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

Bresnahan R, Hill RA, Wang J

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[Intervention Review]

Perampanel add-on for drug-resistant focal epilepsy

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ABSTRACT

Background

Epilepsy is one of the most common neurological disorders. Approximately 30% of people with epilepsy are considered to be drug-resistant, and usually need treatment with a combination of other antiepileptic drugs. Perampanel is a newer antiepileptic drug that has been investigated as add-on therapy for drug-resistant focal epilepsy.

Objectives

To evaluate the benefits and harms of perampanel as add-on therapy for people with drug-resistant focal epilepsy.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 20 October 2022.

Selection criteria

We included randomised controlled trials comparing add-on perampanel with placebo.

Data collection and analysis

We used standard Cochrane methods. Our primary outcome was 1. 50% or greater reduction in seizure frequency. Our secondary outcomes were 2. seizure freedom, 3. treatment withdrawal due to any reason, 4. treatment withdrawal due to adverse effects, and 5. adverse effects. We used an intention-to-treat population for all primary analyses. We presented the results as risk ratios (RR) with 95% confidence intervals (CIs), except for individual adverse effects, which we reported with 99% CIs to compensate for multiple testing. We used GRADE to assess certainty of evidence for each outcome.

Main results

We included seven trials involving 2524 participants, all aged over 12 years. The trials were double-blind, randomised, placebo-controlled trials with treatment duration of 12 to 19 weeks. We assessed four trials at overall low risk of bias, and three trials at overall unclear risk of bias, due to risk of detection, reporting, and other biases.

Compared with placebo, participants receiving perampanel were more likely to achieve a 50% or greater reduction in seizure frequency (RR 1.67, 95% CI 1.43 to 1.95; 7 trials, 2524 participants; high-certainty evidence). Compared to placebo, perampanel increased seizure freedom (RR 2.50, 95% CI 1.38 to 4.54; 5 trials, 2323 participants; low-certainty evidence) and treatment withdrawal (RR 1.30, 95% CI 1.03 to 1.63; 7 trials, 2524 participants; low-certainty evidence). Participants treated with perampanel were more likely to withdraw from treatment due to adverse effects compared to those receiving placebo (RR 2.36, 95% CI 1.59 to 3.51; 7 trials, 2524 participants; low-certainty evidence). A higher proportion of participants receiving perampanel reported one or more adverse effects when compared to participants who received placebo (RR 1.17, 95% CI 1.10 to 1.24; 7 trials, 2524 participants; high-certainty evidence). Compared with placebo, participants receiving

perampanel were more likely to experience ataxia (RR 14.32, 99% CI 1.09 to 188.31; 2 trials, 1098 participants; low-certainty evidence), dizziness (RR 2.87, 99% CI 1.45 to 5.70; 7 trials, 2524 participants; low-certainty evidence), and somnolence (RR 1.76, 99% CI 1.02 to 3.04; 7 trials, 2524 participants).

Subgroup analysis indicated that a larger proportion of participants who received perampanel at a dose of 4 mg/day (RR 1.38, 95% CI 1.05 to 1.83; 2 trials, 710 participants), 8 mg/day (RR 1.83, 95% CI 1.51 to 2.22; 4 trials, 1227 participants), or 12 mg/day (RR 2.38, 95% CI 1.86 to 3.04; 3 trials, 869 participants) achieved a 50% or greater reduction in seizure frequency compared to placebo; however, treatment with perampanel 12 mg/day also increased treatment withdrawal (RR 1.77, 95% CI 1.31 to 2.40; 3 trials, 869 participants).

Authors' conclusions

Add-on perampanel is effective at reducing seizure frequency and may be effective at maintaining seizure freedom for people with drug-resistant focal epilepsy. Although perampanel was well-tolerated, there was a higher proportion of treatment withdrawals with perampanel compared with placebo. Subgroup analysis suggested that 8 mg/day and 12 mg/day are the most efficacious perampanel doses; however, the use of 12 mg/day would likely increase the number of treatment withdrawals.

Future research should focus on investigating the efficacy and tolerability of perampanel with longer-term follow-up, as well as exploring an optimal dose.

PLAIN LANGUAGE SUMMARY

Perampanel add-on for drug-resistant focal epilepsy

Key messages

Add-on perampanel is effective at reducing seizure frequency and may maintain seizure freedom for people with drug-resistant focal epilepsy. Perampanel is well-tolerated at doses of 8 mg/day or less.

What is epilepsy?

Epilepsy is one of the most common brain disorders. Approximately 30% of people with epilepsy continue to have seizures (sudden bursts of electrical activity in the brain that change how it works for a short time) despite adequate therapy with antiepileptic medicines. These people are regarded as having drug-resistant epilepsy and usually need treatment with a combination of antiepileptic medicines. Perampanel is a newer antiepileptic medicine that has been investigated as an add-on therapy for drug-resistant focal epilepsy (when seizures originate from one area of the brain).

What did we want to find out?

We wanted to know whether perampanel was effective and tolerable when used as an add-on therapy for people with drug-resistant focal epilepsy.

What did we do?

We searched medical databases for studies investigating the effects of perampanel as add-on therapy in people with drug-resistant focal epilepsy of any age.

What did we find?

We found seven studies that met our criteria. The studies involved 2524 people, who were all aged 12 years and over. During the studies, people received a dose of perampanel (2 mg per day, 4 mg per day, 8 mg per day, or 12 mg per day) or placebo (dummy treatment) as an add-on therapy. The people in the studies received their treatment for 12 to 19 weeks.

Main results

People who received perampanel were more likely to have a 50% or more reduction in the number of seizures that they normally experience. A greater number of people who received perampanel became free from all seizures, but they were also more likely to withdraw from treatment. The results indicated that perampanel 8 mg per day or 12 mg per day were most effective at controlling seizures; however, perampanel 12 mg per day also led to more people withdrawing from treatment.

People taking perampanel were more likely to experience side effects than those taking placebo. The most common side effects included dizziness and sleepiness.

What are the limitations of the evidence?

We judged that most studies were at low risk of bias. When a study has low risk of bias, it means that the effect that the study reports should be reliable. We also assessed the evidence used in this review for certainty. We found high-certainty evidence that perampanel was more

likely to reduce the number of seizures by 50% or more. This means that we are confident that this finding is accurate. There was low-certainty evidence that more people became free of all seizures, withdrew from treatment, and experienced problems with co-ordination, balance, and speech (known as ataxia) or dizziness, meaning that the findings for these measures may be inaccurate.

How up to date is this evidence?

The evidence is current to October 2022.

Summary of findings 1. Perampanel add-on versus placebo for drug-resistant focal epilepsy

Perampanel add-on versus placebo for drug-resistant focal epilepsy

Patient or population: people (aged 12 years and over) with drug-resistant focal epilepsy
Setting: outpatients
Intervention: add-on perampanel (2 mg/day, 4 mg/day, 8 mg/day, and 12 mg/day)
Comparison: add-on placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with perampanel				
≥ 50% reduction in seizure frequency Follow-up: 12–19 weeks	**Study population**		**RR 1.67** (95% CI 1.43 to 1.95)	**2524** (7 RCTs)	⊕⊕⊕⊕ **High**	Perampanel increases the proportion of participants who achieve a ≥ 50% reduction in seizure frequency.
	205 per 1000	**342 per 1000** (293 to 399)				
Seizure freedom Follow-up: 19 weeks	**Study population**		**RR 2.50** (95% CI 1.38 to 4.54)	**2323** (5 RCTs)	⊕⊕⊖⊖ **Low**[a]	Perampanel may increase the proportion of participants who attain seizure freedom.
	18 per 1000	**45 per 1000** (25 to 82)				
Treatment withdrawal due to any reason Follow-up: 12–19 weeks	**Study population**		**RR 1.30** (95% CI 1.03 to 1.63)	**2524** (7 RCTs)	⊕⊕⊖⊖ **Low**[b,c]	Perampanel may increase the proportion of participants who withdraw from treatment due to any reason.
	118 per 1000	**154 per 1000** (122 to 193)				
Treatment withdrawal due to adverse effects Follow-up: 12–19 weeks	**Study population**		**RR 2.36** (95% CI 1.59 to 3.51)	**2524** (7 RCTs)	⊕⊕⊖⊖ **Low**[b,c]	Perampanel may increase the prevalence of treatment withdrawal due to adverse effects.
	37 per 1000	**88 per 1000** (59 to 130)				
Proportion of participants who experienced ≥ 1 adverse effect Follow-up: 12–19 weeks	**Study population**		**RR 1.17** (95% CI 1.10 to 1.24)	**2524** (7 RCTs)	⊕⊕⊕⊕ **High**	Perampanel increases the incidence of participants reporting ≥ 1 adverse effects.
	662 per 1000	**775 per 1000** (728 to 821)				

Proportion of participants who experienced ataxia Follow-up: 19 weeks	**Study population**[d]		**RR 14.32** (99% CI 1.09 to 188.31)	**1098** (2 RCTs)	⊕⊕⊖⊖ **Low**[a]	Perampanel may greatly increase the incidence of ataxia.
	0 per 298	**34 per 800**				
Proportion of participants who experienced dizziness Follow-up: 12–19 weeks	**Study population**		**RR 2.87** (99% CI 1.45 to 5.70)	**2524** (7 RCTs)	⊕⊕⊖⊖ **Low**[e]	Perampanel may increase the incidence of dizziness.
	91 per 1000	**260 per 1000** (131 to 517)				

*__The risk in the intervention group__ (and its 95% or 99% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% or 99% 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 twice for imprecision. Number of events (fewer than 100) did not suffice the optimal information size.
[b]Downgraded once for inconsistency. The direction of effect varied across individual trials. While most trials found a negative effect for perampanel compared to placebo, some found no effect, and one found a positive effect.
[c]Downgraded once for imprecision. Number of events (fewer than 400) did not suffice the optimal information size.
[d]We reported the number of events recorded per number of randomised participants rather than anticipated absolute effects for this outcome as this measure was more informative.
[e]Downgraded twice due to inconsistency. There was statistical heterogeneity across the data ($P < 0.10$; $I^2 = 75\%$).

BACKGROUND

Description of the condition

Epilepsy is one of the most common neurological disorders, with an annual incidence of 68 cases per 100,000 population in the US and Europe, and a prevalence of 6.4 cases per 1000 population (Fiest 2017). Approximately 70 million people worldwide have epilepsy, and it is reported that twice as many people in low-income countries have epilepsy than in high-income countries (Ngugi 2011). Most people with newly diagnosed epilepsy achieve seizure control without major adverse effects; however, approximately 30% of people do not respond to one or more antiepileptic drugs and their epilepsy is considered to be drug resistant (Schuele 2008). In contrast to people with well-controlled seizures, people with drug-resistant epilepsy commonly experience complications and comorbidities, such as cognitive impairment, and psychosocial and psychiatric disorders (Schmidt 2002). Better tolerated and more effective drugs are therefore needed for people with drug-resistant epilepsy.

Description of the intervention

Perampanel, an orally active, non-competitive amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, was approved in 2012 for use in the US (FDA 2015) and the EU (EMA 2021) as add-on treatment for people with focal epilepsy who are 12 years of age and older. When administered orally, perampanel is well absorbed through the gastrointestinal tract, and reaches a peak plasma concentration after 15 minutes to two hours of administration. Its plasma elimination half-life is approximately 105 hours, allowing once daily dosing. About 70% of the active perampanel taken orally is excreted in the faeces in the unchanged form; 30% is excreted through the urine (Franco 2013; Owen 2013; Plosker 2012; Rektor 2013; Shvarts 2013).

How the intervention might work

AMPA receptors, the main mediators of glutamate, mediate fast postsynaptic excitatory neurotransmission in the central nervous system, and are critical for the generation and spread of epileptic seizures (Rogawski 2011; Rogawski 2013). Perampanel is a highly selective, non-competitive AMPA receptor antagonist that may exert its antiepileptic effect through selective inhibition of AMPA receptors (Ceolin 2012; Hanada 2011). It has no significant affinity for kainate or N-methyl-d-aspartate (NMDA) receptors, which is believed to minimise off-target effects (Ceolin 2012; Rogawski 2011).

Why it is important to do this review

The novel antiepileptic agent, perampanel, has demonstrated broad-spectrum antiepileptic effects in animal models of epilepsy (Ceolin 2012; Hanada 2011). This review focused on the use of perampanel as an add-on therapy for people with drug-resistant focal epilepsy, summarising evidence about perampanel's efficacy and tolerability from identified RCTs.

OBJECTIVES

To evaluate the benefits and harms of perampanel as add-on therapy for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they met all the following criteria:

- randomised controlled trials (RCTs) with an adequate method of concealment of randomisation (e.g. use of an interactive voice response system and sealed, opaque envelopes);
- double-blind trials, in which both participants and personnel, or outcome assessors, were blinded to treatment;
- placebo-controlled trials;
- parallel-group or cross-over trials. For cross-over trials, we only included the results gained from the first treatment arm;
- trials that had a treatment duration of at least eight weeks, and recorded baseline seizure data.

