS Web includes RCTs or quasi-RCTs from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including Cochrane Epilepsy. For MEDLINE (Ovid), the coverage end date always lags a few days behind the search date.

Searching other resources

We reviewed the reference lists of retrieved studies to check for additional reports of relevant studies. We also contacted UCB Inc (manufacturers of brivaracetam) and epilepsy experts for ongoing studies and unpublished information.

Data collection and analysis

Selection of studies

The process of selecting studies for inclusion in the review involved merging search results using reference management software and removing duplicates of the same report. Two review authors (RB and MP) screened all titles, abstracts, and keywords of publications identified by the searches to assess trial eligibility. At this stage, we excluded publications describing studies that clearly did not meet the inclusion criteria. We retrieved all potentially relevant papers, and two review authors (RB and MP) independently evaluated the full text of each paper according to the prespecified selection criteria. Any disagreements were resolved by discussion. If disagreements persisted, the third review author (AGM) arbitrated.

Data extraction and management

Two review authors (RB and MP) independently extracted the following information from the included trials, if available. Any disagreements were resolved by discussion.

1. **Methods**
   a. Study design
   b. Method of randomisation
   c. Allocation concealment
   d. Blindness
   e. Study duration
2. **Participants**
   a. Age
   b. Gender
   c. Ethnicity
   d. Type of seizure
   e. Seizure frequency
   f. Epilepsy duration
   g. Inclusion criteria
   h. Exclusion criteria
   i. Total number of participants recruited
   j. Total number of participants randomised
3. **Interventions**
   a. Dosage
   b. Administration method
   c. Treatment duration
   d. Number of background drugs
4. **Outcomes**
   a. Primary outcome
   b. Secondary outcomes
   c. Adverse events
   d. Drug interactions
5. **Follow-up data**
   a. Duration of follow-up period
   b. Total number of participants followed up
   c. Number of losses to follow-up
   d. Reasons for treatment withdrawal

Assessment of risk of bias in included studies

Two review authors (RB and MP) independently assessed the risk of bias of included studies using the Cochrane risk of bias tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The Cochrane risk of bias tool comprises seven specific parameters:

1. random sequence generation;
2. allocation concealment;

3. blinding of participants and personnel;
4. blinding of outcome assessors;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

For each entry, review authors made the judgement (low, high, or unclear risk of bias) and provided support for the judgement either by an agreed-upon review author comment or by a quote taken from the corresponding publication.

We then judged overall risk of bias for each study, again in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed a study at unclear risk of bias for one or more of the key domains as at overall unclear risk of bias. We assessed a study at high risk of bias for one or more of the key domains as at overall high risk of bias. Only if we judged a study to have low risk of bias across all seven domains did we award that study an overall low risk of bias judgement. Any disagreements were resolved by discussion.

Measures of treatment effect

For dichotomous data, we used the risk ratio (RR) with 95% confidence interval (CI) for analysis. For drug interactions, we described the outcome narratively.

Unit of analysis issues

We did not encounter any unit of analysis issues, based on the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dealing with missing data

If data were insufficient or missing, we contacted the manufacturers and original investigators of relevant trials for additional information through personal communication. If we did not receive a response, we analysed available data according to the intention-to-treat (ITT) principle.

Assessment of heterogeneity

We evaluated clinical and methodological heterogeneity amongst trials by comparing the characteristics of participants (age, gender, seizure type, seizure frequency, duration of epilepsy), interventions (dosage, administration method and duration, co-treatments), and study design (randomisation, allocation concealment, blinding methods) between studies.

We evaluated statistical heterogeneity amongst trials using the Chi^2 test with significance set at 0.1, along with the I^2 statistic.

A P value greater than 0.1 in the Chi^2 test ($P > 0.1$) indicated no significant statistical heterogeneity (Deeks 2011).

If a P value was less than or equal to 0.1 in the Chi^2 test, we interpreted heterogeneity according to percentage ranges of the I^2 statistic, as follows (Deeks 2011):

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

*The importance of the observed value of the I^2 statistic depends on 1. the magnitude and direction of effect, and 2. the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test or CI for the I^2 statistic).

Assessment of reporting biases

We originally planned to assess funnel plot asymmetry. Reasons for asymmetry include publication bias, outcome reporting bias, language bias, citation bias, poor methodological design, and heterogeneity. However, given that our review included fewer than 10 studies, funnel plots would have been minimally informative, therefore we did not generate funnel plots as part of this review.

Data synthesis

We analysed the data from included studies using Review Manager 5 (Review Manager 2020). We based our choice of fixed-effect or random-effects model on the extent of heterogeneity. If clinically appropriate and in the absence of substantial statistical heterogeneity based on the I^2 statistic ($I^2 < 50\%$), we analysed data in a meta-analysis using a fixed-effect model. If we found substantial heterogeneity ($I^2 \geq 50\%$), we explored possible factors contributing to the heterogeneity and used a random-effects model to perform meta-analysis.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses according to different dose groups of brivaracetam, such as 50 mg/d and 100 mg/d, for each outcome. In addition, we planned to conduct subgroup analyses according to the different age groups of participants (children younger than 17 years versus adults); however, all the included studies exclusively comprised adult populations.

Sensitivity analysis

We planned to conduct the following sensitivity analyses to test the robustness of the meta-analysis, where possible.

1. Repeating the analysis excluding unpublished studies.
2. Repeating the analysis excluding studies published only as abstracts.

These sensitivity analyses was not required, as all the included studies were published journal articles.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to interpret findings (Schünemann 2011). We used GRADEpro GDT software, GRADEpro GDT [Computer program], to import data from Review Manager 5, Review Manager 2020, and to create a summary of findings table for the main comparison of the review (brivaracetam compared to placebo). We assessed the primary outcome, 50% or greater reduction in seizure frequency, and the secondary outcomes of seizure freedom, treatment withdrawal, and adverse events, to provide an overall certainty of evidence judgement based on the GRADE approach, which was then included in Summary of findings 1. This information is of importance for healthcare decision-making and considers eight important criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect, and dose-response

gradient). We used these overall certainty of evidence judgements to guide our conclusions.

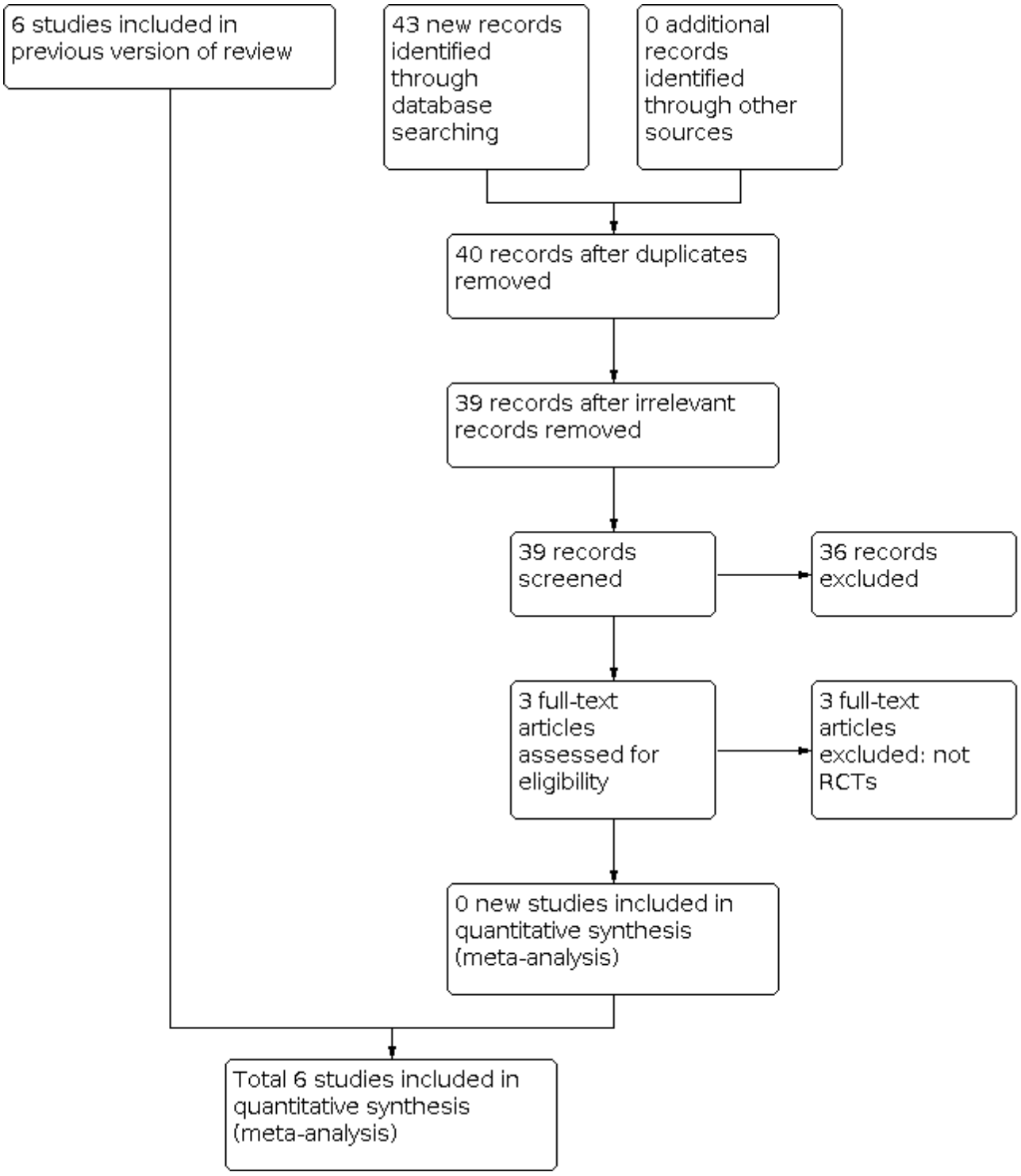
RESULTS

Description of studies

Results of the search

The latest search (7 September 2021) identified a total of 43 records for potential inclusion in the review (Figure 1). We removed 3 duplicate records, leaving 40 eligible records. We then discarded one of these records due to irrelevance. Of the remaining 39 records, we excluded a further 36 records at based on title and abstract, again due to irrelevance. We retrieved and reviewed the full texts for the three records that remained after the initial screening stage. We found no studies eligible for inclusion, thus no new studies were included in the review.

Figure 1. Study flow diagram.



The search carried out on 1 August 2019 identified six studies that were included in the meta-analyses (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013).

Included studies

We did not find any new studies in this update.

In the previous version of this review, we included six studies. All six studies were randomised, double-blind, placebo-controlled trials, with a parallel-group design. For details of the included studies, see Characteristics of included studies.

Biton 2014 was a multicentre study conducted across Australia, Brazil, Canada, Mexico, and the United States, including a total of 400 participants. Participants were aged 16 to 70 and had

drug-resistant focal epilepsy. Most participants were receiving two concomitant antiepileptic drugs (AEDs) at baseline; however, some participants were receiving more than three AEDs. Participants were required to undergo an eight-week baseline period before randomisation to one of four treatment groups. Participants next entered a 12-week treatment period, during which they received 5, 20, or 50 mg/d brivaracetam treatment, or matching placebo, with no uptitration. After completing the trial, participants were given the option to enter an open-label extension.

French 2010 was a multicentre study with sites based in Brazil, India, Mexico, and the United States. The study included a total of 208 participants. All participants were between 16 and 65 years of age and had well-characterised focal epilepsy. Participants were required to be taking one or two concomitant AEDs at baseline. Similar to Biton 2014, most participants were receiving two concomitant AEDs, and a small subset of participants were receiving more than three AEDs. Eligible participants were randomised to one of four treatment groups (5, 20, or 50 mg/d brivaracetam or matching placebo) after completion of the four-week baseline period. The treatment period was seven weeks long and did not include an uptitration period. Upon completion of the treatment period, participants were offered entry into a long-term open-label extension study.

Klein 2015 was a multicentre study conducted at sites across North America, Western Europe, Eastern Europe, Latin America, and Asia, that enrolled and randomised a total of 768 participants. Eligible participants were between 16 and 80 years of age and had well-characterised drug-resistant focal epilepsy. Most participants were receiving two concomitant AEDs at baseline. Only four participants (< 1%) were receiving three or more AEDs. Participants were required to complete an eight-week baseline period before randomisation. After successful completion of the baseline period, participants were randomised into one of three treatment groups: 100 mg/d brivaracetam, 200 mg/d brivaracetam, or placebo. Participants then undertook a 12-week treatment period, followed by a 4-week downtitration period. Participants were then given the opportunity to enter an open-label extension study.

Kwan 2014 was a multicentre study that recruited a total of 480 participants from sites in Austria, Belgium, the Czech Republic, Germany, Hong Kong, India, Italy, Norway, Republic of South Africa, Russian Federation, Singapore, South Korea, Sweden, Taiwan, and Ukraine. Participants were aged 16 to 70 years, and 90% had drug-resistant focal epilepsy. The remaining 10% had drug-resistant generalised epilepsy. Participants were required to be taking one to three concomitant AEDs; most participants were receiving two or more AEDs (45.4%). It is notable that a much larger proportion of participants in this study (37.3%) were receiving three or more AEDs compared with the other studies. Participants completed a four-week baseline period before they were randomised to one of two treatment arms: 20 to 150 mg/d brivaracetam or matching placebo, at a ratio of 3:1, respectively. As a consequence, a much larger number of participants were randomised to the experimental brivaracetam group than to the placebo control group. The study consisted of a 16-week treatment period that comprised an eight-week dose-finding phase and an eight-week maintenance phase. During the dose-finding phase, the dosage was uptitrated in a stepwise manner on a two-weekly basis, dependent on observed efficacy and participants' tolerability. The optimal dose achieved was then maintained over the final eight-week period. After the treatment period, participants underwent a two-week downtitration period before they were offered entry into one of two open-label follow-up studies.

Ryvlin 2014 was a multicentre study with sites in Poland, France, Germany, Spain, Italy, Switzerland, Hungary, Finland, the Netherlands, Belgium, the United Kingdom, and India. A total of 398 participants were enrolled in the study. All participants were aged 16 to 70 years and had received a diagnosis of focal epilepsy. Participants were required to be receiving treatment with one or two AEDs at baseline, although a small proportion (4%) were receiving three or more AEDs. After completion of an eight-week baseline period, participants were randomised to one of four treatment groups: 20 mg/d brivaracetam, 50 mg/d brivaracetam, 100 mg/d brivaracetam, or placebo. The study comprised a 12-week treatment period (without uptitration), followed by a two-week downtitration period, before participants were offered entry into an open-label extension study.

van Paesschen 2013 was a multicentre study conducted in sites in Belgium, the Czech Republic, Finland, France, Germany, the Netherlands, Poland, Spain, and the United Kingdom. A total of 157 participants were recruited into this study. Participants were aged 16 to 65 years and had drug-resistant focal epilepsy. Participants were required to be receiving one or two concomitant AEDs. Again, the largest proportion of participants were taking two concomitant AEDs at baseline, with only 6% taking three or more AEDs. Randomisation took place after completion of a four-week baseline period. Participants were randomised to one of three treatment groups: 50 mg/d brivaracetam, 150 mg/d brivaracetam, or matching placebo. The treatment period consisted of a three-week uptitration followed by a seven-week maintenance phase, and therefore lasted 10 weeks. After trial completion, participants were asked whether they wished to enter an open-label extension study.

Excluded studies

In the current update, we excluded three studies because they were not RCTs (Brandt 2020; Lattanzi 2021; Szaflarski 2020). In the previous review, we excluded one study at the full-text screening stage because it was not an RCT but was instead a meta-analysis of two studies that had already been included in the review (Lacroix 2007). We summarised the reasons for exclusion in Characteristics of excluded studies.

Ongoing studies

We were unable to include another study that was ongoing and for which no results had yet been published (see Characteristics of ongoing studies) (NCT03083665).

Risk of bias in included studies

Summaries of our judgements for each risk of bias domain across the included studies are presented in Figure 2 and Figure 3. Support for our risk of bias judgements, including quotations from the publications and specific review author comments, can be found in the risk of bias sections of the Characteristics of included studies tables. Our assessment of each risk of bias domain for all the included studies is presented below. We judged that two studies had low risk of bias overall (French 2010; Klein 2015), and the other four studies had unclear risk of bias overall (Biton 2014; Kwan 2014; Ryvlin 2014; van Paesschen 2013).

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

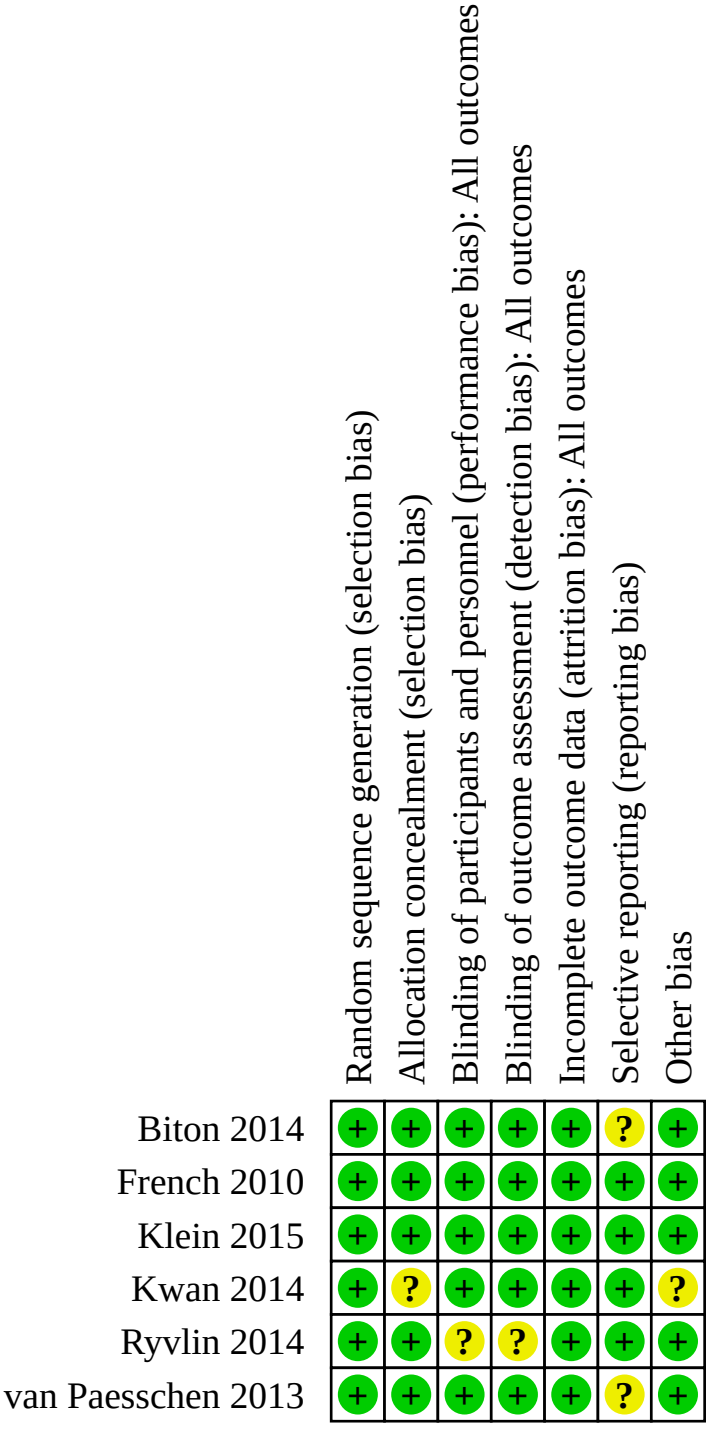
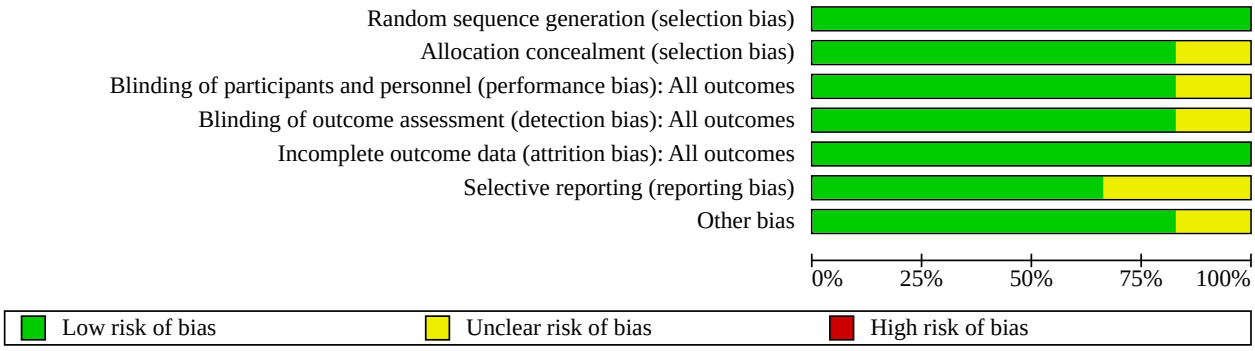


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All six included studies provided details regarding randomisation of participants, therefore we assessed all the studies as at low risk of bias for random sequence generation. Five studies specified that randomisation was achieved using the random permuted blocks method with stratification (Biton 2014; French 2010; Klein 2015; Kwan 2014; van Paesschen 2013). The remaining study instead used a central randomisation system, although, again, randomisation was stratified (Ryvlin 2014).

With regard to allocation concealment, three of the included studies described using an interactive voice response system to ensure allocation concealment (Biton 2014; Klein 2015; Ryvlin 2014). Two studies used a central randomisation system, which, again, enabled allocation to be effectively concealed (French 2010; van Paesschen 2013). We judged that these five studies all had low risk of bias for allocation concealment. We assessed the remaining study as at unclear risk of bias as any methods used to conceal allocation were not described (Kwan 2014).

Blinding

Five of the included studies were double-blind and specified that they used matching placebo tablets to maintain blinding (Biton 2014; French 2010; Klein 2015; Kwan 2014; van Paesschen 2013). One study further described that tablets of various strengths were used, so that all participants took two tablets per dose, regardless of their actual randomised dosage of brivaracetam or allocation to placebo (Klein 2015). This further ensured that blinding was maintained. All participants and study personnel were adequately blinded by the matching placebo, therefore we assessed these five studies to be at low risk of performance bias.

Efficacy outcomes were self-reported by participants in seizure diaries. Accordingly, participants were regarded as the outcome assessors. As described above, participants were effectively blinded by the matching placebo and, as a result, their reporting of outcomes was not affected or biased by treatment allocation. Likewise, because the studies were double-blind, the investigators, including those responsible for data analysis, would also have been effectively blinded. We therefore assessed all five studies as having a low risk of bias with regard to detection bias for outcome assessment (Biton 2014; French 2010; Klein 2015; Kwan 2014; van Paesschen 2013).

The remaining study, Ryvlin 2014, did not report any methods used to maintain blinding, therefore we assessed this study as being at unclear risk of both performance and detection bias.

Incomplete outcome data

We rated all included studies as at low risk of attrition bias (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). All six studies reported the attrition rate and conducted an ITT analysis. In actuality, however, only two of these studies utilised a strict ITT population whereby all participants who were randomised were analysed (Kwan 2014; van Paesschen 2013). The other four studies instead used a modified ITT population, most commonly excluding participants who did not receive at least one dose of the study drug (Biton 2014; French 2010; Klein 2015; Ryvlin 2014). However, for each study, no more than 1% of participants were excluded from the ITT population, therefore we assessed these studies as at low risk of attrition bias. All participants excluded from the ITT analyses conducted within the studies were reinstated in the ITT analyses performed in this review.

Selective reporting

We assessed four of the included studies as at low risk of reporting bias (French 2010; Klein 2015; Kwan 2014; Ryvlin 2014). Despite not supplying a trial protocol, each of the four studies reported results for all the outcome measures prespecified in the methods section of their respective publications. Another study similarly reported the results of its prespecified outcomes (Biton 2014); however, the study authors failed to provide results for the placebo group for one of the outcome measures, that is the number of participants reporting one or more adverse events. This introduced reporting bias and precluded inclusion of this study in the meta-analysis for that outcome. We assessed this study as at unclear risk of reporting bias. The remaining study, van Paesschen 2013, provided a trial protocol; however, not all intended outcomes identified in the trial protocol were reported in subsequent publications. We also assessed this study as at unclear risk of reporting bias.

Other potential sources of bias

We identified another source of potential bias in the Kwan 2014 study, which randomised participants to the experimental brivaracetam group and the placebo control group at a ratio of 3:1, respectively. This produced an uneven distribution of participants

between the two treatment groups. Unequal allocation ratios reduce the statistical power of a trial and negatively impact the ability of that trial to detect a therapeutic effect (Hey 2014). Kwan 2014 did, however, complete a power calculation and determined that a sample size of 376 participants would be required to detect a 16% reduction in baseline-adjusted weekly focal seizure frequency compared to placebo. Kwan 2014 actually recruited 480 participants, therefore exceeding the estimated sample size. This trial should thus have retained adequate statistical power to be able to detect a therapeutic effect, despite the unequal allocation ratio.

Nevertheless, unequal allocation ratios are further associated with a greater placebo effect (Hey 2014). As a result, the unequal allocation ratio used could still have distorted the perceived therapeutic effect, despite the compensatory sample size calculation. For this reason, we assessed Kwan 2014 as at unclear risk of other bias.

Effects of interventions

See: **Summary of findings 1** Brivaracetam compared to placebo as add-on therapy for focal epilepsy

See Summary of findings 1 for the main comparison: brivaracetam compared to placebo for add-on therapy for focal epilepsy.

Five of the included studies used well-defined, escalated doses of brivaracetam for the experimental treatment groups (Biton 2014; French 2010; Klein 2015; Ryvlin 2014; van Paesschen 2013). In contrast, the Kwan 2014 study utilised a flexible dosing regimen, whereby participants began on 20 mg/d brivaracetam or placebo, and then increased their dose up to 150 mg/d, depending on the efficacy that they experienced and their tolerability of the study drug. Although it was reported that most participants in both the brivaracetam and placebo treatment groups achieved the highest dosages of 100 mg/d and 150 mg/d, the dose was not standardised amongst participants. As a result, the data extracted from Kwan 2014 could not be included in the subgroup analysis for drug dose for any of the outcomes listed.

Notably, and also of importance to the analyses, two of the included studies each excluded eight participants from their ITT populations, despite having randomised these participants to a treatment group (Biton 2014; Klein 2015). Klein 2015 specified that participants must have received one or more doses of study drug and must have provided at least one postbaseline diary entry, thus explaining the exclusion of some participants. Biton 2014 stated that participants must have received one or more doses of study drug, justifying the exclusion of four participants; however, the researchers then excluded an additional four participants - three due to serious non-compliance, and one as a clinical outlier. We reinstated the 16 excluded participants in our ITT analysis, to ensure that it fully adhered to the 'once randomised, always analysed' principle. We repeated this for each of the outcomes analysed and reported on this below.

1. 50% or greater reduction in seizure frequency

All six included studies, involving a total of 2411 ITT participants, contributed to this outcome analysis (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Participants receiving brivaracetam are probably more likely to achieve a 50% or greater reduction in seizure frequency compared to those who receive placebo (risk ratio (RR) 1.81, 95% confidence interval (CI) 1.53 to 2.14; moderate-certainty evidence; Analysis 1.1). Subgroup analysis by dose of brivaracetam did not suggest any difference in 50% or greater reduction in seizure frequency dependent on dose. Doses of 20 mg/d (RR 1.64, 95% CI 1.18 to 2.27), 50 mg/d (RR 2.00, 95% CI 1.50 to 2.66), 100 mg/d (RR 1.81, 95% CI 1.42 to 2.30), and 200 mg/d (RR 1.76, 95% CI 1.33 to 2.33) brivaracetam are all associated with a greater proportion of participants achieving a 50% or greater reduction in seizure frequency than placebo (Analysis 1.1).