Types of participants

People of any age with focal epilepsy, defined as seizures that only affect part of the brain at onset, including simple focal, complex focal, or secondary generalised tonic-clonic seizures, who failed to respond to one or more antiepileptic drugs; or with drug-resistant focal epilepsy, defined as people who had not achieved sustained seizure freedom during adequate trials of two tolerated and appropriately chosen antiepileptic drugs were eligible for inclusion (International League Against Epilepsy definition (Kwan 2010)).

Types of interventions

The intervention treatment group received perampanel, in addition to one or more existing antiepileptic drugs, from the time of randomisation.

The control group received a matched placebo, in addition to one or more existing antiepileptic drugs, from the time of randomisation.

Types of outcome measures

50% or greater reduction in seizure frequency

The proportion of participants with a 50% or greater reduction in seizure frequency from prerandomisation baseline to the end of the treatment period. We chose this outcome because it is often reported in this type of study and can be calculated for studies that did not report it, provided that baseline seizure data were recorded.

Seizure freedom

The proportion of participants with seizure freedom during the whole treatment period (i.e. from first dose of study drug to the end of the treatment period).

Treatment withdrawal due to any reason

We used the proportion of participants who withdrew, for any reason, during the course of the treatment period as a measure of global effectiveness. Treatment may be withdrawn because of adverse effects, lack of efficacy, a combination of both, or due to another reason.

Treatment withdrawal due to adverse effects

Adverse effects are usually the main reason for treatment withdrawal in trials of shorter duration, therefore, we also assessed the proportion of participants who had treatment withdrawn specifically as a result of adverse effects.

Adverse effects

- Proportion of participants who experienced at least one adverse effect.
- Proportion of participants experiencing any common adverse effects in relation to perampanel; specifically dizziness, somnolence, fatigue, ataxia, and headache.

Search methods for identification of studies

Electronic searches

We searched the following databases on 20 October 2022:

- Cochrane Register of trials (CRS Web), using the search strategy given in Appendix 1;
- MEDLINE (Ovid, 1946 to 19 October 2022), using the search strategy given in Appendix 2.

CRS Web includes randomised or quasi-randomised, controlled trials from Specialized Registers of Cochrane Review Groups, including Epilepsy; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; Embase; ClinicalTrials.gov; and the World Health Organization International Clinical Trials Registry Platform (ICTRP). In MEDLINE (Ovid) the coverage end date always lags a few days behind the search date.

We also conducted electronic database searches on: 24 November 2015, 26 June 2017, 25 August 2018, 19 September 2019, and 1 June 2021.

Searching other resources

We reviewed the reference lists of the retrieved trials to search for any additional reports of relevant trials. We contacted the pharmaceutical manufacturer Eisai Inc., which produces perampanel, to obtain relevant data, and the original investigators of the relevant trials to identify any additional published or unpublished data. We also handsearched abstracts published from June 2018 to October 2022 from International Epilepsy Congress meetings.

Data collection and analysis

Selection of studies

Two review authors (RB and RH) independently read the titles and abstracts of all reports identified by the search strategies implemented in August 2018, September 2019, June 2021, and October 2022 and assessed their eligibility for the review. Two separate review authors (Y Xiao and J Huang) screened the titles and abstracts of all reports identified by the previous searches, conducted in November 2015 and June 2017. Once we had retrieved the full text of all the potentially relevant papers, each review author independently evaluated the full text of each paper for inclusion. We resolved any disagreements by discussion, or with a third author (JW) acting as an arbitrator.

Data extraction and management

Two review authors (RB and RH) independently extracted the following data, using a data extraction form:

- participants: total and number in each group, age, gender, seizure types, seizure frequency at the time of randomisation, exclusion criteria;
- methods: study design, study duration, randomisation method, allocation concealment method, blinding methods;
- interventions: details of perampanel treatment, such as administration method, dosage, and duration; number of background drugs;
- outcomes: proportion of participants with a 50% or greater reduction in seizure frequency; proportion of participants with seizure freedom during the whole treatment period; proportion of participants who withdrew during the course of the treatment period for any reason; proportion of participants experiencing dizziness, somnolence, fatigue, and headache, or other clinically important adverse effects reported in the included trials;
- other: country and setting, publication year, sources of funding, intention-to-treat (ITT) analysis.

The review authors had no disagreements about the data extraction.

Assessment of risk of bias in included studies

Two review authors (RB and RH) independently assessed the risk of bias of the included trials using the RoB 1 tool recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The RoB 1 tool consists of seven parameters: 1. random sequence generation, 2. allocation concealment, 3. blinding of participants and personnel, 4. blinding of outcome assessment, 5. incomplete outcome data, 6. selective outcome reporting, and 7. other bias. For each entry, we provided our judgement ('low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias), followed by a description of the design, conduct, or observations that underlie the judgement (Higgins 2011). The review authors had no disagreement in assessing the risk of bias.

Measures of treatment effect

We analysed data according to the ITT principle. For dichotomous outcomes (50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal), we used risk ratios (RRs) with 95% confidence intervals (CIs) to analyse the outcomes. For individual adverse effects, we used 99% CIs to make allowance for multiple hypothesis testing. For the primary analysis, we assumed that participants who did not complete follow-up, or for whom there were inadequate seizure data, were non-responders.

Unit of analysis issues

We did not include any cross-over studies in this review, therefore, did not encounter any unit of analysis issues. If we were to identify a cross-over study that was eligible for inclusion in a future review update, we would extract data from the first treatment period only, and then treat these data as though they had been derived from a parallel-group study. This would prevent data from the same participant contributing to both the intervention and control treatment groups, and avoid any unit of analysis issues.

Dealing with missing data

We attempted to obtain additional information and missing data from the study authors and the sponsoring company through personal communication. Some unpublished data for subgroup analysis were not available from the sponsor at present. Once the data become available, we will add them to an update of this review. We used ITT analysis to account for missing data.

Assessment of heterogeneity

We evaluated clinical and methodological heterogeneity of included trials by comparing the characteristics of participants (age, baseline seizure frequency, epilepsy duration, and geographical origin of included participants), interventions (administration dose and duration, co-interventions), and study design (randomisation, allocation concealment, and blinding methods) between studies. We evaluated statistical heterogeneity using the Chi^2 test and the I^2 statistic. A P value equal to, or greater than 0.10 from the Chi^2 test indicated no significant statistical heterogeneity. When the P value was less than 0.10 from the Chi^2 test, we interpreted the heterogeneity according to the percentage ranges of the I^2 statistic, as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity[a];
- 50% to 90%: may represent substantial heterogeneity[a];
- 75% to 100%: represents considerable heterogeneity[a].

[a]The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects and the strength of the evidence for heterogeneity (e.g. P value from the Chi^2 test or a CI for the I^2 statistic).

Assessment of reporting biases

We requested trial protocols in order to examine whether the outcomes of interest, stated in the trial protocol, were reported and analysed in the respective study reports. When the protocol was not provided, we compared the methods section of the study reports against the results section and stated that this was the case in the risk of bias table.

We included a limited number of studies so we were unable to investigate potential publication biases using funnel plots and visually inspect them for asymmetry to assess reporting bias, according to the approach outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We used Review Manager 5 (RevMan 5) to synthesise the available data (Review Manager 2014). We used a fixed-effect or a random-effects model dependent mainly on the results of the Chi^2 test and the I^2 statistic for heterogeneity (Higgins 2011). If a P value was greater than 0.10, indicating no significant statistical heterogeneity, we used a fixed-effect model. If a P value was less than 0.10 but the I^2 statistic indicated no important or moderate heterogeneity, we used a fixed-effect model. If a P value was less than 0.10 and the I^2 statistic indicated substantial heterogeneity, we first explored factors contributing to clinical heterogeneity to determine whether a subgroup analysis according to clinical subgroups was needed. If the substantial heterogeneity could not readily be explained, we adopted a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis according to the different ages of participants (children younger than 17 years versus adults), and the different doses of perampanel (e.g. 2 mg/day, 4 mg/day, 8 mg/day, or 12 mg/day). However, because of the limited data gained from the included studies, we only conducted the subgroup analysis according to different doses of perampanel, not according to different ages of the participants.

Sensitivity analysis

We intended to conduct sensitivity analyses, whereby we would exclude studies that had missing data for the primary outcome (i.e. data were not available in the original reports, or were not supplied by the study authors following correspondence) from the meta-analysis. All seven studies provided data for 50% or greater reduction in seizure frequency therefore it was not necessary to conduct the planned sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to summarise findings, as detailed in the GRADE handbook (Schünemann 2013). We exported data from Review Manager 5 to GRADEpro GDT software to create a summary of findings table (GRADEpro GDT; Review Manager 2014). We assessed the certainty of the evidence for outcomes across five domains (risk of bias; inconsistency; indirectness; imprecision; publication bias), according to the GRADE guidelines (Balshem 2011).

We selected the following outcomes as the most important, to include in the summary of findings table: 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal due to any reason, treatment withdrawal due to adverse effects, and the proportion of participants who experienced at least one adverse effect. We also included the two adverse effects that demonstrated the largest effect size for all doses of perampanel versus placebo (i.e. the proportion of participants who experienced ataxia, and the proportion of participants who experienced dizziness). This enabled us to assess whether the estimated effect size was likely to be an accurate reflection of the true treatment effect.

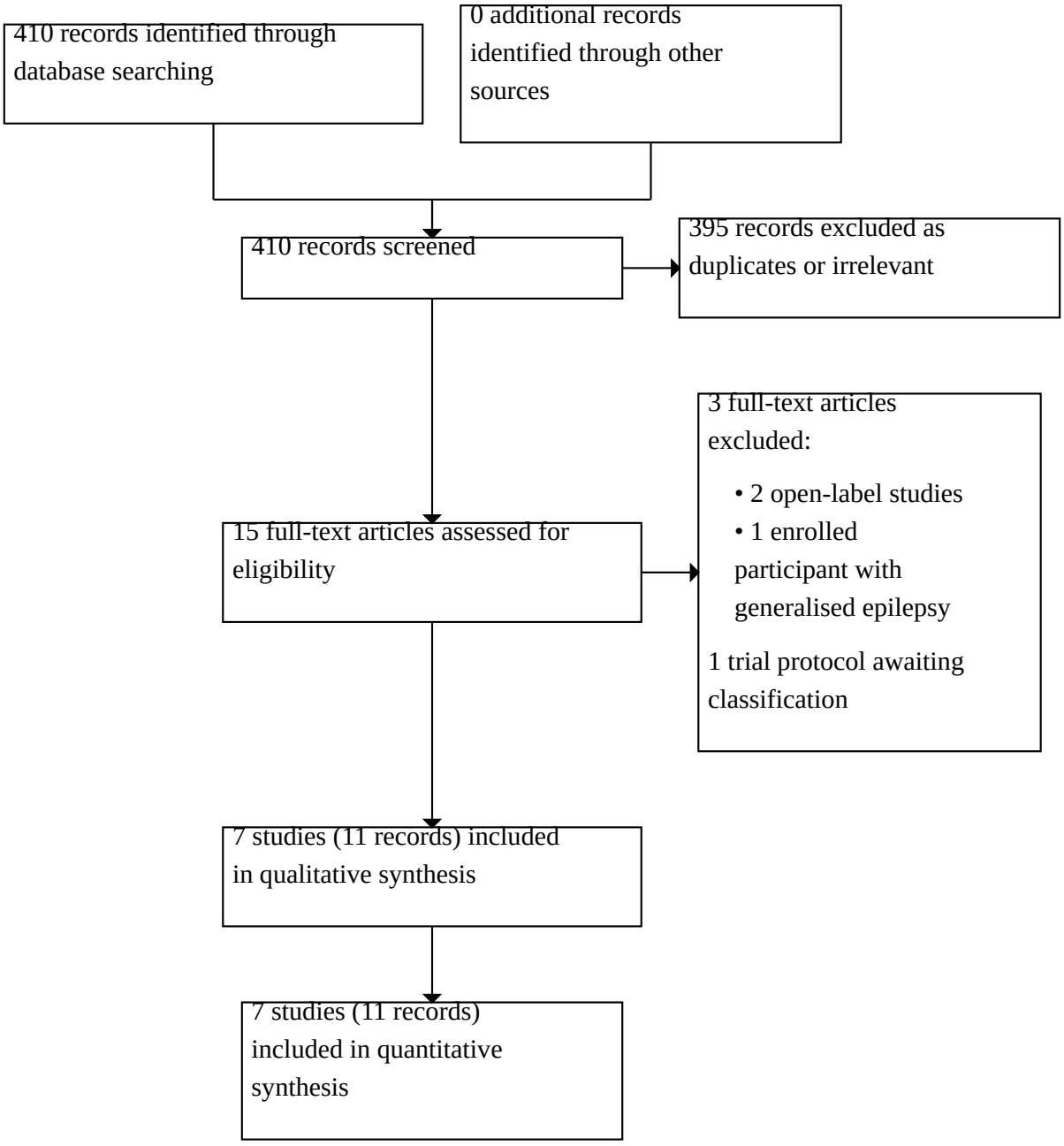
RESULTS

Description of studies

Results of the search

We identified 410 potentially relevant records using the search strategies. After reviewing the titles and abstracts, we excluded 395 records, as they were either duplicates or were irrelevant. We obtained the full-text reports of the remaining 15 records. We excluded three studies (French 2015; Montouris 2015; Toledo 2016). We identified 11 records that were eligible for inclusion. In some cases, multiple records linked to a single study, whilst in contrast, one record described two individual studies (Krauss 2012 (study 206); Krauss 2012 (study 208)). We included seven studies (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Krauss 2012 (study 206); Krauss 2012 (study 208); Lagae 2016; Nishida 2018). See Figure 1. We incorporated data from all seven studies into the meta-analysis.