2. Seizure freedom

All six studies, involving a total of 2411 ITT participants, were included in this outcome analysis (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Participants receiving brivaracetam may be more likely to experience seizure freedom, specifically almost six times more likely, than those receiving placebo (RR 5.89, 95% CI 2.30 to 15.13; low-certainty evidence; Analysis 1.2). We noted no statistically significant heterogeneity within the data set ($Chi^2 = 0.83$, $df = 5$, $P = 0.97$, $I^2 = 0\%$) for seizure freedom. Subgroup analysis stratified by dose showed that participants may be more likely to achieve seizure freedom regardless of dose received. However, participants receiving the higher doses of 50 mg/d (RR 5.39, 95% CI 1.42 to 20.49), 100 mg/d (RR 7.19, 95% CI 1.93 to 26.85), and 200 mg/d (RR 5.24, 95% CI 1.16 to 23.68) showed the largest risk ratios for seizure freedom compared to placebo.

3. Treatment withdrawal

All six studies, involving a total of 2411 ITT participants, reported the number of treatment withdrawals and thus contributed to the outcome analysis (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Overall, participants randomised to brivaracetam may be slightly more likely to withdraw from treatment compared to those randomised to placebo (RR 1.27, 95% CI 0.94 to 1.74; low-certainty evidence; Analysis 1.3).

Notably, however, we detected statistically significant heterogeneity within the data set consisting of all doses of brivaracetam ($Chi^2 = 7.32$, $df = 5$, $P = 0.20$, $I^2 = 32\%$), as well as within the individual dose subgroups during subgroup analysis. This was particularly evident when compared to the complete absence of heterogeneity observed in the efficacy outcomes, that is 50% or greater seizure reduction and seizure freedom. Heterogeneity was most prominent in the 5 mg/d ($Chi^2 = 2.36$, $df = 1$, $P = 0.12$, $I^2 = 58\%$) and 100 mg/d ($Chi^2 = 2.05$, $df = 1$, $P = 0.15$, $I^2 = 51\%$) brivaracetam subgroups, although it is important to note that the levels of heterogeneity remained statistically insignificant. Of greatest concern was that the direction of effect varied between studies. French 2010 and van Paesschen 2013 reported a greater incidence of treatment withdrawal amongst participants receiving placebo compared to those receiving brivaracetam, whereas Biton 2014 and Klein 2015 reported the opposite, with more participants randomised to brivaracetam withdrawing from treatment compared to those randomised to placebo.

4. Adverse events

All six studies, involving a total of 2411 ITT participants, reported and stated the reasons for treatment withdrawal (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Data from all six studies were therefore included in

the outcome analysis for the proportion of participants who experienced adverse events leading to treatment withdrawal. The analysis showed that participants who receive brivaracetam may be around 50% more likely to withdraw from treatment due to adverse events compared to those who receive placebo (RR 1.54, 95% CI 1.02 to 2.33; low-certainty evidence; Analysis 1.4).

Subgroup analysis showed that participants who received 5 mg/d (RR 2.06, 95% CI 0.71 to 5.96), 100 mg/d (RR 1.91, 95% CI 1.01 to 3.59), or 200 mg/d (RR 1.78, 95% CI 0.83 to 3.82) brivaracetam may be more likely to withdraw from treatment due to adverse events than those who received placebo. Furthermore, the data reported for the comparison 5 mg/d brivaracetam versus placebo again displayed more heterogeneity ($Chi^2 = 2.12$, $df = 1$, $P = 0.15$, $I^2 = 53\%$) than had been associated with the other outcomes, although this was not statistically significant. Most noticeably, French 2010 again observed the opposite treatment effect to that reported by the other studies included in this analysis.

In contrast to the other outcome analyses, only five studies, comprising 2011 participants, fully reported the proportion of participants who experienced at least one adverse event, and thus contributed to the outcome analysis performed (French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Biton 2014 failed to report the incidence of participants in the placebo group reporting one or more adverse events and was therefore excluded from the analysis. We found no difference in the proportion of participants experiencing one or more adverse events between those receiving brivaracetam and those receiving placebo (RR 1.08, 95% CI 1.00 to 1.17; moderate-certainty evidence; Analysis 1.5). Subgroup analysis supported this observation, with the risk ratios for all six doses remaining close to 1.00.

5. Drug interactions

Five of the included studies, involving a total of 1643 participants, described drug interactions in their publications (Biton 2014; French 2010; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Specifically, all five studies referenced the interaction of brivaracetam with concomitant levetiracetam use.

Biton 2014 noted that a smaller proportion of participants experienced a 50% or greater reduction in seizure frequency after receiving brivaracetam if they were using levetiracetam concomitantly. Furthermore, Biton 2014 recognised that the median per cent reduction from baseline in weekly partial-onset seizure frequency was lower in participants using concomitant levetiracetam.

French 2010 also demonstrated that a reduced proportion of participants achieved a 50% or greater reduction in seizure frequency, dependent on concomitant levetiracetam use. However, the authors of this study were unable to comment on the significance of this result because of the small number of participants included in the observation.

Similarly, Kwan 2014 reported that only 13% of participants receiving brivaracetam and taking concomitant levetiracetam experienced a 50% or greater reduction in seizure frequency, compared to 34% of participants not using concomitant levetiracetam. Kwan 2014 also stated that participants using concomitant levetiracetam experienced a smaller baseline-adjusted per cent reduction in weekly focal seizure frequency than levetiracetam-naive participants.

Ryvlin 2014 agreed that, in general, a greater proportion of participants who were levetiracetam-naive or who had previously used levetiracetam but since discontinued its use achieved a 50% or greater reduction in seizure frequency, and that participants concomitantly using levetiracetam experienced a lesser reduction in seizure frequency.

van Paesschen 2013 reported that 26% of participants receiving brivaracetam and using concomitant levetiracetam attained a 50% or greater reduction in seizure frequency, as opposed to 32% and 47% of participants with prior levetiracetam use and levetiracetam-naive participants, respectively. Placebo responses showed the opposite trend, but were also more consistent. Results showed that 27% of participants receiving placebo and using concomitant levetiracetam were responders, achieving a 50% or greater reduction in seizure frequency, whilst 22% of participants receiving placebo with prior levetiracetam use or who were levetiracetam-naive were responders.

All five studies consistently reported that a decreased proportion of participants randomised to brivaracetam achieved a 50% or greater reduction in seizure frequency when using levetiracetam concomitantly. These studies also implied that there was an overall decrease in the efficacy of brivaracetam with concomitant levetiracetam use, as demonstrated by the smaller reduction in seizure frequency observed.

DISCUSSION

Summary of main results

Since the publication of the previous version of this review, we have not found any new studies that met our inclusion criteria.

The review evaluated the efficacy and tolerability of brivaracetam when used as an add-on treatment for people with drug-resistant epilepsy. Six studies (2411 participants) contributed to the analyses performed in this review (Biton 2014; French 2010; Klein 2015; Kwan 2014; Ryvlin 2014; van Paesschen 2013). We assessed two of the included studies to have as low risk of bias (French 2010; Klein 2015), and four studies to have an unclear risk of bias (Biton 2014; Kwan 2014; Ryvlin 2014; van Paesschen 2013). Participants receiving brivaracetam were more likely than those receiving placebo to experience a 50% or greater reduction in seizure frequency, and to achieve seizure freedom. Although participants receiving brivaracetam were more likely than those receiving placebo to withdraw from treatment due to adverse events, the overall treatment withdrawal rate (withdrawal for any reason) was only slightly greater for participants receiving brivaracetam compared to placebo. Moreover, there was no difference in the number of participants experiencing one or more adverse events when receiving brivaracetam versus placebo. With regard to drug interactions, the general consensus across all five included studies indicates that concomitant levetiracetam use diminishes the efficacy of brivaracetam with respect to both the responder rate and, more generally, the observed reduction in seizure frequency, despite no statistical analysis.

Subgroup analysis according to dosage suggested that no dose-response relationship is associated with brivaracetam use. Notably,

the effect size observed was fairly consistent across all doses. However, the subgroup analysis did provide some information regarding possible doses of brivaracetam for clinical use. Doses of 50 mg/d, 100 mg/d, and 200 mg/d brivaracetam were all associated with a higher proportion of participants achieving a 50% or greater reduction in seizure frequency, as well as seizure freedom, compared to placebo.

It is interesting to note that 150 mg/d brivaracetam did not display a significant therapeutic effect compared to placebo. However, this subgroup yielded limited data, with only one study involving 104 participants included in the subgroup analysis (van Paesschen 2013). Consequently, this subgroup may have been underpowered, which could potentially explain the lack of efficacy noted.

The conclusions presented here should be applied cautiously due to the limited numbers of studies and participants included in each subgroup analysis.

Overall completeness and applicability of evidence

Although we did perform a subgroup analysis according to dose groups of brivaracetam, caution must be taken when interpreting and extrapolating the results. The number of participants included in each subgroup analysis ranged from 104 to 717 per subgroup analysis. This highlights that there may be inadequacies in statistical power for some of the subgroup analyses. Consequently, this review can provide only limited information regarding the efficacy of specific brivaracetam doses.

We also intended to conduct a subgroup analysis involving participant age, but were unable to do so as all six of the included studies utilised exclusively adult populations. We are therefore unable to comment on the efficacy of brivaracetam when used for children. Additionally, we are unable to adequately discuss the application of brivaracetam in drug-resistant generalised epilepsy, although we included this population in the review. Notably, only the Kwan 2014 study included participants with drug-resistant generalised epilepsy. Kwan 2014 did state that brivaracetam appeared to be more efficacious for participants with generalised epilepsy than for those with focal onset epilepsy. However, the small sample size of participants with generalised epilepsy precluded any formal statistical analysis within the study, thus preventing us from drawing any conclusions. The finding does highlight the potential efficacy of brivaracetam in generalised epilepsy, and emphasises the need for future research.

Quality of the evidence

We assessed two of the included studies to be at low risk of bias (French 2010; Klein 2015). Both studies described effective methods used for randomisation, allocation concealment, and blinding, and there was no suspicion of attrition or reporting bias. We assessed the remaining four studies as at unclear risk of bias (Biton 2014; Kwan 2014; Ryvlin 2014; van Paesschen 2013). We judged each of the four studies to be at unclear risk of bias for one or two of the risk of bias domains. We assessed all other domains to be at low risk of bias. One study did not declare the method used for allocation concealment (Kwan 2014), whilst another study failed to adequately describe any method of blinding (Ryvlin 2014). We suspected two studies of selective reporting (Biton 2014; van Paesschen 2013). Biton 2014 did not report data for the placebo group for one of their outcome measures, and van Paesschen 2013 did not report all outcomes predefined in the trial protocol. We further assessed Kwan 2014 to be at unclear risk of other bias, namely for using an unequal allocation ratio, which can lead to an exaggerated placebo effect.

As a result, we downgraded the certainty of evidence once for all outcomes due to concerns about unclear risk of bias across four of the included studies. We rated the certainty of evidence as moderate for the following outcomes: 50% or greater reduction in seizure frequency and proportion of participants who experienced any adverse events.

We rated the certainty of evidence as low for the remaining three outcomes, that is seizure freedom, treatment withdrawal for any reason, and treatment withdrawal due to adverse events. We downgraded these outcomes once more for imprecision due to the small number of events constituting the analysis.

We did consider downgrading the certainty of evidence a further level for all outcomes with regard to indirectness due to lack of data concerning the effect of add-on brivaracetam in children and in individuals with generalised epilepsy, specifically. However, we judged that the data provided by the included studies sufficiently answered the original research question, that is whether brivaracetam is efficacious and tolerable as an add-on therapy for people with drug-resistant epilepsy, despite inclusion of no or limited data about these subgroups of participants. We therefore did not think that indirectness was serious enough to permit further downgrading of the certainty of evidence. Instead, we emphasise that the findings reported are applicable only to adults, and mainly to those with focal epilepsy. The findings of the review might not necessarily be relevant or applicable to adults with generalised epilepsy.

Consequently, we can be fairly confident of the accuracy of the conclusions made regarding the outcomes of 50% or greater reduction in seizure frequency and proportion of participants likely to experience any adverse events. Our observations concerning the outcomes of seizure freedom, treatment withdrawal for any reason, and treatment withdrawal specifically due to adverse events are less certain.

It is worth noting that all six studies were sponsored by UCB Pharma, the manufacturer of brivaracetam. Although this pharmaceutical sponsorship does not contribute to the risk of bias or to the GRADE assessment, it could potentially lead to funding bias. However, it is generally accepted that if a study is methodologically sound and the protocol is correctly adhered to, the conduct, and therefore findings, of the study should not be affected by funding bias.

Potential biases in the review process

We are unaware of any sources of bias in our conduct of the review. As per the review protocol, we (two review authors) independently assessed the eligibility of studies identified by the search strategies for inclusion, extracted the relevant data, and completed both risk of bias and GRADE assessments. We requested all protocols as planned; however, we were only provided with the trial protocol for the van Paesschen 2013 study. We also could not obtain missing data for the Biton 2014 study regarding the proportion of participants in the placebo group that experienced one or more

adverse events. Although both events could potentially bias the review, both instances were outside our control.

Agreements and disagreements with other studies or reviews

The findings of the current review are consistent with the observations made in other systematic reviews, which similarly assessed the efficacy and tolerability of brivaracetam (Lattanzi 2016; Ma 2015; Tian 2015). These other systematic reviews likewise reported risk ratios for both the 50% responder rate and the seizure freedom rate. All review authors similarly concluded that brivaracetam is an efficacious add-on therapy for drug-resistant epilepsy. However, it is important to note that the systematic reviews identified specifically focused on the use of brivaracetam as an add-on therapy for drug-resistant focal epilepsy, therefore excluding participants with generalised epilepsy from their analyses. From this perspective, our review provides additional, novel information to that available in these other systematic reviews.

As observed in our review, the risk ratio for seizure freedom demonstrated an especially large effect for brivaracetam compared to placebo in two of the reviews (Lattanzi 2016; Ma 2015). One review also completed a subgroup analysis according to dosage, reporting that any dose above 5 mg/d was associated with a significant therapeutic effect. In our review, we similarly observed that all doses of brivaracetam greater than 5 mg/d were associated with a higher responder rate compared to placebo. However, we instead suggest that doses of 50 mg/d brivaracetam and greater are efficacious for managing drug-resistant epilepsy. Doses of 50 mg/d and above of brivaracetam were consistently more effective than placebo across the two efficacy outcomes, that is responder rate and seizure freedom.

With regard to drug interactions, Lattanzi 2016 further conducted a subgroup analysis to investigate the effect of levetiracetam status on responsiveness to brivaracetam. In accordance with our findings, Lattanzi 2016 emphasised that concomitant use of levetiracetam reversed the significant difference in the 50% responder rate normally observed with add-on brivaracetam.

In addition to confirming the efficacy of brivaracetam, the other systematic reviews also assessed its tolerability. All three reviews emphasised that brivaracetam was well tolerated (Lattanzi 2016; Ma 2015; Tian 2015), and one review reported risk ratios for treatment withdrawal that were very similar to those reported here. Another review (Zhu 2017), which specifically investigated the safety and tolerability of brivaracetam, reported that brivaracetam was not significantly associated with serious adverse events or treatment withdrawal for any reason or due to adverse events.

It is interesting to note that in our review, data from the French 2010 study appear to disagree with those from other included studies with regard to treatment withdrawal - an outcome concerning tolerability. Specifically, French 2010 reported that treatment withdrawal for any reason and due to adverse events was greater amongst participants randomised to placebo than amongst those randomised to brivaracetam. Although the number of participants who withdrew from treatment during the study was low overall (placebo: 6 versus brivaracetam: 5), it is notable that this study also reported the shortest treatment period (7 weeks versus 10 to 16 weeks in duration). Similarly, van Paesschen 2013, which also reported a shorter treatment period compared to the other studies (10 weeks versus 12 to 16 weeks in duration), likewise reported a higher rate for treatment withdrawal for any reason for participants randomised to placebo compared to those randomised to brivaracetam. Length of the treatment period could thus potentially explain the heterogeneity observed.

The findings and conclusions of our review regarding both efficacy and the safety profile of brivaracetam thus appear to be consistent with the findings of currently available systematic reviews, thereby generating further support for the argument that brivaracetam is effective in treating drug-resistant epilepsy when used as an add-on therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-certainty evidence shows that brivaracetam, when used as an add-on for adults with drug-resistant focal epilepsy, is effective in reducing seizure frequency. Limited information is available regarding the efficacy of brivaracetam in adults with drug-resistant generalised epilepsy; however, a small sample trial suggests that brivaracetam could display increased effectiveness in this population compared to its use in focal epilepsy. Additionally, our findings strongly suggest that brivaracetam should not be used in conjunction with concomitant levetiracetam due to the reduced efficacy reported.

The current review suggests that brivaracetam is associated with a good tolerability profile. However, evidence concerning treatment withdrawal - an important outcome for determining drug safety - was of low certainty and therefore must be interpreted cautiously. In contrast, evidence for the proportion of participants to experience any adverse events, another outcome that contributes to drug safety, was of moderate certainty and demonstrated only a relatively slight increase in prevalence. We did not, however, investigate the prevalence of individual adverse events; this should be addressed in subsequent reviews.

We must again emphasise that the evidence for this review was derived from randomised controlled trials that exclusively studied adult populations, principally individuals with drug-resistant focal epilepsy, and not with generalised epilepsy. This review therefore shows that overall brivaracetam is a fairly tolerable and effective drug for use specifically in adults with drug-resistant focal epilepsy.

Implications for research

All current conclusions are based on relatively short-term studies that have largely focused on populations with drug-resistant focal epilepsy. More trials including participants with drug-resistant generalised epilepsy are necessary for full assessment as to whether brivaracetam also displays efficacy in this population, as is suspected in this review. Additional trials should aim to incorporate multiple doses of brivaracetam to help ascertain a recommended specific dose for clinical use, and should be conducted over longer periods of time. Long-term studies are required to assess the long-term safety and tolerability of brivaracetam. It is recommended that after the safety profile of brivaracetam is ascertained, additional studies should be conducted to determine the efficacy of brivaracetam in children. Together, these additional studies and subsequent meta-analyses could more accurately inform clinical practice.

ACKNOWLEDGEMENTS

This review update 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 author(s) and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care.

We thank Qin Zhou, Cai-you Hu, Wei Zhang, and Yong-hong Huang for their contributions to the review protocol.

REFERENCES

References to studies included in this review

Biton 2014 *{published data only}*

* Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S.Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. *Epilepsia* 2014;**55**(1):57-66. [PMID: 24446953]

Pack AM.Brivaracetam, a novel antiepileptic drug: is it effective and safe? Results from one phase III randomized trial. *Epilepsy Currents* 2014;**14**(4):196-8. [DOI: 10.5698/1535-7597-14.4.196]

French 2010 *{published data only}*

French J, von Rosenstiel P.Efficacy and tolerability of brivaracetam as adjunctive treatment for adults with refractory partial-onset seizures. *Epilepsia* 2007;**48**(Suppl 7):78, Abstract no: p149.

French JA, Brodsky A, von Rosenstiel P, Brivaracetam N01193 Study Group.Efficacy and tolerability of 5, 20 and 50 mg/day brivaracetam (UCB 34714) as adjunctive treatment in adults with refractory partial-onset seizures. *Epilepsia* 2007;**48**(Suppl 6):400, Abstract no: C.04.

* French JA, Costantini C, Brodsky A, von Rosenstiel P, N01193 Study Group.Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. *Neurology* 2010;**75**(6):519-25. [PMID: 20592253]

Klein 2015 *{published data only}*

Klein P, Doty P, Elmoufti S, Whitesides J, Gold M.Predictors of response in patients with epilepsy in a double-blind, placebo-controlled study of brivaracetam. *Epilepsia* 2015;**56**(Suppl 1):111, Abstract no: p0435.

Klein P, Schiemann J, Sperling M, Whitesides J, Liang W, Stalvey T.A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of brivaracetam in adult patients with partial onset seizures. *Epilepsy Currents* 2015;**15**(Suppl 1):379, Abstract no: 2.417.

* Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, et al.A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. *Epilepsia* 2015;**56**(12):1890-8. [PMID: 26471380]

Kwan 2014 *{published data only}***2006-006346-34**

Kwan P, Johnson M, Merschhemke M, Lu S.Adujunctive brivaracetam in adults with uncontrolled generalized seizures: sub-population analysis of the results of a randomized, double-blind, placebo-controlled trial. In: 64th Annual Meeting of the American Epilepsy Society; 2010 Dec 3-7; San Antonio (TX). American Epilepsy Society, 2010. [ABSTRACT NO: 1.267] [URL: https://cms.aesnet.org/abstractslisting/adjunctive-brivaracetam-in-adults-with-uncontrolled-generalized-seizures--sub-population-analysis-of-the-results-of-a-randomized--double-blind--placebo-controlled-trial]

Kwan P, Johnson ME, Falter U, Pietteur VB, Brodsky AC, von Rosenstiel P.Safety and tolerability of brivaracetam as adjunctive treatment in adults with refractory epilepsy: randomized, double-blind, placebo-controlled trial. *Epilepsia* 2009;**50**(Suppl 11):107-8, Abstract no: 1.219.

Kwan P, Johnson ME, Merschhemke M, Lu S.Safety and tolerability of adjunctive brivaracetam in adults with uncontrolled epilepsy: randomized, double-blind, placebo-controlled trial. *Epilepsia* 2010;**51**(Suppl 4):152, Abstract no: p514.

* Kwan P, Trinka E, van Paesschen W, Rektor I, Johnson ME, Lu S.Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. *Epilepsia* 2014;**55**(1):38-46. [PMID: 24116853]

Ryvlin 2014 *{published data only}*

Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S.Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. *Epilepsia* 2014;**55**(1):47-56. [PMID: 24256083]

van Paesschen 2013 *{published data only}*

van Paesschen W, Brodsky A, Brivaracetam N01114 Study Group.Efficacy and tolerability of 50 and 150 mg/day brivaracetam (UCB 34714) as adjunctive treatment in adults with refractory partial-onset epilepsy. *Epilepsia* 2007;**48**(Suppl 6):329, Abstract no: 3.218.

* van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P.Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. *Epilepsia* 2013;**54**(1):89-97. [PMID: 22813235]

van Paesschen W, von Rosenstiel P.Efficacy and tolerability of brivaracetam as adjunctive treatment for adults with refractory partial-onset epilepsy. *Epilepsia* 2007;**48**(Suppl 7):56-7, Abstract no: 064.

References to studies excluded from this review

Brandt 2020 *{published data only}*

Brandt C, Klein P, Badalamenti V, Gasalla T, Whitesides J.Safety and tolerability of adjunctive brivaracetam in epilepsy: in-depth pooled analysis. *Epilepsy & Behaviour* 2020;**103**(Pt A):106864. [PMID: 31937513]

Lacroix 2007 *{published data only}*

Lacroix B, von Rosenstiel P, Sargentini-Maier ML.Population pharmacokinetics of brivaracetam in patients with partial epilepsy. *Epilepsia* 2007;**48**(Suppl 6):333-4, Abstract no: 3.230.

Lattanzi 2021 *{published data only}*

Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Chiesa V, Dainese F, et al.Adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on First Italian netwoRk STudy (BRIVAFIRST). *CNS Drugs* 2021;**35**(12):1289-1301

(Erratum in: CNS Drugs. 2021;35(12):1329-1331). [DOI: 10.1007/s40263-021-00856-3] [PMID: 34476770]

Szaflarski 2020 *{published data only}*

Szaflarski JP, Sadek A, Greve B, Williams P, Varner JA, Moseley BD.Randomized open-label trial of intravenous brivaracetam versus lorazepam for acute treatment of increased seizure activity. *Epilepsy & Behaviour* 2020;**109**:107127. [PMID: 32417382]

References to ongoing studies

NCT03083665 *{published data only}*

NCT03083665.A study to evaluate the efficacy and safety of adjunctive brivaracetam in Asian subjects (>=16 to 80 years of age) with epilepsy [A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in Asian subjects (>=16 to 80 years of age) with partial seizures with or without secondary generalization]. clinicaltrials.gov/ct2/show/NCT03083665 (first received 20 March 2017).

Additional references

Bialer 2010

Bialer M, Johannessen S, Levy RH, Perucca E, Tomson T, White HS.Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). *Epilepsy Research* 2010;**92**(2-3):89-124. [PMID: 20970964]

Chu-Shore 2010

Chu-Shore CJ, Thiele EA.New drugs for pediatric epilepsy. *Seminars in Pediatric Neurology* 2010;**17**(4):214-23. [PMID: 21183127]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG.Chapter 9. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

GRADEpro GDT [Computer program] [Computer program]

GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime) Hamilton (ON): McMaster University (developed by Evidence prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime). Version accessed 10 December 2021. Available at gradepro.org.

Hey 2014

Hey SP, Kimmelman J.The questionable use of unequal allocation in confirmatory trials. *Neurology* 2014;**82**(1):77-9. [PMID: 24306005]

Higgins 2011

Higgins JPT, Altman DG.Chapter 8. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Johannessen Landmark 2008

Johannessen Landmark C, Johannessen SI.Pharmacological management of epilepsy: recent advances and future prospects. *Drugs* 2008;**68**(14):1925-39. [PMID: 18778117]

Kasteleijn-Nolst Trenité 2007

Kasteleijn-Nolst Trenité DG, Genton P, Parain D, Masnou P, Steinhoff BJ, Jacobs T, et al.Evaluation of brivaracetam, a novel SV2A ligand, in the photosensitivity model. *Neurology* 2007;**69**(10):1027-34. [PMID: 17785672]

Lattanzi 2016

Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M.Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. *Neurology* 2016;**86**(14):1344-52. [PMID: 26944275]

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al.Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Ma 2015

Ma J, Huang S, You C.Adjunctive brivaracetam for patients with refractory partial seizures: a meta-analysis of randomized placebo-controlled trials. *Epilepsy Research* 2015;**114**:59-65. [PMID: 26088886]

Nicolas 2012

Nicolas JM, Chanteux H, Rosa M, Watanabe S, Stockis A.Effect of gemfibrozil on the metabolism of brivaracetam in vitro and in human subjects. *Drug Metabolism and Disposition* 2012;**40**(8):1466-72. [PMID: 22538270]

Review Manager 2020 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan).Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Schulze-Bonhage 2011

Schulze-Bonhage A.Brivaracetam for the treatment of epilepsy. *Expert Opinion on Pharmacotherapy* 2011;**12**(12):1959-66. [PMID: 21682662]

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al.Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Tian 2015

Tian X, Yuan M, Zhou Q, Wang X.The efficacy and safety of brivaracetam at different doses for partial-onset epilepsy: a meta-analysis of placebo-controlled studies. *Expert Opinion on Pharmacotherapy* 2015;**16**(12):1755-67. [PMID: 26165169]

von Rosenstiel 2007

von Rosenstiel P.Brivaracetam (UCB 34714). *Neurotherapeutics* 2007;**4**(1):84-7. [PMID: 17199019]

Werhahn 2010

Werhahn KJ, Biton V, Johnson ME, Merschhemke M, Lu S.Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from two randomized, double-blind, placebo-controlled trials. *Epilepsia* 2010;**51**(Suppl 4):150, Abstract no: p507.

WHO 2013

World Health Organization.Epilepsy. www.who.int/mental_health/neurology/epilepsy/en/index.html (accessed 5 June 2014).