Figure 1. Study flow diagram.



We identified one study awaiting classification (NCT03780907). We did not identify any ongoing trials or unpublished data.

Included studies

See Characteristics of included studies table.

Study design

All seven trials were multicentre, double-blind, randomised placebo-controlled trials. Four were multiple-dose trials (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Nishida 2018).

Six trials included either a four-week or six-week baseline period (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Krauss 2012 (study 206); Krauss 2012 (study 208); Nishida 2018). One study only included a one-week prospective baseline period (Lagae 2016). Five trials consisted of a six-week titration and 13-week maintenance period (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Lagae 2016; Nishida 2018). One study had an eight-week titration period and a four-week maintenance period (Krauss 2012 (study 206)), while another had a 12-week titration period and a four-week maintenance period (Krauss 2012 (study 208)).

Population

Four trials included young people and adults, specifically people aged 12 years and over (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Nishida 2018). The mean age was well-balanced between treatment groups and ranged from 32.3 (standard deviation (SD) 12.3) years to 36.7 (SD 14.6) years across the four trials (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Nishida 2018). One study only included young people (aged 12 to 18 years; Lagae 2016), and two trials only included adults (aged 18 to 70 years; Krauss 2012 (study 206); Krauss 2012 (study 208)).

Three trials recruited people from Europe, Australia, and the US (French 2013 (study 305); Krauss 2012 (study 206); Lagae 2016). However, French 2013 (study 305) also recruited people from South Africa and Lagae 2016 also recruited people from Asia. French 2012 (study 304) recruited people from the USA and South America. Krauss 2012 and Krauss 2012 (study 208) recruited people from Australia and Europe. Krauss 2012 also recruited people from Asia. Nishida 2018 recruited people from Asia and Australia.

Intervention

Four trials used multiple doses (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Nishida 2018). French 2012 (study 304) and French 2013 (study 305) investigated two doses (8 mg/day and 12 mg/day), while Krauss 2012 and Nishida 2018 investigated three doses (4 mg/day, 8 mg/day, and 12 mg/day).

Krauss 2012 (study 206) and Krauss 2012 (study 208)) were two consecutive phase II RCTs. Krauss 2012 (study 206) investigated the tolerability of perampanel at low doses and titrated people up to a maximum of 4 mg/day, whereas Krauss 2012 (study 208) investigated the tolerability of higher doses of perampanel (up to 12 mg/day). Lagae 2016 titrated participants up to a target dose of 8 mg/day to 12 mg/day.

Outcomes

All seven included trials reported the efficacy outcomes of responder rate (50% or greater reduction in seizure frequency during the maintenance period relative to baseline) and percent change in seizure frequency per 28 days from baseline to maintenance phase. Three studies specified that responder rate was the primary outcome (French 2013 (study 305); Krauss 2012 (study 206); Krauss 2012 (study 208)). Four studies specified that percent change in seizure frequency per 28 days from baseline to maintenance phase was the primary outcome (French 2012 (study 304); Krauss 2012; Lagae 2016; Nishida 2018).

Excluded studies

We excluded three studies because of wrong population (generalised epilepsy), and wrong study design (open-label; French 2015; Montouris 2015; Toledo 2016). See Characteristics of excluded studies for details.

Studies awaiting classification

We identified one record that currently had no results available (NCT03780907). We entered it as a study awaiting classification until more study information becomes available. We will include it in an update of the review once we have the data. See Characteristics of studies awaiting classification for details.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

The results of the risk of bias assessments for the included studies are summarised in Figure 2 and Figure 3. Details are provided in the risk of bias table associated with the Characteristics of included studies table. We rated all the included studies to have either a low or unclear risk of bias. Each of the domains are now discussed, separately.

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

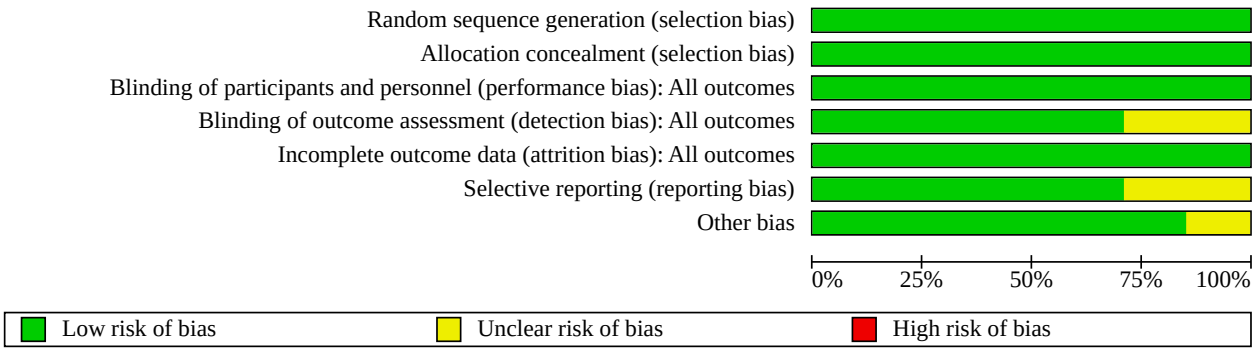
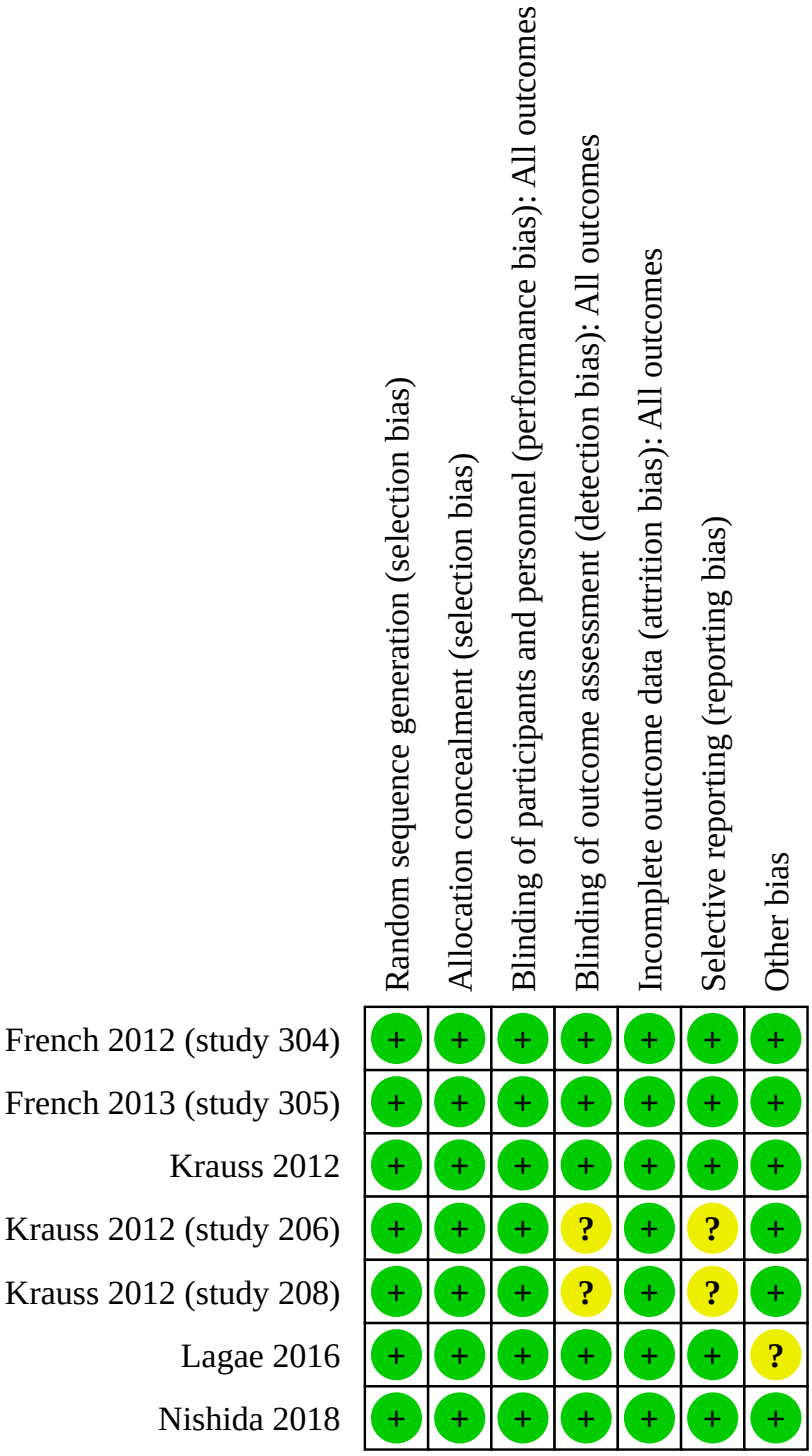


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were reported as randomised. Four studies reported that they used a computer-generated randomisation method (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Lagae 2016); one study used an interactive voice-response system to randomise participants (Nishida 2018). The remaining two studies did not describe the method used to generate the randomised sequence or the method used for allocation concealment in the study reports (Krauss 2012 (study 206); Krauss 2012 (study 208)). Through correspondence, the study authors clarified that they used a computer-generated central randomisation method. Therefore, we assessed all seven studies at low risk of selection bias for random sequence generation.

Three studies specified that an independent statistician was responsible for locking and storing the allocation sequence, once generated, thus ensuring adequate allocation concealment (French 2012 (study 304); French 2013 (study 305); Krauss 2012). Two studies used an interactive voice-response system to guarantee adequate allocation concealment (Lagae 2016; Nishida 2018). The remaining two randomised studies did not provide information on allocation concealment in their reports, but upon our request, they informed us that they used an interactive voice-response system to perform allocation (Krauss 2012 (study 206); Krauss 2012 (study 208)). Consequently, we judged all seven studies at low risk of selection bias for allocation concealment.

Blinding

All studies stated that they were double-blind, however, only four studies provided sufficient details on blinding in their associated publications (French 2012 (study 304); French 2013 (study 305); Lagae 2016; Nishida 2018). The study investigators, participants, and outcome assessors were all effectively blinded to treatment since the control group was given matching placebo. The remaining three studies did not provide specific details of the blinding method used (Krauss 2012; Krauss 2012 (study 206); Krauss 2012 (study 208)). Upon request, the trial authors provided protocols, which clarified that blinding of the study investigators and participants was achieved by matching placebo. Therefore, we judged all seven included studies at low risk of performance bias for blinding of participants and study personnel.

In their protocols, five studies stated that their statistical analyses plans were finalised prior to the unblinding of data. Consequently, all data entry would have been completed before database unblinding, and, although the outcome assessors were not blind to participants' treatment allocation at the time of analysing the data, they would have adhered to the predetermined statistical analysis plan once allocation was revealed.

We judged that five studies successfully implemented all necessary precautions to minimise detection bias and were at low risk (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Lagae 2016; Nishida 2018). In contrast, the other two studies failed to provide details for the blinding of outcome assessment in either the study publication or the trial protocol and were at unclear risk of detection bias (Krauss 2012 (study 206); Krauss 2012 (study 208)).

Incomplete outcome data

All seven studies reported the number of and the reasons for treatment withdrawals (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Krauss 2012 (study 206); Krauss 2012 (study 208); Lagae 2016; Nishida 2018). Importantly, in all studies the attrition rate was less than 20% of the randomised population and all seven studies performed ITT analyses. Consequently, all studies were at low risk of attrition bias.

Selective reporting

We contacted Eisai Inc, the sponsor of the included studies, to request the associated trial protocols, which they provided. Therefore, we were able to identify the prespecified outcomes, and compare them to the outcomes reported in the study publications. Five studies provided clear descriptions of their prespecified outcomes and fully reported them suggesting no reporting bias (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Lagae 2016; Nishida 2018). We judged them at low risk of reporting bias.

Two studies failed to report several of the secondary outcome that were prespecified in the trial protocol, including outcomes related to seizure frequency, but did fully report our outcomes of interest (Krauss 2012 (study 206); Krauss 2012 (study 208)). Therefore, we judged them at unclear risk of reporting bias, as it was not clear whether the incomplete reporting of these outcomes would affect or impact the findings of this review.