Zhu 2017

Zhu L-N, Chen D, Chen T, Xu D, Chen S-H, Liu L.The adverse event profile of brivaracetam: a meta-analysis of randomized controlled trials. *Seizure* 2017;**45**:7-16. [PMID: 27898363]

References to other published versions of this review

Bresnahan 2019

Bresnahan R, Panebianco M, Marson AG.Brivaracetam add-on therapy for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No: CD011501. [DOI: 10.1002/14651858.CD011501.pub2]

Zhou 2015

Zhou Q, Hu CY, Zhang W, Huang YH.Brivaracetam add-on therapy for epilepsy. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No: CD011501. [DOI: 10.1002/14651858.CD011501]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Biton 2014

Study characteristics	
Methods	**Study design:** phase III, randomised, double-blind, PBO-controlled, parallel-group, multicentre **Countries:** Australia, Brazil, Canada, Mexico, the United States **Duration:** 1. Prospective baseline period (8 weeks) 2. Treatment period (12 weeks) 3. Downtitration period (1 week) or entry into long-term open-label follow-up study
Participants	**Randomised population** BRV 50 mg/d = 102 BRV 20 mg/d = 100 BRV 5 mg/d = 99 PBO = 99 **ITT population:**[a] BRV 50 mg/d = 101 BRV 20 mg/d = 100 BRV 5 mg/d = 97 PBO = 98 **mITT population:**[b] BRV 50 mg/d = 101

Biton 2014 *(Continued)*

	BRV 20 mg/d = 99 BRV 5 mg/d = 96 PBO = 96 **Safety population:**[c] BRV 50 mg/d = 101 BRV 20 mg/d = 100 BRV 5 mg/d = 97 PBO = 98 **Age (mean and SD):**[d] ≥ 16 to 70 years BRV 50 mg/d = 38.9 (12.3) BRV 20 mg/d = 37.3 (13.3) BRV 5 mg/d = 38.9 (11.6) PBO = 37.5 (12.6) **Gender, male, n (%):**[d] BRV 50 mg/d = 51 (50.5%) BRV 20 mg/d = 52 (52.0%) BRV 5 mg/d = 49 (50.5%) PBO = 43 (43.9%) **Ethnicity white, n (%):**[d] BRV 50 mg/d = 77 (76.2%) BRV 20 mg/d = 70 (70.0%) BRV 5 mg/d = 73 (75.3%) PBO = 66 (67.3%) **Types of seizure:** drug-resistant focal onset seizures
Interventions	All treatment groups received their respective treatment in 2 equally divided doses per day: BRV 50 mg/d (twice a day) BRV 20 mg/d (twice a day) BRV 5 mg/d (twice a day) PBO (twice a day)
Outcomes	**Primary outcomes:** 1. Per cent reduction over PBO in adjusted FOS frequency per week during the treatment period 2. Per cent reduction over PBO in 28-day adjusted FOS frequency during the treatment period **Secondary outcomes:**

Biton 2014 *(Continued)*

1. ≥ 50% responder rate based on per cent reduction in seizure frequency/week from baseline to the treatment period
2. Seizure freedom rate

Safety and tolerability outcomes:

1. Adverse events and severity
2. Laboratory tests
3. Physical and neurological examination findings
4. Vital signs
5. Electrocardiography recordings

Notes	Trial registry number: N01253, NCT00464269 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "a central randomization method (random permuted blocks) that stratified for concomitant LEV use at study entry ('yes' or 'no')"
Allocation concealment (selection bias)	Low risk	**Quote:** "treatment was assigned via an Interactive Voice Response System using a central randomization method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "matching placebo" was used to maintain blinding **Quote:** "patients and investigators were blinded to treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** participants acted as outcome assessors; participants self-reported seizure frequency by completion of "seizure daily record card" and were effectively blinded by matching placebo. Investigators, including data analysts/statisticians, were also effectively blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported; mITT analysis was conducted, resulting in the exclusion of 3 participants for non-compliance and 1 participant as a clinical outlier. Due to the small number of participants excluded and the valid reasoning provided, study was still assessed as at low risk of bias.
Selective reporting (reporting bias)	Unclear risk	**Comment:** protocol was not provided. All outcomes defined in the methods were reported in the results; however, no data were reported for the number of participants receiving placebo who reported at least 1 adverse event. **Quote:** "the incidence of treatment-emergent adverse events (TEAEs) was similar in all four treatment groups. At least one TEAE was reported during the treatment period of 69 (71.1%) of 97 patients on BRV 5 mg/day, 79 (79.0%) of 100 on BRV 20 mg/day, and 76 (75.2%) of 101 on BRV 50 mg/day"
Other bias	Low risk	**Comment:** none detected

French 2010

Study characteristics

Methods	**Study design:** phase IIb, randomised, double-blind, PBO-controlled, parallel-group, multicentre

French 2010 *(Continued)*

Countries: Brazil, India, Mexico, the United States

Duration:

1. Prospective baseline period (4 weeks)
2. Treatment period w/o uptitration (7 weeks)
3. 2-week drug-free period or entry into long-term open-label follow-up study

Participants	**Randomised population:** BRV 50 mg/d = 52 BRV 20 mg/d = 52 BRV 5 mg/d = 50 PBO = 54 **ITT population:**[a] BRV 50 mg/d = 52 BRV 20 mg/d = 52 BRV 5 mg/d = 50 PBO = 54 **Safety population:**[c] BRV 50 mg/d = 52 BRV 20 mg/d = 52 BRV 5 mg/d = 50 PBO = 54 **Age (mean and SD):**[d] ≥ 16 to 65 years BRV 50 mg/d = 30.9 (11.6) BRV 20 mg/d = 35.3 (13.7) BRV 5 mg/d = 32.7 (12.2) PBO = 33.6 (11.3) **Gender, male, n (%):**[d] BRV 50 mg/d = 28 (53.8%) BRV 20 mg/d = 28 (53.8%) BRV 5 mg/d = 30 (60.0%) PBO = 24 (44.4%) **Ethnicity white, n (%):**[d] BRV 50 mg/d = 12 (23.1%) BRV 20 mg/d = 22 (42.3%)

French 2010 *(Continued)*

	BRV 5 mg/d = 16 (32.0%) PBO = 23 (42.6%) **Types of seizure:** drug-resistant focal onset seizures
Interventions	All treatment groups received tablets, administered in 2 equally divided doses per day, without uptitration: BRV 50 mg/d (twice a day) BRV 20 mg/d (twice a day) BRV 5 mg/d (twice a day) PBO (twice a day)
Outcomes	**Primary outcome:** Per cent reduction over PBO in 28-day adjusted FOS frequency during the treatment period **Secondary outcomes:** Absolute and percentage reduction from baseline in weekly FOS frequency during the treatment period ≥ 50% responder rate for FOS frequency/week from baseline during the treatment period Seizure freedom rate **Safety and tolerability outcomes:** 1. Adverse events 2. Laboratory tests 3. Physical and neurological examination findings 4. Vital signs 5. Electrocardiography recordings
Notes	Trial registry number: N01193, NCT00175825 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "central randomization (random permuted blocks)... stratified for the intake of LEV... and of CBZ"
Allocation concealment (selection bias)	Low risk	**Quote:** "once a patient was eligible to be randomized, the investigator called the Central Randomization Center to receive a kit number to assign to the patient"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "the study was blinded, by use of matching placebo tablets which were identical in shape, size, and color to BRV tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "efficacy assessments were made from information recorded by the patients on daily record cards" **Comment:** participants were the outcome assessors and were adequately blinded throughout the study; moreover, the study was double-blind, mean-

French 2010 *(Continued)*

		ing that investigators, including those responsible for data analysis, would also have been effectively blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported, and ITT analysis was conducted; however, a modified population was actually used. 2 participants were excluded as they did not take at least 1 dose of study drug. Due to the small number of participants excluded and the valid reasoning provided, study was still assessed as at low risk of bias.
Selective reporting (reporting bias)	Low risk	**Comment:** protocol was not provided; however, all outcomes defined in methods were reported in results
Other bias	Low risk	**Comment:** none detected

Klein 2015

Study characteristics	
Methods	**Study design:** phase III, randomised, double-blind, PBO-controlled, parallel-group, multicentre **Countries:** North America, Western Europe, Eastern Europe, Latin America, Asia **Duration:** 1. Prospective baseline period (8 weeks) 2. Treatment period (12 weeks) 3. Downtitration period (4 weeks) 4. Drug-free period (2 weeks) or entry into a long-term follow-up study
Participants	**Randomised population:** BRV 200 mg/d = 251 BRV 100 mg/d = 254 PBO = 263 **ITT population:**[a] BRV 200 mg/d = 249 BRV 100 mg/d = 252 PBO = 259 **Safety population:**[c] BRV 200 mg/d = 250 BRV 100 mg/d = 253 PBO = 261 **Age (mean and SD):**[d] ≥ 16 to 80 years BRV 200 mg/d = 39.8 (12.8) BRV 100 mg/d = 39.1 (13.4)

Klein 2015 *(Continued)*

	PBO = 39.8 (12.5) **Gender, female, n (%):**[d] BRV 200 mg/d = 117 (46.8%) BRV 100 mg/d = 151 (59.7%) PBO = 128 (49.0%) **Ethnicity white, n (%):**[d] BRV 200 mg/d = 182 (72.8%) BRV 100 mg/d = 182 (71.9%) PBO = 189 (72.4%) **Types of seizure:** drug-resistant focal onset seizures
Interventions	All treatment groups received oral film-coated tablets, administered in 2 equally divided doses per day, without uptitration: BRV 200 mg/d (twice a day) BRV 100 mg/d (twice a day) PBO (twice a day)
Outcomes	**Primary outcomes:** 1. Per cent reduction over PBO in 28-day adjusted FOS frequency during the treatment period 2. ≥ 50% responder rate based on per cent reduction in seizure frequency from baseline to the treatment period **Secondary outcomes:** 1. Per cent reduction in seizure frequency from baseline to the treatment period 2. Categorised per cent reduction from baseline in seizure frequency over the treatment period 3. Seizure freedom rate **Safety and tolerability outcomes:** 1. Adverse events 2. Laboratory tests 3. Vital signs 4. Electrocardiography recordings
Notes	Trial registry number: N01358, NCT01261325 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "a 1:1:1 central randomization (random permuted blocks with a block size of three) stratified by country, LEV status (never used vs. prior use), and number of AEDs previously used or discontinued prior to study entry"

Klein 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote:** "patients were assigned to a treatment group at enrollment by an interactive voice/computer response system (IVRS), which was accessed by the investigator"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "all personnel who were involved with the study were blinded to the patients' treatment... Oral film-coated tablets of BRV 10, 25, and 50 mg and matching PBO tablets were used; these tablet strengths were used both to help maintain the blinding"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** participants reported seizure frequency using seizure diaries and were therefore the outcome assessors; participants were sufficiently blinded by the matching placebo. Investigators, including data analysts, were also effectively blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported, and ITT analysis conducted; 8 participants were excluded from the ITT population for the following reasons: discontinuation for unspecified reasons before study drug administration (n = 4), loss to follow-up (n = 1), discontinuation due to a TEAE (n = 2), and withdrawal of consent (n = 1). Due to the small number of participants excluded, study was still assessed as at low risk of bias.
Selective reporting (reporting bias)	Low risk	**Comment:** protocol was not provided; however, all outcomes defined in methods were reported in results
Other bias	Low risk	**Comment:** none detected

Kwan 2014

Study characteristics	
Methods	**Study design:** phase III, randomised, double-blind, PBO-controlled, parallel-group, flexible-dose, multicentre **Countries:** Austria, Belgium, the Czech Republic, Germany, Hong Kong, India, Italy, Norway, Republic of South Africa, Russian Federation, Singapore, South Korea, Sweden, Taiwan, Ukraine **Duration:** 1. Prospective baseline period (4 weeks) 2. Treatment period (16 weeks) including 8-week dose-finding and 8-week maintenance 3. Downtitration period (2 weeks) and drug-free period (2 weeks) or entry into a long-term follow-up study
Participants	**Randomised population:** BRV = 359 PBO = 121 **ITT population:**[a] BRV = 359 PBO = 121 **Safety population:**[c] BRV = 359

Kwan 2014 *(Continued)*

	PBO = 121 **Age (mean and SD):**[d] ≥ 16 to 70 years BRV = 35.6 (11.5) PBO = 36.5 (11.5) **Gender, male, n (%):**[d] BRV = 181 (50.4%) PBO = 69 (57.0%) **Ethnicity white, n (%):**[d] BRV = 209 (58.2%) PBO = 69 (57.0%) **Types of seizure:** drug-resistant focal onset or generalised epilepsy
Interventions	All treatment groups received tablets administered in 2 equally divided doses per day: BRV 20, 50, 100, 150 mg/d (twice a day) PBO (twice a day) For participants randomised to BRV, BRV was initiated at 20 mg/d. Participants were then uptitrated in a stepwise manner to 50, 100, or 150 mg/d at 2-week intervals based on the investigator's assessment of efficacy and tolerability.
Outcomes	**Safety and tolerability outcomes:** 1. Adverse events 2. Discontinuations due to AEs 3. Vital signs 4. Physical and neurological examination findings 5. Laboratory testsElectrocardiography recordings **Primary efficacy outcome:** 1. Per cent reduction in baseline-adjusted FOS frequency/week during the treatment period over PBO **Secondary outcomes:** 1. Median per cent reduction from baseline in FOS frequency/week 2. ≥ 50% responder rate in FOS frequency/week 3. Seizure freedom rate 4. Time to 1st, 5th, and 10th focal seizure
Notes	Trial registry number N01254, NCT00504881 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "patients were randomized 3:1 in random permuted blocks to BRV or PBO at the end of the baseline period. Randomization was stratified by epilep-