Other potential sources of bias

We were unable to determine any other sources of bias for six studies, which we subsequently judged at low risk (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Krauss 2012 (study 206); Krauss 2012 (study 208); Nishida 2018). We noted that one study used an unequal allocation ratio of 2:1 for treatment allocation to perampanel versus placebo. This led to reduced statistical power, which can augment the placebo effect as a higher proportion of participants assume that they are receiving active treatment (Hey 2014). As a result, we awarded the study unclear risk of other bias (Lagae 2016).

Effects of interventions

See: **Summary of findings 1** Perampanel add-on versus placebo for drug-resistant focal epilepsy

See: Summary of findings 1.

Assessment of heterogeneity

There was no evidence of statistical heterogeneity for 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal due to any reason, and treatment withdrawal due to adverse effects. Therefore, we used a fixed-effect model and the Mantel-Haenszel method for these outcomes. We only found evidence of statistical heterogeneity for two of the adverse effect outcomes, dizziness ($P = 0.0006$, $I^2 = 75\%$; Analysis 1.6) and somnolence ($P = 0.0006$, $I^2 = 75\%$; Analysis 1.7). Therefore, we used a random-effects model for these two outcomes only.

Subgroup analysis by perampanel dose

Krauss 2012 (study 206) assessed perampanel 4 mg/day and Krauss 2012 (study 208) assessed perampanel 12 mg/day. In Krauss 2012 (study 206), 82.4% of participants in the perampanel twice daily treatment group (42/51) and perampanel once daily treatment group (42/51) reached the maximum dose of 4 mg/day. Similarly,

82.4% (42/51) of participants in the placebo group successfully titrated up to 4 mg/day placebo. In Krauss 2012 (study 208), only 32% (12/38) of the perampanel-treated participants reached the target dose of 12 mg/day. Of note, only 60% (6/10) of participants in the placebo group reached the target dose of 12 mg/day placebo. Lagae 2016 evaluated a dose range of 8 mg/day to 12 mg/day.

The other four studies investigated set doses of 2 mg/day, 4 mg/day, 8 mg/day, or 12 mg/day (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Nishida 2018).

We used the data from Krauss 2012 (study 206), Krauss 2012 (study 208), and Lagae 2016 for the overall efficacy and tolerability analysis for the outcome measures, but not for subgroup analysis that analysed different doses of perampanel.

Primary outcome

50% or greater reduction in seizure frequency

All seven studies (2524 participants) contributed data to the 50% or greater reduction in seizure frequency analysis.

The study reports excluded 14 participants from the primary analyses, as they did not complete at least one seizure frequency data record (French 2012 (study 304); Krauss 2012; Krauss 2012 (study 206); Lagae 2016; Nishida 2018), or provide valid baseline seizure frequency data (Krauss 2012 (study 208); Lagae 2016). We included them in our outcome analyses as non-responders, using an ITT approach.

Participants receiving perampanel were more likely to achieve a 50% or greater reduction in seizure frequency than those receiving placebo (RR 1.67, 95% CI 1.43 to 1.95; 7 studies, 2524 participants; Analysis 1.1).

When analysing the results according to different doses, those taking perampanel were more likely to experience a 50% or greater reduction in seizures than those receiving placebo for 4 mg/day (RR 1.38, 95% CI 1.05 to 1.83; 2 studies, 710 participants), 8 mg/day (RR 1.83, 95% CI 1.51 to 2.22; 4 studies, 1227 participants), and 12 mg/day (RR 2.38, 95% CI 1.86 to 3.04; 3 studies, 869 participants). The results were inconclusive for perampanel 2 mg/day versus placebo (RR 1.15, 95% CI 0.76 to 1.76; 1 study, 365 participants; Analysis 1.1).

Secondary outcomes

Seizure freedom

Five studies (2323 participants analysed) contributed to the seizure freedom analysis (French 2012 (study 304); French 2013 (study 305); Krauss 2012; Lagae 2016; Nishida 2018).

Four studies excluded 12 participants from their original outcome analysis, because they did not complete at least one seizure frequency data record, or provide valid baseline seizure frequency data (French 2012 (study 304); Krauss 2012; Lagae 2016; Nishida 2018). For the purposes of this review, we included the previously excluded participants as non-responders in the ITT analysis.

Participants receiving perampanel were more likely to achieve seizure freedom compared to placebo (RR 2.50, 95% CI 1.38 to 4.54; 5 studies, 2323 participants; Analysis 1.2). Participants receiving 4 mg/day (RR 4.20, 95% CI 1.19 to 14.76; 2 studies, 710 participants), 8 mg/day (RR 3.85, 95% CI 1.51 to 9.86; 4 studies, 1227 participants), and 12 mg/day (RR 4.87, 95% CI 1.54 to 15.43; 3 studies, 869 participants) were more likely to achieve seizure freedom than those receiving placebo, but those receiving perampanel 2 mg/day were not (RR 1.54, 95% CI 0.26 to 9.12; 1 study, 365 participants; Analysis 1.2).

Treatment withdrawal

All seven studies (2524 participants) contributed to this outcome analysis.

The number of and the reasons for treatment withdrawals were reported. Adverse effects were the main reason for treatment withdrawal in all studies.

Treatment withdrawal due to any reason

Participants receiving perampanel were at higher risk of treatment withdrawal due to any reason than those receiving placebo (RR 1.30, 95% CI 1.03 to 1.63; 7 studies, 2524 participants; Analysis 1.3).

Subgroup analysis showed that only participants who received perampanel 12 mg/day were at increased risk of treatment withdrawal compared to placebo (RR 1.77, 95% CI 1.31 to 2.40; 3 studies, 869 participants). Participants receiving other doses of perampanel were no more prone to treatment withdrawal than those receiving placebo (2 mg/day: RR 1.41, 95% CI 0.81 to 2.45; 1 study, 365 participants; 4 mg/day: RR 0.82, 95% CI 0.54 to 1.25; 2 studies, 710 participants; 8 mg/day: RR 1.26, 95% CI 0.95 to 1.68; 4 studies, 1227 participants; Analysis 1.3).

Treatment withdrawal due to adverse effects

Participants who received perampanel were more likely to withdraw due to adverse effects compared to placebo (RR 2.36, 95% CI 1.59 to 3.51; 7 studies, 2524 participants; Analysis 1.4). Those who received the higher perampanel doses were more likely to withdraw because of adverse effects than participants who received placebo (8 mg/day: RR 2.24, 95% CI 1.39 to 3.61; 4 studies, 1227 participants; 12 mg/day: RR 4.19, 95% CI 2.52 to 6.96; 3 studies, 869 participants); those who received the lower perampanel doses were not (2 mg/day: RR 1.71, 95% CI 0.64 to 4.62; 1 study, 365 participants; 4 mg/day: RR 1.12, 95% CI 0.52 to 2.43; 2 studies, 710 participants; Analysis 1.4).

Adverse effects

All seven studies reported adverse effects, most of which were mild to moderate in severity. No participants experienced sudden unexpected death in epilepsy during treatment.

We selected the following common adverse effects, associated with taking antiepileptic drugs: dizziness, somnolence, fatigue, headache, and ataxia.

Proportion of participants who experienced at least one adverse effect

A slightly larger proportion of participants receiving perampanel experienced at least one adverse effect, compared to those receiving placebo (RR 1.17, 95% CI 1.10 to 1.24; 7 studies, 2524 participants; Analysis 1.5). Participants receiving the higher perampanel doses were more likely to report at least one adverse effect than those receiving placebo (8 mg/day: RR 1.18, 95% CI 1.10 to 1.26; 4 studies, 1227 participants; 12 mg/day: RR 1.23, 95% CI 1.15 to 1.31; 3 studies, 869 participants); those receiving the lower perampanel doses were not (2 mg/day: RR 1.13, 95% CI 0.95 to 1.35;

1 study, 365 participants; 4 mg/day: RR 1.10, 95% CI 0.99 to 1.23; 2 studies, 710 participants; Analysis 1.5).

Proportion of participants experiencing any common adverse effects

Compared to placebo, participants receiving perampanel were more likely to experience dizziness (RR 2.87, 99% CI 1.45 to 5.70; 7 studies, 2524 participants; Analysis 1.6), somnolence (RR 1.76, 99% CI 1.02 to 3.04; 7 studies, 2524 participants; Analysis 1.7), and ataxia (RR 14.32, 99% CI 1.09 to 188.31; 2 studies, 1096 participants; Analysis 1.9). However, this was not the case for fatigue (RR 1.67, 99% CI 0.98 to 2.85; 5 studies, 2136 participants; Analysis 1.8), or headache (RR 0.96, 99% CI 0.69 to 1.34; 7 studies, 2524 participants; Analysis 1.10).

Participants who received the higher doses perampanel were more likely to experience dizziness than those who received placebo (8 mg/day: RR 3.71, 99% CI 2.53 to 5.45; 4 studies, 1227 participants; 12 mg/day: RR 5.63, 99% CI 3.29 to 9.64; 3 studies, 869 participants; Analysis 1.6). Compared to placebo, participants who received perampanel 8 mg/day were more likely to experience somnolence (RR 1.83, 99% CI 1.03 to 3.27; 4 studies, 1227 participants; Analysis 1.7); and those receiving perampanel 12 mg/day were more likely to experience ataxia (RR 22.44, 99% CI 1.62 to 311.20; 2 studies, 612 participants; Analysis 1.9). Participants who received perampanel 2 mg/day and 4 mg/day did not experience more dizziness, somnolence, fatigue, ataxia, or headache than participants who received placebo.

DISCUSSION

Summary of main results

This systematic review investigated the short-term efficacy and tolerability of perampanel, when used as an add-on therapy for people with drug-resistant focal epilepsy. We included seven studies with 2524 participants. Four studies (1227 participants) assessed the effects of different doses of perampanel compared to placebo (French 2012 (study 304); French 2013 (study 305); Krauss 2012 (study 206); Nishida 2018).

Overall, participants who received perampanel were more likely to achieve a 50% or greater reduction in seizure frequency and seizure freedom compared to participants who received placebo. However, they were also more likely to withdraw from treatment. A larger proportion of participants who received perampanel 4 mg/day, 8 mg/day, or 12 mg/day achieved a 50% or greater reduction in seizure frequency compared to those who received placebo, and a much larger proportion achieved seizure freedom. The results for participants who received perampanel 2 mg/day versus those who received placebo were inconclusive for 50% reduction in seizure frequency, seizure freedom, and withdrawal from the study.

Participants who received perampanel were more likely to experience one or more adverse effects compared to participants who received placebo. The most commonly reported adverse effect was dizziness and most of the reported adverse effects were mild to moderate in severity. A larger proportion of participants who received perampanel 8 mg/day and 12 mg/day experienced one or more adverse effects than those who received perampanel 2 mg/day or 4 mg/day. Specifically, those who received perampanel 8 mg/day were more likely to experience dizziness and somnolence compared to placebo while those who received perampanel 12 mg/day were more likely to experience dizziness and ataxia. Participants who received perampanel 12 mg/day were more likely to withdraw from treatment (for any reason) compared to placebo. Comparative results for participants who received perampanel 2 mg/day or 4 mg/day versus those who received placebo were inconclusive for individual adverse effects and for withdrawal from treatment.

Our results found that perampanel, given in doses between 2 mg/day and 12 mg/day, should be well-tolerated when used as an add-on therapy; the effects appear to be dose-related. Doses of perampanel 4 mg/day or higher appear to have greater efficacy for participants with drug-resistant focal epilepsy compared to placebo. However, perampanel 12 mg/day might increase the rate of treatment withdrawal, and the likelihood of experiencing adverse effects compared to placebo. Therefore, care is required when achieving a balance between efficacy and tolerability.

Overall completeness and applicability of evidence

Although the primary results of this review found that perampanel was more likely to decrease seizure activity than placebo, it is difficult to ascertain the most efficacious dose to be used as an add-on therapy for people with drug-resistant focal epilepsy. This was mainly because there were a limited number of included studies, and limited data available for the different doses. As a result, the meta-analysis and subgroup analysis is most likely underpowered. Similarly, only two studies provided data for ataxia, therefore, the effect size estimated may not be accurate. Care is required when interpreting the true significance of these results.

Notably, all the included studies focused on investigating the short-term efficacy and tolerability of perampanel. The longer-term efficacy and tolerability still needs to be addressed. Additionally, the included studies only assessed add-on perampanel in people over the age of 12 years, therefore, these findings cannot be generalised to children younger than 12 years old.

Quality of the evidence

Summary of findings 1 shows the GRADE ratings for seven of the assessed outcomes: 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal due to any reason, treatment withdrawal due to adverse effects, the proportion of participants who experienced at least one adverse effect, proportion of participants who experienced ataxia, and proportion of participants who experienced dizziness.

We assessed all seven studies to be of good methodological quality, as a result of the low risk of bias detected within studies. Some studies did not describe methodological details; however, we were able to clarify these details via correspondence with the study authors and the study sponsor, Eisai Inc, who supplied the trial protocol for each of the included studies. We judged that the studies were largely free of bias, and we did not consider that it was necessary to downgrade the evidence for any of the outcomes for risk of bias.