Kwan 2014 *(Continued)*

		sy type (focal or generalized) (International League Against Epilepsy, 1989), concomitant levetiracetam (LEV) use (yes or no), and geographic region"
Allocation concealment (selection bias)	Unclear risk	**Comment:** details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "matching PBO tablets" **Comment:** appropriate measures were taken to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "the date and number of seizures were recorded using a daily record card" **Comment:** outcomes were self-reported by participants, who remained appropriately blinded throughout the study; moreover, the study was double-blind, meaning that investigators, including those responsible for data analysis, would also have been effectively blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported, and ITT analysis was conducted, which correctly included all randomised participants
Selective reporting (reporting bias)	Low risk	**Comment:** protocol was not provided; however, all outcomes defined in methods were reported in results
Other bias	Unclear risk	**Quote:** "patients were randomized 3:1 in random permuted blocks to BRV or PBO" **Comment:** 3:1 randomisation ratio produces uneven treatment group sizes, which reduces the statistical power and can augment the placebo effect (Hey 2014)

Ryvlin 2014

Study characteristics	
Methods	**Study design:** phase III, randomised, double-blind, PBO-controlled, multicentre **Countries:** Poland, India, France, Germany, Spain, Italy, Switzerland, Hungary, Finland, the Netherlands, Belgium, the United Kingdom **Duration:** 1. Prospective baseline period (8 weeks) 2. Treatment period (12 weeks) 3. Downtitration period (2 weeks) and drug-free period (2 weeks) or entry into a long-term follow-up study
Participants	**Randomised population:** BRV 100 mg/d = 100 BRV 50 mg/d = 99 BRV 20 mg/d = 99 PBO = 100

Ryvlin 2014 *(Continued)*

	ITT population:[a] BRV 100 mg/d = 100 BRV 50 mg/d = 99 BRV 20 mg/d = 99 PBO = 100 **Safety population:**[c] BRV 100 mg/d = 100 BRV 50 mg/d = 99 BRV 20 mg/d = 99 PBO = 100 **Age (mean and SD):**[d] ≥ 16 to 70 years BRV 100 mg/d = 38.0 (13.1) BRV 50 mg/d = 38.9 (13.6) BRV 20 mg/d = 35.7 (12.5) PBO = 36.4 (13.0) **Gender, male, n (%):**[d] BRV 100 mg/d = 58 (58.0%) BRV 50 mg/d = 54 (54.5%) BRV 20 mg/d = 61 (61.6%) PBO = 54 (54.0%) **Ethnicity white, n (%):**[d] BRV 100 mg/d = 76 (76.0%) BRV 50 mg/d = 76 (76.8%) BRV 20 mg/d = 76 (76.8%) PBO = 77 (77.0%) **Type of seizure:** drug-resistant focal onset seizures
Interventions	All treatment groups received their respective treatment in 2 equally divided doses per day: BRV 100 mg/d (twice a day) BRV 50 mg/d (twice a day) BRV 20 mg/d (twice a day) PBO (twice a day)
Outcomes	**Primary outcome:** 1. Per cent reduction over PBO in baseline-adjusted FOS frequency/week over the treatment period

Ryvlin 2014 *(Continued)*

	Secondary outcomes: 1. Median per cent reduction in seizure frequency/week from baseline to the treatment period 2. ≥ 50% responder rate based on per cent reduction in seizure frequency/week from baseline to the treatment period 3. Seizure freedom rate **Safety and tolerability outcomes:** 1. Adverse events 2. Laboratory tests 3. Physical and neurological examination findings 4. Vital signs 5. Electrocardiography recordings
Notes	Trial registry number: N01252, NCT00490035 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "central randomisation... stratified by geographic region and concomitant use of LEV"
Allocation concealment (selection bias)	Low risk	**Quote:** "treatment was assigned using central randomization via an interactive voice response system (IVRS)"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "double-blind" **Comment:** no evidence or explanation of blinding provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "patients recorded the occurrence of seizures on daily record cards" **Comment:** participants were responsible for the self-reporting of outcome measures; however, no information is provided on blinding of participants or study personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported, and ITT analysis was conducted. 1 participant was excluded from any analysis; however, that participant died from a subdural haematoma before taking any study drug.
Selective reporting (reporting bias)	Low risk	**Comment:** protocol was not provided; however, all outcomes defined in methods were reported in results
Other bias	Low risk	**Comment:** none detected

van Paesschen 2013

Study characteristics

Methods	**Study design:** phase IIb, randomised, double-blind, PBO-controlled, parallel-group, multicentre **Countries:** Belgium, the Czech Republic, Finland, France, Germany, the Netherlands, Poland, Spain, the United Kingdom

van Paesschen 2013 *(Continued)*

	Duration: 1. Prospective baseline period (4 weeks) 2. Treatment period (10 weeks: 3 weeks uptitration and 7 weeks maintenance) 3. Conversion period (2 weeks): entry into a long-term open-label follow-up study or downtitration (2 weeks)
Participants	**Randomised population:** BRV 150 mg/d = 52 BRV 50 mg/d = 53 PBO = 52 **ITT population:**[a] BRV 150 mg/d = 52 BRV 50 mg/d = 53 PBO = 52 **Safety population:**[c] BRV 150 mg/d = 52 BRV 50 mg/d = 53 PBO = 52 **Age (mean and SD):**[d] ≥ 16 to 65 years BRV 150 mg/d = 34.4 (10.1) BRV 50 mg/d = 38.2 (12.1) PBO = 40.0 (11.7) **Gender, male, n (%):**[d] BRV 150 mg/d = 21 (40.4%) BRV 50 mg/d = 24 (45.3%) PBO = 25 (48.1%) **Ethnicity white, n (%):**[d] BRV 150 mg/d = 52 (100.0%) BRV 50 mg/d = 53 (100.0%) PBO = 51 (98.1%) **Type of seizure:** drug-resistant focal onset seizures
Interventions	All treatment groups received their respective treatment via oral capsules in 2 equally divided doses per day: BRV 150 mg/d (twice a day) BRV 50 mg/d (twice a day)

van Paesschen 2013 *(Continued)*

	PBO (twice a day) Participants randomised to BRV 150 mg/d began the uptitration period on a dose of 50 mg/d. After 1 week, the dosage was increased to 100 mg/d, and was then increased again to 150 mg/d after 2 weeks. Participants were permitted 1 fallback during the maintenance period to 100 mg/d. Participants randomised to BRV 50 mg/d started at a dose of 25 mg/d and were uptitrated to 50 mg/d after 1 week. They were again permitted 1 fallback to 25 mg/d during the maintenance period. Participants randomised to placebo continued to receive placebo during the uptitration and maintenance periods.
Outcomes	**Primary outcome:** 1. Per cent reduction in baseline-adjusted FOS frequency/week over PBO during the maintenance period **Secondary outcomes:** 1. Reduction in FOS frequency/week over PBO during the treatment period 2. Per cent reduction from baseline in FOS frequency/week (maintenance and treatment periods) 3. ≥ 50% responder rate in FOS seizure frequency from baseline during maintenance and treatment periods 4. Seizure freedom rate **Safety and tolerability outcomes:** 1. Treatment-emergent adverse events 2. Physical and neurological examinations 3. Vital signs 4. Clinical laboratory tests 5. Electrocardiography recordings
Notes	Trial registry number: N01114, NCT00175929 Sponsored by the manufacturer of BRV (UCB Pharma)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "central randomization method (random permuted blocks) stratified for concomitant use of LEV... and carbamazepine (CBZ)"
Allocation concealment (selection bias)	Low risk	**Quote (from protocol):** "each investigator will receive numbered subjects' kits. When a subject is determined to be eligible for randomization (at visit 2), the Investigator or designee will call the Central Randomization Center (CRC) and will be assigned a subject's kit number, according to the operating manual given by CRC"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "efficacy assessments were made using data recorded by the patients on daily record cards and assessed by the investigator at each study visit" **Comment:** participants were adequately blinded by matching placebo; the study was double-blind, meaning that investigators, including those responsible for data analysis, would also have been blinded

van Paesschen 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** attrition was reported, and ITT analysis was conducted; no randomised participants were excluded from the ITT population
Selective reporting (reporting bias)	Unclear risk	**Comment:** protocol was provided; not all outcomes defined in the protocol were reported in the journal article **Quote:** "secondary efficacy outcomes included..."
Other bias	Low risk	**Comment:** none detected

AE: adverse event; AED: antiepileptic drug; BRV: brivaracetam; CBZ: carbamazepine; ECG: electrocardiogram; FOS: focal onset seizure; ITT: intention-to-treat; IVRS: interactive voice response system; LEV: levetiracetam; mITT: modified intention-to-treat; PBO: placebo; SD: standard deviation; TEAEs: treatment-emergent adverse effects.
[a]ITT population was defined as all randomised participants who received at least one dose (≥ 1) of study drug, with the exception of Klein 2015, who defined ITT as all randomised participants who received at least one dose (≥ 1) of study drug and had at least one (≥ 1) postbaseline seizure diary entry.
[b]Biton 2014 used a modified intention-to-treat population, excluding four participants (three for extreme non-compliance and one as a clinical outlier).
[c]Klein 2015 defined safety population as all randomised participants who received at least one dose (≥ 1) of study drug. For all other studies, the safety population was identical to the ITT population.
[d]Calculated using the safety population.

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

Study	Reason for exclusion
Brandt 2020	Not an RCT
Lacroix 2007	Study was a meta-analysis of 2 trials already included in the review.
Lattanzi 2021	Not an RCT
Szaflarski 2020	Not an RCT

RCT: randomised controlled trial

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

NCT03083665

Study name	A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in Asian subjects (≥ 16 to 80 years of age) with partial seizures with or without secondary generalization
Methods	Randomised, double-blind, placebo-controlled, multicentre study with parallel-group design **Countries:** Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand
Participants	**Age:** 16 to 80 years **Type of seizure:** uncontrolled focal onset seizures with or without secondary generalisation
Interventions	All treatment groups received tablets, administered in 2 equally divided doses per day, without up-titration:

NCT03083665 *(Continued)*	
	Film-coated tablets BRV 50 mg/d PBO
Outcomes	**Primary outcome:** 1. Per cent change in FOS frequency during the 12-week treatment period **Secondary outcomes:** 1. ≥ 50% responder rate based on FOS frequency per 28 days from baseline to the treatment period 2. Per cent change in FOS frequency per 28 days from baseline to the treatment period 3. Categorised per cent change in FOS frequency per 28 days from baseline to the treatment period 4. All seizure frequency (focal, generalised, and unclassified epileptic seizures) per 28 days during the 12-week treatment period 5. Percentage of participants who are seizure-free (focal, all epileptic seizures) during the 12-week treatment period 6. Time to nth (n = 1, 5, 10) focal seizure during the 12-week treatment period **Safety and tolerability outcomes:** 1. Brivaracetam plasma concentration 2. Adverse events and severity 2. Laboratory tests 3. Electrocardiogram 4. Vital signs 5. Physical and neurological examination findings 6. Mental and psychiatric status
Starting date	22 August 2017
Contact information	UCBCares@ucb.com
Notes	Sponsored by UCB Pharma

AE: adverse event; BRV: brivaracetam; ECG: electrocardiography; FOS: focal onset seizures; PBO: placebo.

DATA AND ANALYSES

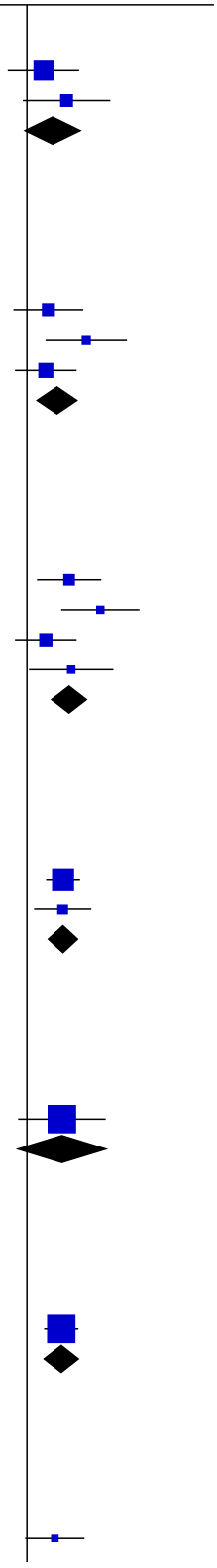
Comparison 1. Brivaracetam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 50% or greater reduction in seizure frequency (responder rate)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 5 mg/d BRV	2	302	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.97, 2.40]
1.1.2 20 mg/d BRV	3	504	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.18, 2.27]
1.1.3 50 mg/d BRV	4	611	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.50, 2.66]
1.1.4 100 mg/d BRV	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.42, 2.30]
1.1.5 150 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.86, 3.65]
1.1.6 200 mg/d BRV	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.33, 2.33]
1.1.7 All doses	6	2411	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.53, 2.14]
1.2 Seizure freedom	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 5 mg/d BRV	2	302	Risk Ratio (M-H, Fixed, 95% CI)	3.87 [0.65, 22.96]
1.2.2 20 mg/d BRV	3	551	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.65, 13.61]
1.2.3 50 mg/d BRV	4	611	Risk Ratio (M-H, Fixed, 95% CI)	5.39 [1.42, 20.49]
1.2.4 100 mg/d BRV	2	717	Risk Ratio (M-H, Fixed, 95% CI)	7.19 [1.93, 26.85]
1.2.5 150 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.91]
1.2.6 200 mg/d BRV	1	514	Risk Ratio (M-H, Fixed, 95% CI)	5.24 [1.16, 23.68]
1.2.7 All doses	6	2411	Risk Ratio (M-H, Fixed, 95% CI)	5.89 [2.30, 15.13]
1.3 Treatment withdrawal	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 5 mg/d BRV	2	302	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.93, 4.09]
1.3.2 20 mg/d BRV	3	504	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.40, 1.55]
1.3.3 50 mg/d BRV	4	611	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.56, 1.77]
1.3.4 100 mg/d BRV	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.88, 2.35]
1.3.5 150 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.19]
1.3.6 200 mg/d BRV	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.89, 2.88]
1.3.7 All doses	6	2411	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.94, 1.74]
1.4 Proportion of participants who experienced	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
adverse events leading to treatment withdrawal				
1.4.1 5 mg/d BRV	2	302	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.71, 5.96]
1.4.2 20 mg/d BRV	3	504	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.46, 2.72]
1.4.3 50 mg/d BRV	4	611	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.58, 2.76]
1.4.4 100 mg/d BRV	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.01, 3.59]
1.4.5 150 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.26, 8.61]
1.4.6 200 mg/d BRV	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.83, 3.82]
1.4.7 All doses	6	2411	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.02, 2.33]
1.5 Proportion of participants who experienced any adverse events	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 5 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.67, 1.39]
1.5.2 20 mg/d BRV	2	305	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.86, 1.30]
1.5.3 50 mg/d BRV	3	410	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.91, 1.25]
1.5.4 100 mg/d BRV	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.04, 1.31]
1.5.5 150 mg/d BRV	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.22]
1.5.6 200 mg/d BRV	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.99, 1.29]
1.5.7 All doses	5	2011	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.00, 1.17]