We downgraded the evidence for three outcomes due to inconsistency. Despite there being no heterogeneity according to the I^2 statistic for treatment withdrawal due to any reason (I^2 = 0%), or treatment withdrawal due to adverse effects (I^2 = 4%), it was necessary to downgrade the certainty of evidence one level for these outcomes because the direction of effect varied greatly between studies. Specifically, some studies indicated a

negative effect for perampanel (increased treatment withdrawal with perampanel versus placebo), one study predicted a positive effect (decreased treatment withdrawal with perampanel versus placebo), whilst some predicted no effect (treatment withdrawal rate with perampanel roughly matched that observed with placebo). There was heterogeneity across the data for the outcome the proportion of participants who experienced dizziness ($P < 0.001$, $I^2 = 75$). Due to the degree of heterogeneity, we downgraded the certainty of evidence two levels for inconsistency.

For four outcomes, we downgraded the certainty of evidence for imprecision. We downgraded two outcomes (treatment withdrawal due to any reason and treatment withdrawal due to adverse effects) by one level because there were between 100 and 400 events for each of the outcomes. We downgraded the other two (seizure freedom and ataxia) by two levels because there were fewer than 100 events for each outcome. In both situations, the number of events did not satisfy the optimal information size.

Overall, we evaluated that two outcomes (50% or greater reduction in seizure frequency and proportion of participants who experienced at least one adverse effect) were supported by high-certainty evidence. For these outcomes, we are confident that the effect we estimated and reported is an accurate reflection of the true effect of perampanel. We assessed that five outcomes (seizure freedom, treatment withdrawal due to any reason, treatment withdrawal due to adverse effects, ataxia, and dizziness) were supported by low-certainty evidence. For these outcomes, we are uncertain whether the effect predicted is an accurate reflection of the true effect of perampanel.

Potential biases in the review process

Upon reflection, the review authors did not introduce any potential biases into the review process. The review authors had no conflict of interests in relation to the review.

Agreements and disagreements with other studies or reviews

The primary findings of our review are consistent with those from other systematic reviews and meta-analyses, mainly because the outcome measures and inclusion criteria were similar across the reviews (Hsu 2013; Khan 2013; Steinhoff 2013). A pooled dose–response analysis of data from three phase III studies and a subsequent open-label extension study found that increasing the dose of perampanel from 8 mg/day to 12 mg/day can further improve the reduction in seizure frequency (Kramer 2014). A separate pooled post-hoc analyses of data from three of the phase III studies of perampanel for people with drug-resistant epilepsy demonstrated that a larger proportion of participants who received perampanel 4 mg/day (28.5%), 8 mg/day (35.3%), or 12 mg/day (35.0%) achieved a 50% or greater reduction in seizure frequency, compared with only 19.3% of participants in the placebo group (Steinhoff 2013). This is consistent with our findings that there may be a dose-dependent responsiveness to perampanel for people with drug-resistant focal epilepsy.

Two reviews also reported that the rates of treatment withdrawal due to adverse effects were higher in the perampanel 8 mg/day and 12 mg/day groups than in the perampanel 2 mg/day and 4 mg/day groups (Hsu 2013; Steinhoff 2013). The authors concluded that, overall, perampanel was well-tolerated and that most adverse effects were mild to moderate in severity (Steinhoff 2013). The most common adverse effects were dizziness, somnolence, and headache (Steinhoff 2013).

The review findings suggest that although the efficacy of perampanel may be dose-dependent, tolerability must also be considered when increasing the dose. This again supports the findings of our review.

AUTHORS' CONCLUSIONS

Implications for practice

Our review found that perampanel is tolerable and is effective at reducing seizure frequency and may be effective at maintaining seizure freedom when used as an add-on therapy for people with drug-resistant focal epilepsy. However, perampanel may lead to a higher proportion of treatment withdrawals. The most efficacious doses appear to be 4 mg/day, 8 mg/day, and 12 mg/day; however, perampanel 12 mg/day may lead to more treatment withdrawals. Lower doses of perampanel (4 mg/day and 8 mg/day) may maintain its therapeutic effectiveness, whilst avoiding adverse effects more prevalent with higher doses.

Overall, the evidence suggests that perampanel is a well-tolerated drug, with the most prevalent adverse effects including dizziness and somnolence. Notably, most adverse effects were mild to moderate in severity.

Implications for research

Future research should focus on investigating the efficacy and tolerability of perampanel with a longer-term follow-up, and should more closely explore an optimal dose. It would also be useful if future research investigated the use of add-on perampanel in children below the age of 12 years, a population for which we identified minimal literature for the current review.

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- Sign-off Editor (final editorial decision): Tony Marson
- Managing Editor (provided editorial guidance to authors, edited the update, conducted editorial policy checks): Rachael Kelly
- Information Specialist (conducted electronic literature searches): Graham Chan
- Editorial Assistant (co-ordinated the peer review process): Ellen Dougan
- Copy Editor (copy editing and production): Anne Lawson

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

French 2012 (study 304)

Study characteristics	
Methods	**Study design:** randomised, multicentre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** 6 weeks **Titration period:** 6 weeks **Maintenance period:** 13 weeks
Participants	**Setting:** 68 centres across Argentina, Canada, Chile, Mexico, and the US **Randomised population:** 388 participants randomised (133 to perampanel 8 mg/day; 134 to perampanel 12 mg/day; 121 to placebo) **Perampanel 8 mg/day:** 65 males and 68 females (mean age: 35.8 (SD 14.2) years) **Perampanel 12 mg/day:** 69 males and 65 females (mean age: 36.7 (SD 14.6) years) **Placebo:** 54 males and 67 females (mean age: 35.6 (SD 14.7) years) **Inclusion criteria:** aged ≥ 12 years, diagnosed with focal-onset seizures, with or without secondary generalisation according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures, had failed ≥ 2 AEDs, and were taking stable doses of up to 3 approved AEDs. The baseline clinical characteristics were comparable amongst the 3 groups.
Interventions	**Group 1:** perampanel 8 mg/day **Group 2:** perampanel 12 mg/day **Group 3:** placebo
Outcomes	**Primary outcomes** • Change in seizure frequency per 28 days from baseline to double-blind phase • Responder rate (≥ 50% reduction in seizure frequency during the maintenance period relative to baseline) **Safety outcomes** • Adverse effects • Treatment withdrawals • Clinical laboratory parameters • Vital signs • ECGs • Physical and neurological examinations • Photosensitivity • Withdrawal questionnaires
Notes	1 participant randomised to the perampanel 12 mg/day group was treated for 1 day and did not complete a seizure frequency data record, and, therefore, was excluded from the ITT analysis for efficacy. Eisai Inc sponsored the study. Trial registry number: NCT00699972

French 2012 (study 304) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a computer-generated random allocation sequence."
Allocation concealment (selection bias)	Low risk	Quote: "allocation sequence approved and locked after review by an independent statistician. Kit numbers were generated for blinded study drug/kit dispensing."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "… phase III studies, 304 and 305, had identical methodology… Placebo patients were given matching placebo pills." Comment: quote above was obtained from French 2013 (study 305). French 2012 (study 304) utilised the same adequate blinding method as study 305.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Details will be specified in the statistical analysis plan (SAP), which will be finalized before database unblinding." Comment: although the outcome assessors were not blinded, we are satisfied that all necessary measures were taken to avoid detection bias. All data were entered and all statistical analyses preplanned, therefore, knowledge of treatment allocation during analyses would not have impacted outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. 1 randomised participant was excluded from ITT analysis; however, this was declared and justified.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol was provided; all prespecified outcomes were reported.
Other bias	Low risk	Comment: none detected.

French 2013 (study 305)

Study characteristics

Methods	**Study design:** randomised, multicentre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** 6 weeks **Titration period:** 6 weeks **Maintenance period:** 13 weeks
Participants	**Setting:** 78 centres in Australia, Austria, Belgium, Germany, Finland, France, the UK, Greece, India, Israel, Italy, the Netherlands, Russia, Sweden, the US, and South Africa **Randomised population:** 386 participants randomised (129 to perampanel 8 mg/day, 121 to perampanel 12 mg/day, 136 to placebo) **Perampanel 8 mg/day:** 65 males and 64 females (mean age: 36.7 (SD 14.4) years) **Perampanel 12 mg/day:** 50 males and 71 females (mean age: 35.5 (SD 14.1) years) **Placebo:** 71 males and 65 females (mean age: 34.4 (SD 13.6) years)

French 2013 (study 305) *(Continued)*

	Inclusion criteria: aged ≥ 12 years, diagnosed with simple or complex focal seizures, with or without secondary generalisation according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures, had failed ≥ 2 AEDs, and were taking stable doses of up to 3 approved AEDs.
Interventions	**Group 1:** perampanel 8 mg/day **Group 2:** perampanel 12 mg/day **Group 3:** placebo
Outcomes	**Primary outcomes** • Responder rate (≥ 50% reduction in seizure frequency during the maintenance period relative to baseline) • Percent change in seizure frequency per 28 days from baseline to double-blind phase **Secondary outcome** • Percent change in complex focal plus secondarily generalised seizure frequency from baseline to double-blind phase **Safety outcomes** • Adverse effects • Treatment withdrawals • Clinical laboratory parameters • Vital signs • ECG studies • Physical and neurological examinations • Photosensitivity • Withdrawal questionnaires
Notes	Eisai Inc sponsored the study (replicated study design of French 2012 (study 304)). Trial registry number: NCT00699582

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a computer-generated random allocation sequence."
Allocation concealment (selection bias)	Low risk	Comment: allocation sequence was approved and locked after review by an independent statistician. Quote: "Kit numbers were generated for blinded study drug/kit dispensing by the investigator."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo patients were given matching placebo pills."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Details will be specified in the statistical analysis plan (SAP), which will be finalized before database unblinding." Comment: although the outcome assessors themselves were not blinded, we are satisfied that all necessary measures were taken to avoid detection bias. All data were entered, and all statistical analyses preplanned, therefore,

French 2013 (study 305) *(Continued)*

		knowledge of treatment allocation during analyses would not have impacted outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. ITT analysis was conducted. 3 randomised participants were excluded from the ITT population; however, this was declared and justified.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol was provided; all prespecified outcomes were reported.
Other bias	Low risk	Comment: none detected.

Krauss 2012

Study characteristics	
Methods	**Study design:** randomised, multicentre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** 6 weeks **Titration period:** 6 weeks **Maintenance period:** 13 weeks
Participants	**Setting:** 116 centres in 24 countries from Europe, Asia, and Australia **Randomised population:** 706 participants randomised (180 to perampanel 2 mg/day, 172 to perampanel 4 mg/day, 169 to perampanel 8 mg/day, and 185 to placebo **Perampanel 2 mg/day:** 85 males and 95 females (mean age: 33.8 (SD 13.6) years) **Perampanel 4 mg/day:** 88 males and 84 females (mean age: 33.6 (SD 12.2) years) **Perampanel 8 mg/day:** 77 males and 92 females (mean age: 34.6 (SD 12.8) years) **Placebo:** 95 males and 90 females (mean age: 33.4 (SD 12.6) years) **Inclusion criteria:** aged ≥ 12 years, diagnosed with simple or complex focal seizures, with or without secondary generalisation according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures, had failed ≥ 2 AEDs, and were taking stable type and dose of 1–3 AEDs
Interventions	**Group 1:** perampanel 2 mg/day **Group 2:** perampanel 4 mg/day **Group 3:** perampanel 8 mg/day **Group 4:** placebo
Outcomes	**Primary outcomes** • Percent change in seizure frequency per 28 days • Responder rate (50% or greater reduction in seizure frequency) **Secondary outcome** • Percent change in the frequency of complex focal seizures plus secondary generalised seizures • Dose–response analysis of the percent change in seizure frequency **Safety outcomes**

Krauss 2012 *(Continued)*

- Adverse effects
- Treatment withdrawals due to adverse effects
- Clinical laboratory parameters
- Vital signs
- ECGs
- Physical and neurological examinations
- Photosensitivity
- Withdrawal questionnaires

Notes	1 participant randomised to the placebo group was treated for 1 day and did not complete a seizure frequency data record, and, therefore, was excluded from the ITT analysis for efficacy. Eisai Inc sponsored the study. Trial registry number: NCT00700310

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random allocation sequence."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation sequence approved and locked after review by an independent statistician. Kit numbers were generated for blinded study drug/kit dispensing by the investigator."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from trial protocol): "The double-blind design of this study will be maintained through the use of matching placebo, and all study drugs will be replaced and labelled so as to be indistinguishable between treatment groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Details will be specified in the statistical analysis plan (SAP), which will be finalized before database unblinding." Comment: although the outcome assessors themselves were not blinded, we are satisfied that all necessary measures were taken to avoid detection bias. All data were entered, and all statistical analyses preplanned, therefore, knowledge of treatment allocation during analyses would not have impacted outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. 1 randomised participant was excluded from ITT analysis; however, this was declared and justified.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol was provided. Results of Quality of Life in Epilepsy questionnaire and photosensitivity questionnaire were not reported. All outcomes relating to seizure frequency and type prespecified were reported. As these were the measures that we used in the meta-analysis, we continued to award a low risk of bias.
Other bias	Low risk	Comment: none detected.

Krauss 2012 (study 206)

Study characteristics

Krauss 2012 (study 206) *(Continued)*

Methods	**Study design:** randomised, double-blind, placebo-controlled, dose-escalation, parallel-group phase II study **Baseline period:** 4 weeks **Titration period:** 8 weeks **Maintenance period:** 4 weeks **Transition period:** 2 weeks
Participants	**Setting:** 43 centres in Australia, Europe, and the US **Randomised population:** 153 participants randomised (51 to perampanel twice daily, 51 to perampanel once daily, 51 to placebo) **Perampanel twice daily:** 22 males and 29 females (mean age: 40.0 (SD 11.4) years) **Perampanel once daily:** 22 males and 29 females (mean age: 42.5 (SD 12.1) years) **Placebo:** 23 males and 28 females (mean age: 38.1 (SD 11.6) years) The baseline clinical characteristics were comparable amongst the 3 groups. **Inclusion criteria:** aged 18–70 years, diagnosed with focal seizures, with or without secondary generalisation, had failed ≥ 3 AEDs, and were taking stable type and dose of 1 or 2 AEDs.
Interventions	**Group 1:** perampanel 0.5–2.0 mg twice-daily **Group 2:** perampanel 1–4 mg perampanel once daily **Group 3:** placebo (Both groups 1 and 2 received 1–4 mg/day perampanel via separate dosing regimens)
Outcomes	**Primary outcomes** • Responder rate (≥ 50% reduction in seizure frequency during the maintenance period relative to baseline) • Percent change in seizure frequency per 28 days from baseline to maintenance phase **Safety outcomes** • Adverse effects (frequency and severity) and serious adverse effects • Physical and neurological examinations • ECGs • Clinical laboratory evaluations
Notes	1 participant from perampanel twice daily group was excluded from ITT analysis for efficacy, because there were no postbaseline seizure frequency data. Eisai Inc sponsored the study. Trial registry number: NCT00144690

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: authors clarified that they used a computer-generated central randomisation.

Krauss 2012 (study 206) *(Continued)*

Allocation concealment (selection bias)	Low risk	Comment: upon our request, authors clarified that they adopted an interactive voice response system to dispense the drugs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from trial protocol): "matching placebo tablet."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no details were provided regarding the blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. 1 randomised participant was excluded from ITT analysis; however, this was declared and justified.
Selective reporting (reporting bias)	Unclear risk	Comment: trial protocol was provided. Several secondary efficacy outcomes specified in the protocol were not reported, e.g. proportion of participants experiencing 25% to 50%, 50% to 75%, or > 75% reduction in seizure frequency from baseline to treatment period, proportion of seizure-free days during treatment period, Clinical Global Impression of Change, Patient's Global Impression of Change, and Seizure Severity questionnaire results.
Other bias	Low risk	Comment: none detected.

Krauss 2012 (study 208)

Study characteristics	
Methods	**Study design:** randomised, double-blind, placebo-controlled, dose-escalation, parallel-group phase II study **Baseline period:** 4 weeks **Titration period:** 12 weeks **Maintenance period:** 4 weeks
Participants	**Setting:** 17 centres in Australia and Europe **Randomised population:** 48 participants randomised (38 to perampanel 2–12 mg/day; 10 to placebo) **Perampanel 2–12 mg/day:** 18 males and 20 females (mean age: 40.7 (SD 12.0) years) **Placebo:** 5 males and 5 females (mean age: 45.5 (SD 12.1) years) **Inclusion criteria:** aged 18–70 years, diagnosed with focal seizures, with or without secondary generalisation, had failed ≥ 3 AEDs, and were taking stable type and dose of 1–3 AEDs. The baseline clinical characteristics were comparable between groups.
Interventions	**Group 1:** perampanel 2–12 mg/day **Group 2:** placebo
Outcomes	**Primary outcomes** • Responder rate (≥ 50% reduction in seizure frequency during the treatment period, relative to baseline),

Krauss 2012 (study 208) *(Continued)*

- Percent change in seizure frequency per 28 days from baseline to treatment phase

Safety outcomes

- Adverse effects (frequency and severity) and serious adverse effects
- Physical and neurological examinations
- ECGs
- Clinical laboratory evaluations

Notes	1 participant from placebo group was excluded from ITT analysis for efficacy due to invalid baseline seizure frequency data. Eisai Inc sponsored the study. Trial registry number: NCT00416195

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: the authors clarified that they used a computer-generated central randomisation.
Allocation concealment (selection bias)	Low risk	Comment: upon our request, the authors clarified that they adopted an interactive voice response system to dispense the drugs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from trial protocol): "matching placebo tablet."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no details were provided regarding the blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. 1 randomised participant was excluded from ITT analysis; however, this was declared and justified.
Selective reporting (reporting bias)	Unclear risk	Comment: trial protocol was provided. Several secondary efficacy outcomes specified in the protocol were not reported, e.g. proportion of participants experiencing 25–50%, 50–75%, or > 75% reduction in seizure frequency from baseline to treatment period, proportion of seizure-free days during treatment period, Clinical Global Impression of Change, Patient's Global Impression of Change, and Seizure Severity questionnaire results.
Other bias	Low risk	Comment: none detected.

Lagae 2016

Study characteristics

Methods	**Study design:** randomised, multicentre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** 1 week **Titration period:** 6 weeks

Lagae 2016 *(Continued)*

	Maintenance period: 13 weeks
Participants	**Setting:** 11 countries from North America, Europe, Asia, and Australia **Randomised population:** 133 participants randomised (85 to perampanel 8–12 mg/day; 48 to placebo) **Perampanel 8–12 mg/day:** 52 males and 33 females (mean age: 14.3 (SD 1.7) years) **Placebo:** 28 males and 20 females (mean age: 14.3 (SD 1.9) years) **Inclusion criteria:** aged 12–18 years, with an intelligence quotient ≥ 70, and a diagnosis of focal-onset seizures according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures, had ≥ 1 focal-onset seizure during the previous 4 weeks, despite a stable regimen of 1–3 AEDs
Interventions	**Group 1:** perampanel 8–12 mg/day **Group 2:** placebo
Outcomes	**Primary outcomes** • Percent change in seizure frequency per 28 days during treatment phase, relative to baseline • Responder rate (≥ 50% reduction in seizure frequency during the maintenance phase, relative to baseline) • Seizure freedom **Secondary outcome** • Percent change in complex focal, plus secondary generalised seizure frequency from baseline to double-blind phase **Safety outcomes** • Child Behaviour Checklist • Adverse effects
Notes	2 participants from the perampanel 8–12 mg/day group and 2 participants from the placebo group were excluded from ITT analysis for efficacy, because they did not receive ≥ 1 dose of perampanel, or they did not provide ≥ 1 postbaseline seizure frequency data report. Eisai Inc sponsored the study. Trial registry number: NCT01161524

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from protocol): "Randomization will be performed centrally by an Interactive Voice-Response System (IVRS) vendor that will generate a randomization list with a pseudorandom number generator."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "… patients received perampanel 2 mg/day or matching placebo."

Lagae 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The statistical analyses described in this section will be performed for the Core Study as further outlined in the SAP (statistical analysis plan), which will be finalized prior to the unblinding of the database." Comment: although the outcome assessors themselves were not blinded, we are satisfied that all necessary measures were taken to avoid detection bias. All data were entered, and all statistical analyses preplanned, therefore, knowledge of treatment allocation during analyses would not have impacted outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. 4 randomised participants were excluded from ITT analysis; however, this was declared and justified.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol was provided; all prespecified outcomes were reported.
Other bias	Unclear risk	Quote: "randomization … in a 2:1 ratio." Comment: unequal allocation leads to reduced statistical power and can augment the placebo effect (Hey 2014).

Nishida 2018

Study characteristics	
Methods	**Study design:** randomised, multicentre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** 6 weeks **Titration period:** 6 weeks **Maintenance period:** 13 weeks
Participants	**Setting:** 119 centres across Australia, China, Japan, Malaysia, Republic of Korea, Taiwan, and Thailand **Randomised population:** 710 participants randomised (176 to perampanel 4 mg/day, 177 to perampanel 8 mg/day, 180 to perampanel 12 mg/day, 177 to placebo) **Perampanel 4 mg/day:** 80 males and 94 females (mean age: 33.1 (SD 13.2) years) **Perampanel 8 mg/day:** 91 males and 84 females (mean age: 33.6 (SD 14.1) years) **Perampanel 12 mg/day:** 87 males and 93 females (mean age: 32.3 (SD 12.3) years) **Placebo:** 86 males and 89 females (mean age: 34.5 (SD 13.2) years) **Inclusion criteria:** aged ≥ 12 years, with a diagnosis of focal-onset seizures according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures, had ≥ 5 focal-onset seizures during baseline, despite a stable regimen of 1–3 AEDs
Interventions	**Group 1:** perampanel 4 mg/day **Group 2:** perampanel 8 mg/day **Group 3:** perampanel 12 mg/day **Group 4:** placebo
Outcomes	**Primary outcomes**

Nishida 2018 *(Continued)*

- Percent change in focal-onset seizure frequency per 28 days (double-blind phase vs baseline)

Secondary outcome

- 50% responder rate (≥ 50% reduction in seizure frequency during the maintenance phase relative to baseline)
- Percent change in complex focal and secondary generalised seizure frequency
- Clinical Global Impression of Change

Safety outcomes

- Treatment-emergent adverse effects
- Clinical laboratory tests (biochemistry, haematology, and urinalysis)
- Vital signs
- Weight monitoring
- 12-lead ECG

Notes	6 participants were excluded from ITT analysis for efficacy, because they did not receive ≥ 1 dose of perampanel, or they did not provide any seizure frequency data during the double-blind phase. Eisai Inc sponsored the study. Trial registry number: NCT01618695

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were prestratified based on country and concomitant AEDs … and randomised (1:1:1:1) using an IVRS (interactive voice response system)." Comment: although exact details were not provided, it is very likely that the method of randomisation was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Use of an interactive voice response system facilitates allocation concealment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study drugs were packaged and labelled so as to be indistinguishable."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "SAP (statistical analysis plan) for the Core Study will be finalized before treatment unblinding." Comment: although the outcome assessors themselves were not blinded, we are satisfied that all necessary measures were taken to avoid detection bias. All data were entered, and all statistical analyses preplanned, therefore, knowledge of treatment allocation during analyses would not have impacted outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of, and the reasons for, withdrawals were carefully reported. The distribution of 3/6 participants excluded from the ITT population between the treatment groups was not disclosed in the publication, but was confirmed by author correspondence.
Selective reporting (reporting bias)	Low risk	Comment: trial protocol was provided; all prespecified outcomes were reported.

Nishida 2018 *(Continued)*

Other bias	Low risk	Comment: none detected.

AED: antiepileptic drug; ECG: electrocardiogram; ITT: intention-to-treat; SD: standard deviation.

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

Study	Reason for exclusion
French 2015	Participants enrolled had idiopathic generalised epilepsy
Montouris 2015	Open-label extension study
Toledo 2016	Open-label study

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

NCT03780907

Methods	**Study design:** randomised, single-centre, double-blind, placebo-controlled, parallel-group trial **Baseline period:** unknown **Titration period:** unknown **Maintenance period:** unknown
Participants	**Setting:** 1 centre in Germany **Randomised population:** 18 participants **Inclusion criteria:** aged 18–65 years, diagnosed with simple or complex partial seizures, with or without secondary generalisation, or primary generalised tonic-clonic seizures according to the International League against Epilepsy, and were taking a stable dose of 1 or 2 AEDs
Interventions	**Group 1:** perampanel 1 mg/day **Group 2:** perampanel 2 mg/day **Group 3:** placebo
Outcomes	**Primary outcomes** • Treatment emergent adverse effects • Clinical Global Impression of Tolerability • Area under the curve (0–24 hours) of perampanel • Maximum observed plasma concentration of perampanel • Time to maximum concentration of perampanel • Minimum steady-state plasma concentration of perampanel • Mean plasma concentration of perampanel • Peak-to-trough fluctuation of perampanel • Observed accumulation ratio of perampanel **Secondary outcomes** • Change from baseline of Bond and Lader Scale • Change from baseline of peak saccadic velocity

NCT03780907 *(Continued)*	• Number of participants receiving other antiepileptic agents during treatment • Percent change from baseline of failed saccades • Mean trough concentrations of perampanel • Number of seizures • Clinical Global Impression of Change
Notes	Eisai Inc sponsored the study.