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

Study or Subgroup	BRV Events	BRV Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 5 mg/d BRV						
Biton 2014	21	99	16	99	64.9%	1.31 [0.73 , 2.36]
French 2010	16	50	9	54	35.1%	1.92 [0.93 , 3.95]
Subtotal (95% CI)		**149**		**153**	**100.0%**	**1.53 [0.97 , 2.40]**
Total events:	37		25			
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.1.2 20 mg/d BRV						
Biton 2014	23	100	16	99	35.9%	1.42 [0.80 , 2.53]
French 2010	23	52	9	54	19.7%	2.65 [1.36 , 5.19]
Ryvlin 2014	27	99	20	100	44.4%	1.36 [0.82 , 2.26]
Subtotal (95% CI)		**251**		**253**	**100.0%**	**1.64 [1.18 , 2.27]**
Total events:	73		45			
Heterogeneity: Chi² = 2.73, df = 2 (P = 0.26); I² = 27%						
Test for overall effect: Z = 2.96 (P = 0.003)						
1.1.3 50 mg/d BRV						
Biton 2014	33	102	16	99	30.0%	2.00 [1.18 , 3.40]
French 2010	29	52	9	54	16.3%	3.35 [1.76 , 6.37]
Ryvlin 2014	27	99	20	100	36.8%	1.36 [0.82 , 2.26]
van Paesschen 2013	19	53	9	52	16.8%	2.07 [1.03 , 4.15]
Subtotal (95% CI)		**306**		**305**	**100.0%**	**2.00 [1.50 , 2.66]**
Total events:	108		54			
Heterogeneity: Chi² = 4.66, df = 3 (P = 0.20); I² = 36%						
Test for overall effect: Z = 4.75 (P < 0.00001)						
1.1.4 100 mg/d BRV						
Klein 2015	98	254	56	263	73.3%	1.81 [1.37 , 2.40]
Ryvlin 2014	36	100	20	100	26.7%	1.80 [1.12 , 2.88]
Subtotal (95% CI)		**354**		**363**	**100.0%**	**1.81 [1.42 , 2.30]**
Total events:	134		76			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 4.83 (P < 0.00001)						
1.1.5 150 mg/d BRV						
van Paesschen 2013	16	52	9	52	100.0%	1.78 [0.86 , 3.65]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**1.78 [0.86 , 3.65]**
Total events:	16		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.1.6 200 mg/d BRV						
Klein 2015	94	251	56	263	100.0%	1.76 [1.33 , 2.33]
Subtotal (95% CI)		**251**		**263**	**100.0%**	**1.76 [1.33 , 2.33]**
Total events:	94		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.92 (P < 0.0001)						
1.1.7 All doses						
Biton 2014	77	301	16	99	13.2%	1.58 [0.97 , 2.58]
French 2010	68	154	9	54	7.2%	2.65 [1.42 , 4.94]

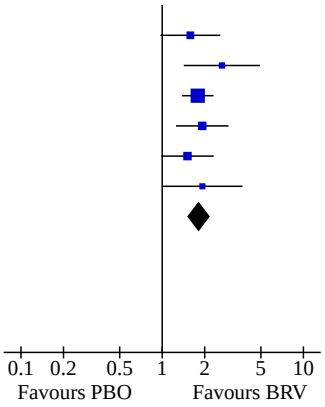


Analysis 1.1. (Continued)

Biton 2014	77	301	16	99	13.2%	1.58 [0.97 , 2.58]
French 2010	68	154	9	54	7.3%	2.65 [1.42 , 4.94]
Klein 2015	192	505	56	263	40.3%	1.79 [1.38 , 2.31]
Kwan 2014	114	359	20	121	16.4%	1.92 [1.25 , 2.95]
Ryvlin 2014	90	298	20	100	16.4%	1.51 [0.98 , 2.32]
van Paesschen 2013	35	105	9	52	6.6%	1.93 [1.00 , 3.70]
Subtotal (95% CI)		**1722**		**689**	**100.0%**	**1.81 [1.53 , 2.14]**
Total events:	576		130			

Heterogeneity: Chi² = 2.53, df = 5 (P = 0.77); I² = 0%

Test for overall effect: Z = 6.87 (P < 0.00001)



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

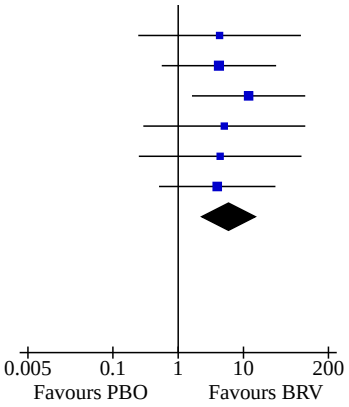
Study or Subgroup	BRV Events	BRV Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 5 mg/d BRV						
Biton 2014	1	99	0	99	34.2%	3.00 [0.12 , 72.76]
French 2010	4	50	1	54	65.8%	4.32 [0.50 , 37.36]
Subtotal (95% CI)		**149**		**153**	**100.0%**	**3.87 [0.65 , 22.96]**
Total events:	5		1			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.2.2 20 mg/d BRV						
Biton 2014	1	100	0	99	21.9%	2.97 [0.12 , 72.05]
French 2010	4	99	1	54	56.4%	2.18 [0.25 , 19.03]
Ryvlin 2014	2	99	0	100	21.7%	5.05 [0.25 , 103.87]
Subtotal (95% CI)		**298**		**253**	**100.0%**	**2.98 [0.65 , 13.61]**
Total events:	7		1			
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
1.2.3 50 mg/d BRV						
Biton 2014	4	102	0	99	20.3%	8.74 [0.48 , 160.20]
French 2010	4	52	1	54	39.3%	4.15 [0.48 , 35.95]
Ryvlin 2014	0	99	0	100		Not estimable
van Paesschen 2013	5	53	1	52	40.4%	4.91 [0.59 , 40.57]
Subtotal (95% CI)		**306**		**305**	**100.0%**	**5.39 [1.42 , 20.49]**
Total events:	13		2			
Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.47 (P = 0.01)						
1.2.4 100 mg/d BRV						
Klein 2015	13	254	2	263	79.7%	6.73 [1.53 , 29.53]
Ryvlin 2014	4	100	0	100	20.3%	9.00 [0.49 , 165.00]
Subtotal (95% CI)		**354**		**363**	**100.0%**	**7.19 [1.93 , 26.85]**
Total events:	17		2			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 2.93 (P = 0.003)						
1.2.5 150 mg/d BRV						
van Paesschen 2013	3	52	1	52	100.0%	3.00 [0.32 , 27.91]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**3.00 [0.32 , 27.91]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.2.6 200 mg/d BRV						
Klein 2015	10	251	2	263	100.0%	5.24 [1.16 , 23.68]
Subtotal (95% CI)		**251**		**263**	**100.0%**	**5.24 [1.16 , 23.68]**
Total events:	10		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.15 (P = 0.03)						
1.2.7 All doses						
Biton 2014	6	301	0	99	11.8%	4.30 [0.24 , 75.73]
French 2010	12	154	1	54	22.2%	4.21 [0.56 , 31.60]

Analysis 1.2. (Continued)

Biton 2014	6	301	0	99	11.8%	4.30 [0.24 , 75.73]
French 2010	12	154	1	54	23.2%	4.21 [0.56 , 31.60]
Klein 2015	23	505	1	263	20.6%	11.98 [1.63 , 88.20]
Kwan 2014	7	359	0	121	11.7%	5.08 [0.29 , 88.35]
Ryvlin 2014	6	298	0	100	11.7%	4.39 [0.25 , 77.26]
van Paesschen 2013	8	105	1	52	21.0%	3.96 [0.51 , 30.84]
Subtotal (95% CI)		**1722**		**689**	**100.0%**	**5.89 [2.30 , 15.13]**
Total events:	62		3			

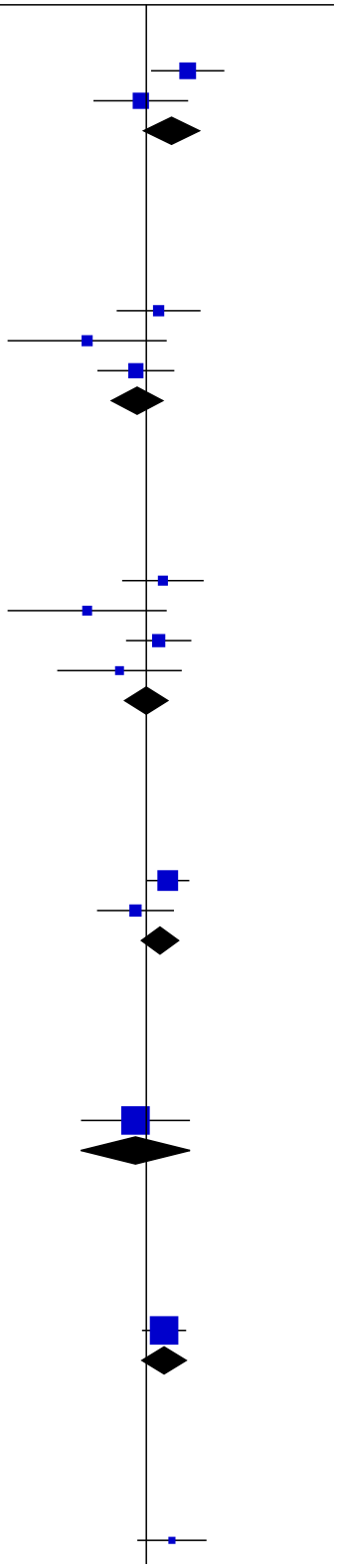
Heterogeneity: $Chi^2 = 0.83$, df = 5 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 3.69 (P = 0.0002)



Analysis 1.3. Comparison 1: Brivaracetam versus placebo, Outcome 3: Treatment withdrawal

Study or Subgroup	BRV Events	BRV Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 5 mg/d BRV						
Biton 2014	15	99	5	99	51.0%	3.00 [1.13 , 7.94]
French 2010	4	50	5	54	49.0%	0.86 [0.25 , 3.04]
Subtotal (95% CI)		**149**		**153**	**100.0%**	**1.95 [0.93 , 4.09]**
Total events:	19		10			
Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 1.78 (P = 0.08)						
1.3.2 20 mg/d BRV						
Biton 2014	7	100	5	99	28.1%	1.39 [0.46 , 4.22]
French 2010	1	52	5	54	27.4%	0.21 [0.03 , 1.72]
Ryvlin 2014	6	99	8	100	44.5%	0.76 [0.27 , 2.10]
Subtotal (95% CI)		**251**		**253**	**100.0%**	**0.78 [0.40 , 1.55]**
Total events:	14		18			
Heterogeneity: Chi² = 2.53, df = 2 (P = 0.28); I² = 21%						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.3.3 50 mg/d BRV						
Biton 2014	8	102	5	99	23.1%	1.55 [0.53 , 4.58]
French 2010	1	52	5	54	22.3%	0.21 [0.03 , 1.72]
Ryvlin 2014	11	99	8	100	36.2%	1.39 [0.58 , 3.31]
van Paesschen 2013	2	53	4	52	18.4%	0.49 [0.09 , 2.56]
Subtotal (95% CI)		**306**		**305**	**100.0%**	**1.00 [0.56 , 1.77]**
Total events:	22		22			
Heterogeneity: Chi² = 4.03, df = 3 (P = 0.26); I² = 26%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.3.4 100 mg/d BRV						
Klein 2015	29	254	17	263	67.6%	1.77 [1.00 , 3.13]
Ryvlin 2014	6	100	8	100	32.4%	0.75 [0.27 , 2.08]
Subtotal (95% CI)		**354**		**363**	**100.0%**	**1.44 [0.88 , 2.35]**
Total events:	35		25			
Heterogeneity: Chi² = 2.05, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.3.5 150 mg/d BRV						
van Paesschen 2013	3	52	4	52	100.0%	0.75 [0.18 , 3.19]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**0.75 [0.18 , 3.19]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.3.6 200 mg/d BRV						
Klein 2015	26	251	17	263	100.0%	1.60 [0.89 , 2.88]
Subtotal (95% CI)		**251**		**263**	**100.0%**	**1.60 [0.89 , 2.88]**
Total events:	26		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.3.7 All doses						
Biton 2014	30	301	5	99	10.8%	1.97 [0.79 , 4.95]
French 2010	6	154	5	54	10.6%	0.42 [0.13 , 1.32]

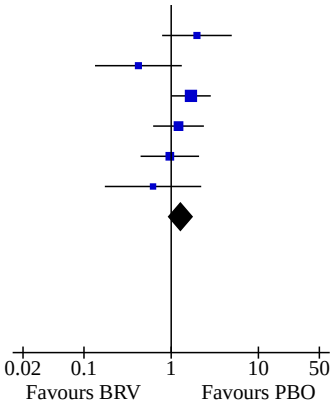


Analysis 1.3. (Continued)