DATA AND ANALYSES

Comparison 1. Perampanel versus placebo

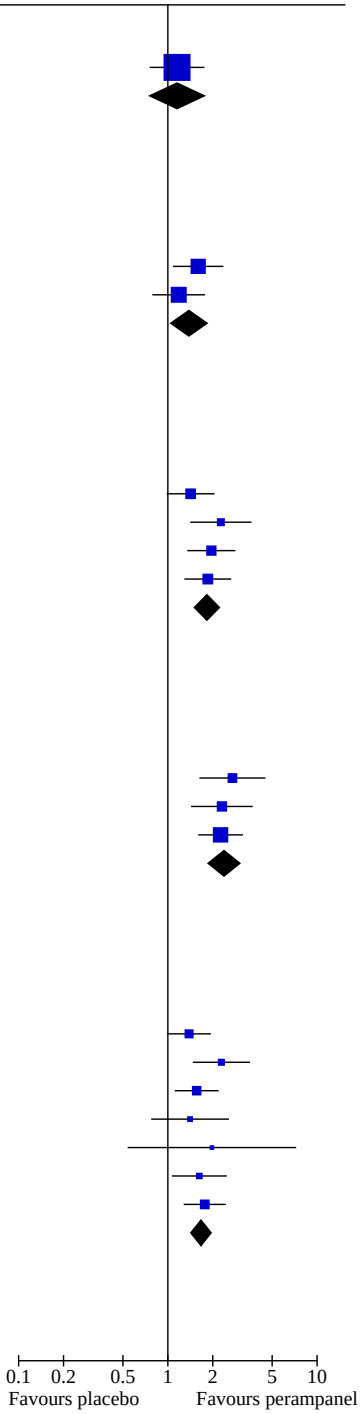
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 50% or greater reduction in seizure frequency	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.76, 1.76]
1.1.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.05, 1.83]
1.1.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.51, 2.22]
1.1.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.86, 3.04]
1.1.5 All doses	7	2524	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.43, 1.95]
1.2 Seizure freedom	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.12]
1.2.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 95% CI)	4.20 [1.19, 14.76]
1.2.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [1.51, 9.86]
1.2.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 95% CI)	4.87 [1.54, 15.43]
1.2.5 All doses	5	2323	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.38, 4.54]
1.3 Treatment withdrawal due to any reason	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.81, 2.45]
1.3.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.25]
1.3.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.95, 1.68]
1.3.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.5 All doses	7	2524	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.03, 1.63]
1.4 Treatment withdrawal due to adverse effects	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.64, 4.62]
1.4.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.52, 2.43]
1.4.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.39, 3.61]
1.4.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [2.52, 6.96]
1.4.5 All doses	7	2524	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.59, 3.51]
1.5 At least one adverse effect	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.95, 1.35]
1.5.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.23]
1.5.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.10, 1.26]
1.5.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.15, 1.31]
1.5.5 All doses	7	2524	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.10, 1.24]
1.6 Dizziness	7		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
1.6.1 2 mg/day	1	365	Risk Ratio (M-H, Random, 99% CI)	1.03 [0.45, 2.32]
1.6.2 4 mg/day	2	710	Risk Ratio (M-H, Random, 99% CI)	2.55 [0.82, 7.93]
1.6.3 8 mg/day	4	1227	Risk Ratio (M-H, Random, 99% CI)	3.71 [2.53, 5.45]
1.6.4 12 mg/day	3	869	Risk Ratio (M-H, Random, 99% CI)	5.63 [3.29, 9.64]
1.6.5 All doses	7	2524	Risk Ratio (M-H, Random, 99% CI)	2.87 [1.45, 5.70]
1.7 Somnolence	7		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
1.7.1 2 mg/day	1	365	Risk Ratio (M-H, Random, 99% CI)	1.88 [0.78, 4.56]
1.7.2 4 mg/day	2	710	Risk Ratio (M-H, Random, 99% CI)	1.29 [0.75, 2.23]
1.7.3 8 mg/day	4	1227	Risk Ratio (M-H, Random, 99% CI)	1.83 [1.03, 3.27]
1.7.4 12 mg/day	3	869	Risk Ratio (M-H, Random, 99% CI)	1.95 [0.72, 5.26]
1.7.5 All doses	7	2524	Risk Ratio (M-H, Random, 99% CI)	1.76 [1.02, 3.04]
1.8 Fatigue	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.8.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 99% CI)	1.64 [0.39, 6.96]
1.8.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 99% CI)	1.78 [0.65, 4.87]
1.8.3 8 mg/day	3	973	Risk Ratio (M-H, Fixed, 99% CI)	1.60 [0.80, 3.22]
1.8.4 12 mg/day	2	614	Risk Ratio (M-H, Fixed, 99% CI)	1.95 [0.91, 4.20]
1.8.5 All doses	6	2136	Risk Ratio (M-H, Fixed, 99% CI)	1.67 [0.98, 2.85]
1.9 Ataxia	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.9.1 4 mg/day	1	353	Risk Ratio (M-H, Fixed, 99% CI)	5.03 [0.09, 269.39]
1.9.2 8 mg/day	2	608	Risk Ratio (M-H, Fixed, 99% CI)	9.38 [0.62, 141.50]
1.9.3 12 mg/day	2	612	Risk Ratio (M-H, Fixed, 99% CI)	22.44 [1.62, 311.20]
1.9.4 All doses	2	1098	Risk Ratio (M-H, Fixed, 99% CI)	14.32 [1.09, 188.31]
1.10 Headache	7		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.10.1 2 mg/day	1	365	Risk Ratio (M-H, Fixed, 99% CI)	1.03 [0.43, 2.45]
1.10.2 4 mg/day	2	710	Risk Ratio (M-H, Fixed, 99% CI)	1.12 [0.59, 2.11]
1.10.3 8 mg/day	4	1227	Risk Ratio (M-H, Fixed, 99% CI)	0.99 [0.64, 1.54]
1.10.4 12 mg/day	3	869	Risk Ratio (M-H, Fixed, 99% CI)	0.94 [0.56, 1.56]
1.10.5 All doses	7	2524	Risk Ratio (M-H, Fixed, 99% CI)	0.96 [0.69, 1.34]

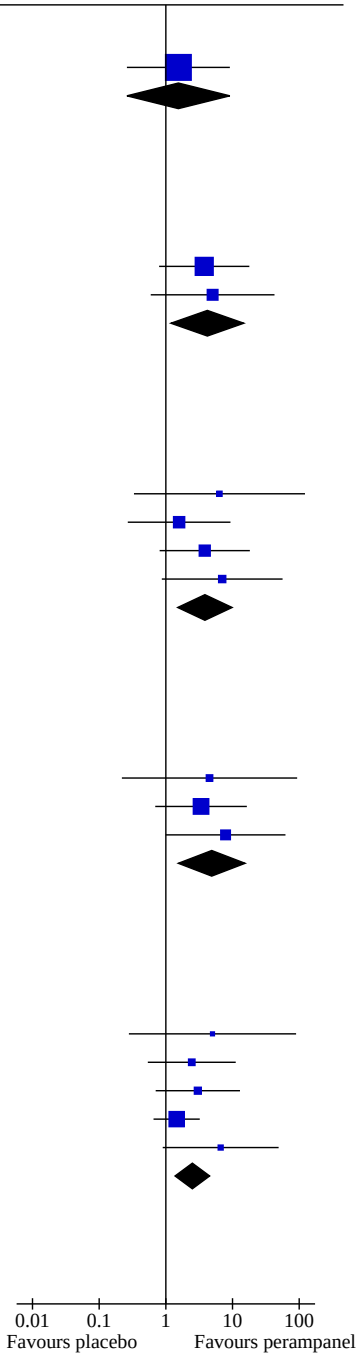
Analysis 1.1. Comparison 1: Perampanel versus placebo, Outcome 1: 50% or greater reduction in seizure frequency

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 2 mg/day						
Krauss 2012	37	180	33	185	100.0%	1.15 [0.76 , 1.76]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**1.15 [0.76 , 1.76]**
Total events:	37		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.1.2 4 mg/day						
Krauss 2012	49	172	33	185	48.4%	1.60 [1.08 , 2.36]
Nishida 2018	40	176	34	177	51.6%	1.18 [0.79 , 1.78]
Subtotal (95% CI)		**348**		**362**	**100.0%**	**1.38 [1.05 , 1.83]**
Total events:	89		67			
Heterogeneity: Chi^2 = 1.09, df = 1 (P = 0.30); I^2 = 8%						
Test for overall effect: Z = 2.27 (P = 0.02)						
1.1.3 8 mg/day						
French 2012 (study 304)	50	133	32	121	28.3%	1.42 [0.98 , 2.06]
French 2013 (study 305)	43	129	20	136	16.4%	2.27 [1.41 , 3.64]
Krauss 2012	59	169	33	185	26.6%	1.96 [1.35 , 2.84]
Nishida 2018	63	177	34	177	28.7%	1.85 [1.29 , 2.66]
Subtotal (95% CI)		**608**		**619**	**100.0%**	**1.83 [1.51 , 2.22]**
Total events:	215		119			
Heterogeneity: Chi^2 = 2.71, df = 3 (P = 0.44); I^2 = 0%						
Test for overall effect: Z = 6.11 (P < 0.00001)						
1.1.4 12 mg/day						
French 2012 (study 304)	48	134	16	121	24.0%	2.71 [1.63 , 4.51]
French 2013 (study 305)	41	121	20	136	26.9%	2.30 [1.43 , 3.71]
Nishida 2018	78	180	34	177	49.0%	2.26 [1.60 , 3.19]
Subtotal (95% CI)		**435**		**434**	**100.0%**	**2.38 [1.86 , 3.04]**
Total events:	167		70			
Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.84); I^2 = 0%						
Test for overall effect: Z = 6.92 (P < 0.00001)						
1.1.5 All doses						
French 2012 (study 304)	98	267	32	121	21.0%	1.39 [0.99 , 1.94]
French 2013 (study 305)	84	250	20	136	12.4%	2.28 [1.47 , 3.55]
Krauss 2012	145	521	33	185	23.3%	1.56 [1.11 , 2.19]
Krauss 2012 (study 206)	31	102	11	51	7.0%	1.41 [0.77 , 2.57]
Krauss 2012 (study 208)	15	38	2	10	1.5%	1.97 [0.54 , 7.25]
Lagae 2016	49	85	17	48	10.4%	1.63 [1.07 , 2.49]
Nishida 2018	181	533	34	177	24.4%	1.77 [1.28 , 2.45]
Subtotal (95% CI)		**1796**		**728**	**100.0%**	**1.67 [1.43 , 1.95]**
Total events:	603		149			
Heterogeneity: Chi^2 = 3.76, df = 6 (P = 0.71); I^2 = 0%						
Test for overall effect: Z = 6.39 (P < 0.00001)						



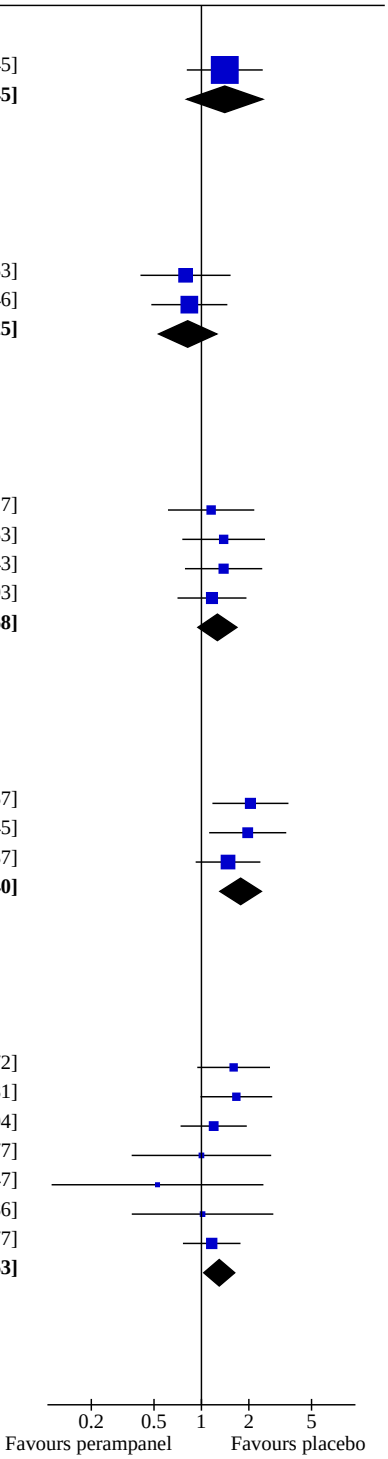
Analysis 1.2. Comparison 1: Perampanel versus placebo, Outcome 2: Seizure freedom