Biton 2014	30	301	5	99	10.8%	1.97 [0.79 , 4.95]
French 2010	6	154	5	54	10.6%	0.42 [0.13 , 1.32]
Klein 2015	55	505	17	263	32.1%	1.68 [1.00 , 2.84]
Kwan 2014	36	359	10	121	21.5%	1.21 [0.62 , 2.37]
Ryvlin 2014	23	298	8	100	17.2%	0.96 [0.45 , 2.09]
van Paesschen 2013	5	105	4	52	7.7%	0.62 [0.17 , 2.21]
Subtotal (95% CI)		**1722**		**689**	**100.0%**	**1.27 [0.94 , 1.74]**
Total events:	155		49			

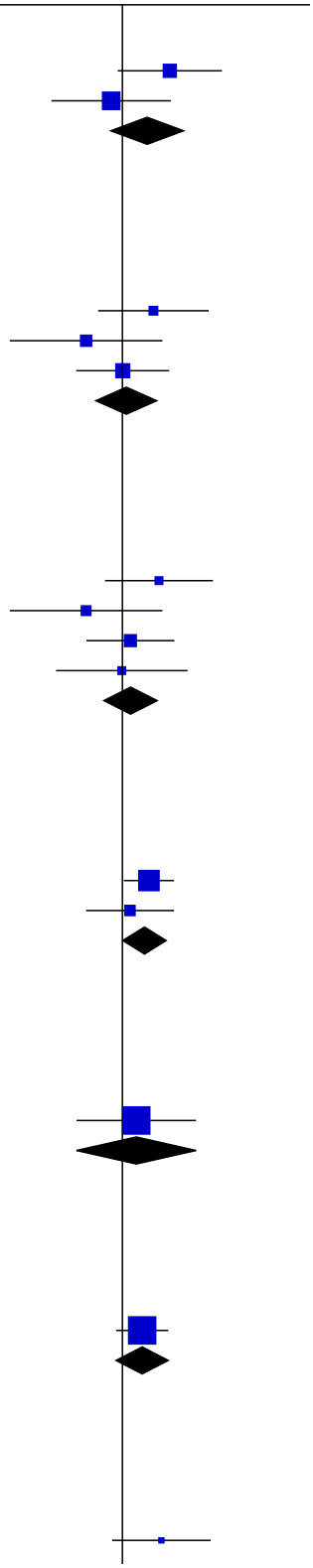
Heterogeneity: Chi² = 7.32, df = 5 (P = 0.20); I² = 32%

Test for overall effect: Z = 1.54 (P = 0.12)



Analysis 1.4. Comparison 1: Brivaracetam versus placebo, Outcome 4: Proportion of participants who experienced adverse events leading to treatment withdrawal

Study or Subgroup	BRV Events	BRV Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 5 mg/d BRV						
Biton 2014	8	99	2	99	40.9%	4.00 [0.87 , 18.37]
French 2010	2	50	3	54	59.1%	0.72 [0.13 , 4.13]
Subtotal (95% CI)		**149**		**153**	**100.0%**	**2.06 [0.71 , 5.96]**
Total events:	10		5			
Heterogeneity: Chi² = 2.12, df = 1 (P = 0.15); I² = 53%						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.4.2 20 mg/d BRV						
Biton 2014	5	100	2	99	22.5%	2.48 [0.49 , 12.46]
French 2010	1	52	3	54	32.9%	0.35 [0.04 , 3.22]
Ryvlin 2014	4	99	4	100	44.6%	1.01 [0.26 , 3.93]
Subtotal (95% CI)		**251**		**253**	**100.0%**	**1.12 [0.46 , 2.72]**
Total events:	10		9			
Heterogeneity: Chi² = 2.01, df = 2 (P = 0.37); I² = 1%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.4.3 50 mg/d BRV						
Biton 2014	6	102	2	99	18.5%	2.91 [0.60 , 14.08]
French 2010	1	52	3	54	26.8%	0.35 [0.04 , 3.22]
Ryvlin 2014	5	99	4	100	36.3%	1.26 [0.35 , 4.56]
van Paesschen 2013	2	53	2	52	18.4%	0.98 [0.14 , 6.71]
Subtotal (95% CI)		**306**		**305**	**100.0%**	**1.27 [0.58 , 2.76]**
Total events:	14		11			
Heterogeneity: Chi² = 2.44, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.4.4 100 mg/d BRV						
Klein 2015	21	254	10	263	71.1%	2.17 [1.04 , 4.53]
Ryvlin 2014	5	100	4	100	28.9%	1.25 [0.35 , 4.52]
Subtotal (95% CI)		**354**		**363**	**100.0%**	**1.91 [1.01 , 3.59]**
Total events:	26		14			
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
1.4.5 150 mg/d BRV						
van Paesschen 2013	3	52	2	52	100.0%	1.50 [0.26 , 8.61]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**1.50 [0.26 , 8.61]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.4.6 200 mg/d BRV						
Klein 2015	17	251	10	263	100.0%	1.78 [0.83 , 3.82]
Subtotal (95% CI)		**251**		**263**	**100.0%**	**1.78 [0.83 , 3.82]**
Total events:	17		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.4.7 All doses						
Biton 2014	19	301	2	99	7.9%	3.12 [0.74 , 13.18]
French 2010	4	154	3	54	11.6%	0.47 [0.11 , 2.02]

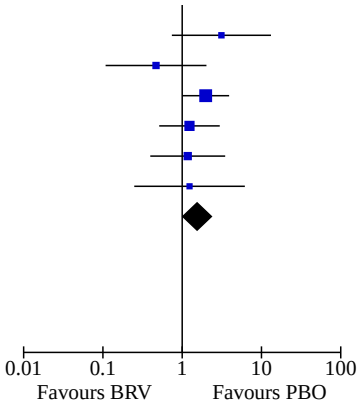


Analysis 1.4. (Continued)

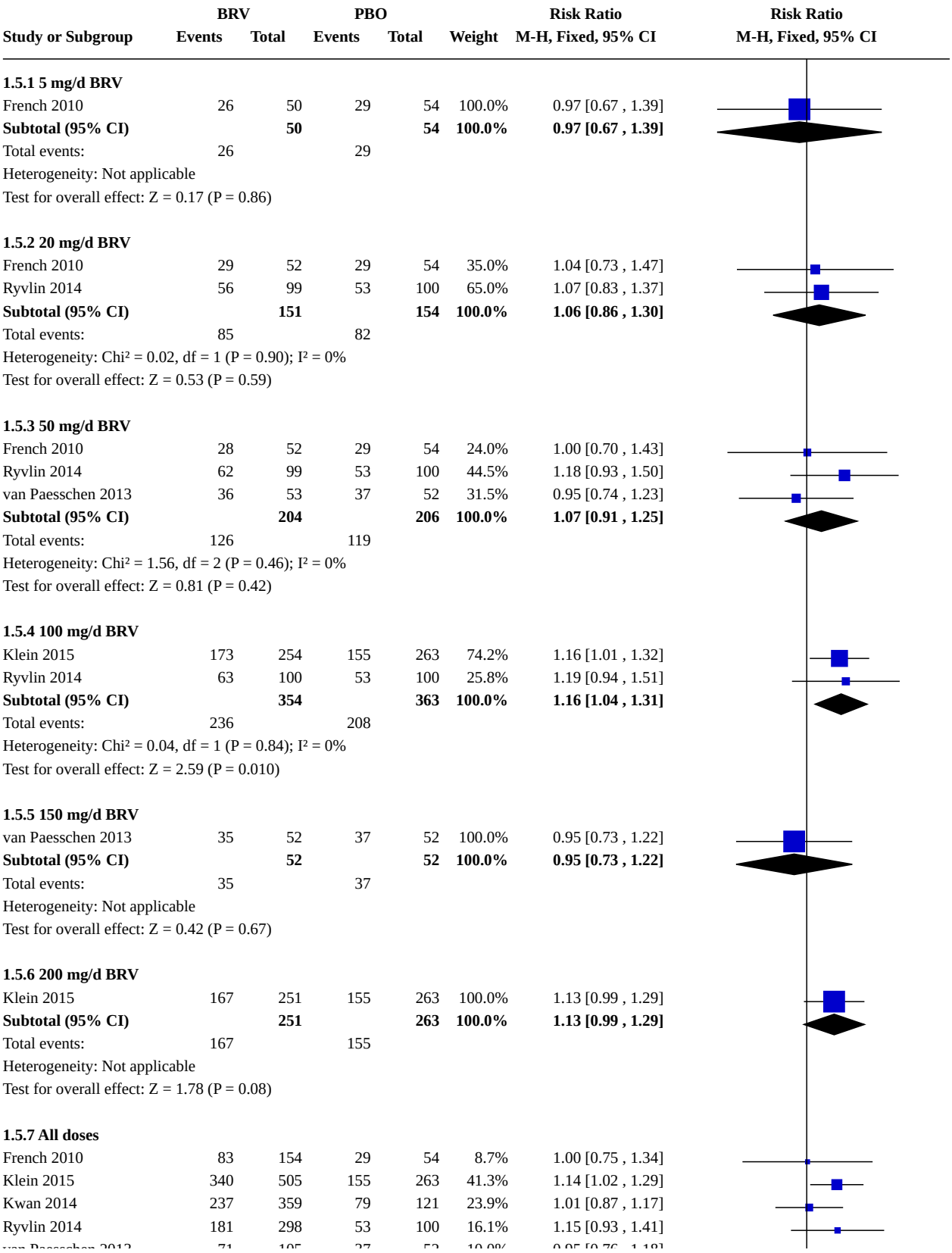
Biton 2014	19	301	2	99	7.9%	3.12 [0.74 , 13.18]
French 2010	4	154	3	54	11.6%	0.47 [0.11 , 2.02]
Klein 2015	38	505	10	263	34.4%	1.98 [1.00 , 3.91]
Kwan 2014	22	359	6	121	23.5%	1.24 [0.51 , 2.98]
Ryvlin 2014	14	298	4	100	15.7%	1.17 [0.40 , 3.49]
van Paesschen 2013	5	105	2	52	7.0%	1.24 [0.25 , 6.17]
Subtotal (95% CI)		**1722**		**689**	**100.0%**	**1.54 [1.02 , 2.33]**
Total events:	102		27			

Heterogeneity: Chi² = 4.55, df = 5 (P = 0.47); I² = 0%

Test for overall effect: Z = 2.05 (P = 0.04)



Analysis 1.5. Comparison 1: Brivaracetam versus placebo, Outcome 5: Proportion of participants who experienced any adverse events

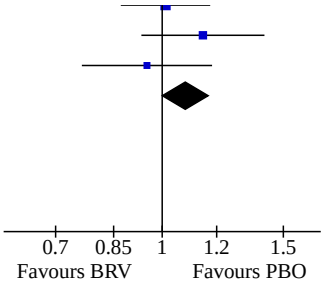


Analysis 1.5. (Continued)

Ryvlin 2014	181	298	53	100	16.1%	1.15 [0.93 , 1.41]
van Paesschen 2013	71	105	37	52	10.0%	0.95 [0.76 , 1.18]
Subtotal (95% CI)		**1421**		**590**	**100.0%**	**1.08 [1.00 , 1.17]**
Total events:	912		353			

Heterogeneity: Chi² = 3.51, df = 4 (P = 0.48); I² = 0%

Test for overall effect: Z = 1.98 (P = 0.05)



APPENDICES

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

1. (Brivaracetam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

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

3. #1 NOT #2

4. >09/10/2018:CRSCREATED

5. #3 AND #4

Appendix 2. MEDLINE (Ovid) search strategy

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

1. Brivaracetam.mp.

2. exp Epilepsy/

3. exp Seizures/

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

5. 2 or 3 or 4

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

7. 5 not 6

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

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 1 and 7 and 13

15. (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=20181008-20210907

19. 17 not (1$ or 2$).ed.

20. 19 and (2018$ or 2019$ or 2020$ or 2021$).dt.

21. 18 or 20

WHAT'S NEW

Date	Event	Description
27 October 2021	New citation required but conclusions have not changed	Conclusions are unchanged.
7 September 2021	New search has been performed	Searches updated 7 September 2021; no new studies were identified.

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 3, 2019

Date	Event	Description
1 August 2019	Amended	Minor copyedits carried out.

CONTRIBUTIONS OF AUTHORS

Rebecca Bresnahan (RB): assessed study eligibility and performed data extraction and risk of bias assessment. Responsible for the primary conduct and writing of this current review update.
Mariangela Panebianco (MP): assessed study eligibility and performed data extraction and risk of bias assessment for this current review update.
Anthony Marson (AGM): arbitrated discussions when necessary.

DECLARATIONS OF INTEREST

Rebecca Bresnahan: nothing to declare.
Mariangela Panebianco: nothing to declare.
Anthony Marson: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool.
Professor Marson is funded in part by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).
Professor Marson is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.
Professor Marson is the Co-ordinating Editor of the Cochrane Epilepsy Group; however, he was not involved in the editorial process of this review update.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review authorship has changed since publication of the review protocol. Rebecca Bresnahan and Mariangela Panebianco have since been instated as two review authors, with Rebecca Bresnahan primarily responsible for the conduct and reporting of the review. Qin Zhou, Cai-you Hu, Wei Zhang, and Yong-hong Huang remain acknowledged for their writing of the original protocol and for their contribution to the Background and Methods sections of the current review, which we adapted from the original review protocol.

We had stated in our protocol that we would assess funnel plot asymmetry as an indication of publication bias. However, as the current review included fewer than 10 studies, we did not produce any funnel plots for defined outcomes.

We had further specified that we would conduct subgroup analyses according to the different dose groups of brivaracetam, as well as the different age groups of participants. However, as all the included studies comprised purely adult patient populations, we were only able to conduct subgroup analysis according to dose groups.

Finally, we had planned to conduct sensitivity analyses where we would repeat the meta-analyses excluding unpublished studies and excluding studies that had been published only as abstracts. However, of the included studies were published as full-length journal articles, therefore neither sensitivity analysis was necessary.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects]; *Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination; *Epilepsy, Generalized [drug therapy]; Pyrrolidinones; Randomized Controlled Trials as Topic; Seizures [drug therapy]

MeSH check words

Adult; Humans