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 2 mg/day						
Krauss 2012	3	180	2	185	100.0%	1.54 [0.26 , 9.12]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**1.54 [0.26 , 9.12]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.2.2 4 mg/day						
Krauss 2012	7	172	2	185	65.9%	3.76 [0.79 , 17.87]
Nishida 2018	5	176	1	177	34.1%	5.03 [0.59 , 42.61]
Subtotal (95% CI)		**348**		**362**	**100.0%**	**4.20 [1.19 , 14.76]**
Total events:	12		3			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
1.2.3 8 mg/day						
French 2012 (study 304)	3	133	0	121	9.7%	6.37 [0.33 , 122.13]
French 2013 (study 305)	3	129	2	136	36.2%	1.58 [0.27 , 9.31]
Krauss 2012	7	169	2	185	35.5%	3.83 [0.81 , 18.19]
Nishida 2018	7	177	1	177	18.6%	7.00 [0.87 , 56.31]
Subtotal (95% CI)		**608**		**619**	**100.0%**	**3.85 [1.51 , 9.86]**
Total events:	20		5			
Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.2.4 12 mg/day						
French 2012 (study 304)	2	134	0	121	15.4%	4.52 [0.22 , 93.19]
French 2013 (study 305)	6	121	2	136	55.1%	3.37 [0.69 , 16.39]
Nishida 2018	8	180	1	177	29.5%	7.87 [0.99 , 62.25]
Subtotal (95% CI)		**435**		**434**	**100.0%**	**4.87 [1.54 , 15.43]**
Total events:	16		3			
Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
1.2.5 All doses						
French 2012 (study 304)	5	267	0	121	4.1%	5.01 [0.28 , 89.84]
French 2013 (study 305)	9	250	2	136	15.5%	2.45 [0.54 , 11.17]
Krauss 2012	17	521	2	185	17.7%	3.02 [0.70 , 12.94]
Lagae 2016	18	85	7	48	53.6%	1.45 [0.65 , 3.23]
Nishida 2018	20	533	1	177	9.0%	6.64 [0.90 , 49.13]
Subtotal (95% CI)		**1656**		**667**	**100.0%**	**2.50 [1.38 , 4.54]**
Total events:	69		12			
Heterogeneity: Chi² = 2.98, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						



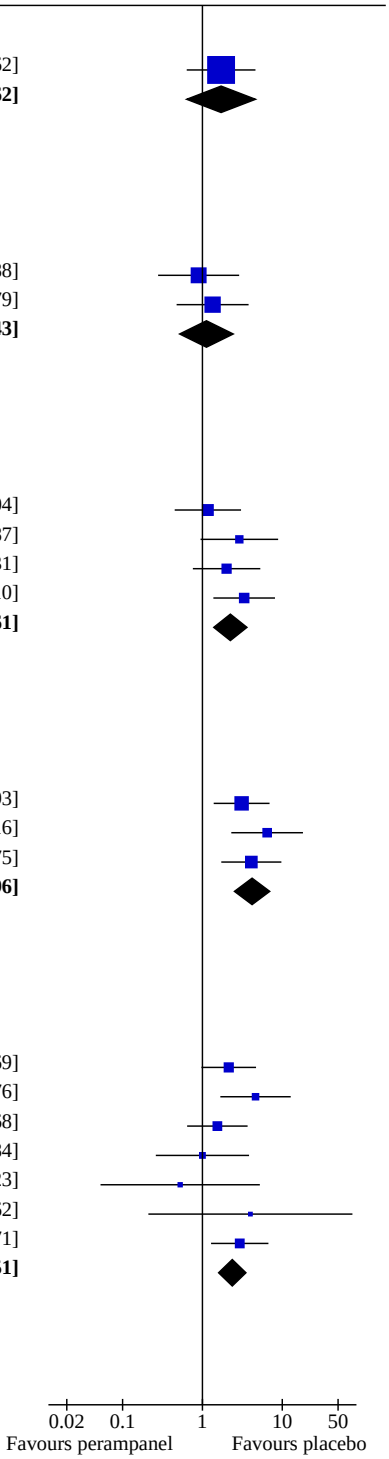
Analysis 1.3. Comparison 1: Perampanel versus placebo, Outcome 3: Treatment withdrawal due to any reason

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 2 mg/day						
Krauss 2012	26	180	19	185	100.0%	1.41 [0.81 , 2.45]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**1.41 [0.81 , 2.45]**
Total events:	26		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.3.2 4 mg/day						
Krauss 2012	14	172	19	185	43.3%	0.79 [0.41 , 1.53]
Nishida 2018	20	176	24	177	56.7%	0.84 [0.48 , 1.46]
Subtotal (95% CI)		**348**		**362**	**100.0%**	**0.82 [0.54 , 1.25]**
Total events:	34		43			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.3.3 8 mg/day						
French 2012 (study 304)	19	133	15	121	21.4%	1.15 [0.61 , 2.17]
French 2013 (study 305)	21	129	16	136	21.2%	1.38 [0.76 , 2.53]
Krauss 2012	24	169	19	185	24.7%	1.38 [0.79 , 2.43]
Nishida 2018	28	177	24	177	32.7%	1.17 [0.70 , 1.93]
Subtotal (95% CI)		**608**		**619**	**100.0%**	**1.26 [0.95 , 1.68]**
Total events:	92		74			
Heterogeneity: Chi² = 0.36, df = 3 (P = 0.95); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.3.4 12 mg/day						
French 2012 (study 304)	34	134	15	121	28.6%	2.05 [1.17 , 3.57]
French 2013 (study 305)	28	121	16	136	27.4%	1.97 [1.12 , 3.45]
Nishida 2018	36	180	24	177	44.0%	1.48 [0.92 , 2.37]
Subtotal (95% CI)		**435**		**434**	**100.0%**	**1.77 [1.31 , 2.40]**
Total events:	98		55			
Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 3.71 (P = 0.0002)						
1.3.5 All doses						
French 2012 (study 304)	53	267	15	121	17.0%	1.60 [0.94 , 2.72]
French 2013 (study 305)	49	250	16	136	17.0%	1.67 [0.99 , 2.81]
Krauss 2012	64	521	19	185	23.0%	1.20 [0.74 , 1.94]
Krauss 2012 (study 206)	10	102	5	51	5.5%	1.00 [0.36 , 2.77]
Krauss 2012 (study 208)	4	38	2	10	2.6%	0.53 [0.11 , 2.47]
Lagae 2016	9	85	5	48	5.3%	1.02 [0.36 , 2.86]
Nishida 2018	84	533	24	177	29.6%	1.16 [0.76 , 1.77]
Subtotal (95% CI)		**1796**		**728**	**100.0%**	**1.30 [1.03 , 1.63]**
Total events:	273		86			
Heterogeneity: Chi² = 3.62, df = 6 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						



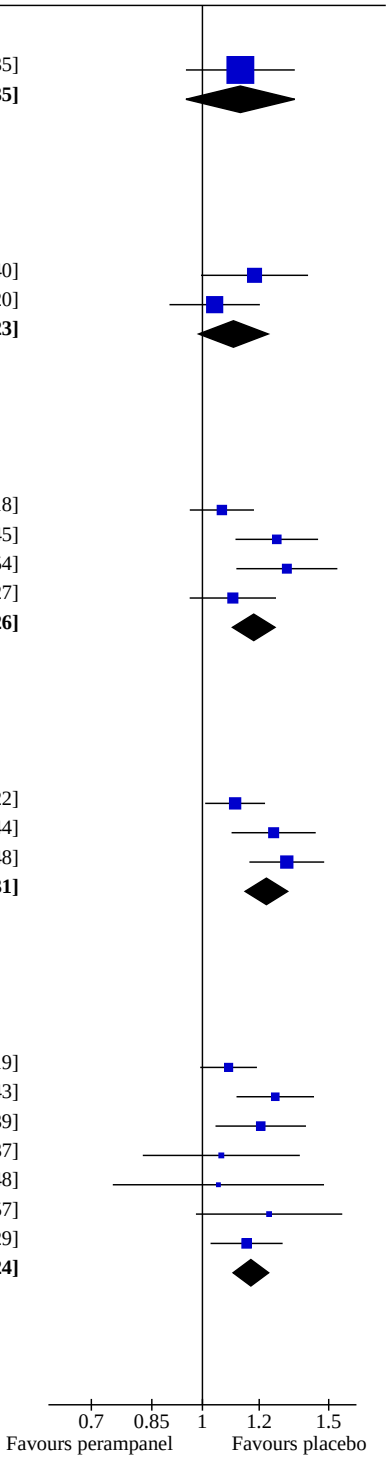
Analysis 1.4. Comparison 1: Perampanel versus placebo, Outcome 4: Treatment withdrawal due to adverse effects

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 2 mg/day						
Krauss 2012	10	180	6	185	100.0%	1.71 [0.64 , 4.62]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**1.71 [0.64 , 4.62]**
Total events:	10		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.4.2 4 mg/day						
Krauss 2012	5	172	6	185	49.1%	0.90 [0.28 , 2.88]
Nishida 2018	8	176	6	177	50.9%	1.34 [0.48 , 3.79]
Subtotal (95% CI)		**348**		**362**	**100.0%**	**1.12 [0.52 , 2.43]**
Total events:	13		12			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.4.3 8 mg/day						
French 2012 (study 304)	9	133	7	121	31.9%	1.17 [0.45 , 3.04]
French 2013 (study 305)	11	129	4	136	17.0%	2.90 [0.95 , 8.87]
Krauss 2012	11	169	6	185	25.0%	2.01 [0.76 , 5.31]
Nishida 2018	20	177	6	177	26.1%	3.33 [1.37 , 8.10]
Subtotal (95% CI)		**608**		**619**	**100.0%**	**2.24 [1.39 , 3.61]**
Total events:	51		23			
Heterogeneity: Chi² = 2.79, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.4.4 12 mg/day						
French 2012 (study 304)	24	134	7	121	42.8%	3.10 [1.38 , 6.93]
French 2013 (study 305)	23	121	4	136	21.9%	6.46 [2.30 , 18.16]
Nishida 2018	25	180	6	177	35.2%	4.10 [1.72 , 9.75]
Subtotal (95% CI)		**435**		**434**	**100.0%**	**4.19 [2.52 , 6.96]**
Total events:	72		17			
Heterogeneity: Chi² = 1.22, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 5.52 (P < 0.00001)						
1.4.5 All doses						
French 2012 (study 304)	33	267	7	121	24.8%	2.14 [0.97 , 4.69]
French 2013 (study 305)	34	250	4	136	13.3%	4.62 [1.68 , 12.76]
Krauss 2012	26	521	6	185	22.8%	1.54 [0.64 , 3.68]
Krauss 2012 (study 206)	6	102	3	51	10.3%	1.00 [0.26 , 3.84]
Krauss 2012 (study 208)	2	38	1	10	4.1%	0.53 [0.05 , 5.23]
Lagae 2016	3	85	0	48	1.6%	3.99 [0.21 , 75.62]
Nishida 2018	53	533	6	177	23.2%	2.93 [1.28 , 6.71]
Subtotal (95% CI)		**1796**		**728**	**100.0%**	**2.36 [1.59 , 3.51]**
Total events:	157		27			
Heterogeneity: Chi² = 6.27, df = 6 (P = 0.39); I² = 4%						
Test for overall effect: Z = 4.28 (P < 0.0001)						



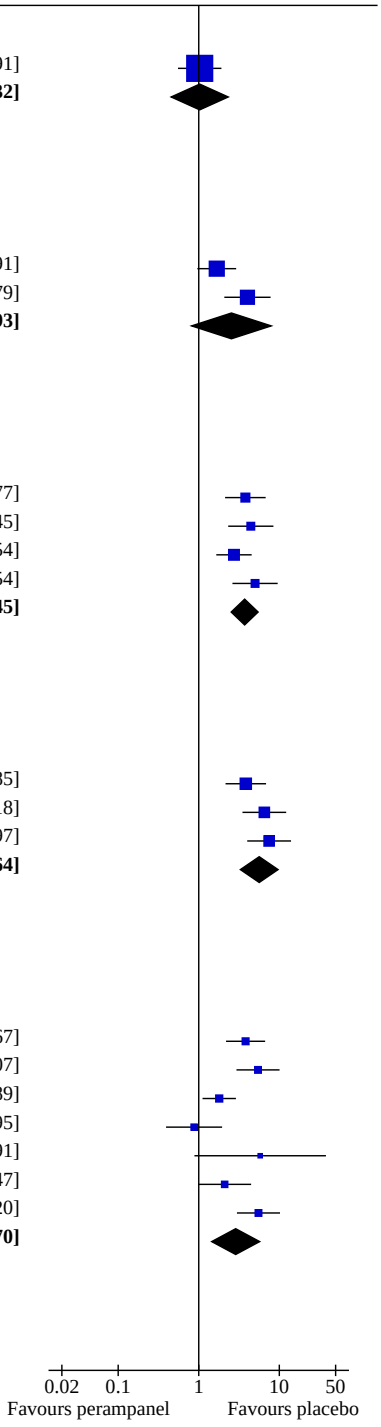
Analysis 1.5. Comparison 1: Perampanel versus placebo, Outcome 5: At least one adverse effect

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 2 mg/day						
Krauss 2012	111	180	101	185	100.0%	1.13 [0.95 , 1.35]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**1.13 [0.95 , 1.35]**
Total events:	111		101			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.5.2 4 mg/day						
Krauss 2012	111	172	101	185	45.5%	1.18 [1.00 , 1.40]
Nishida 2018	121	176	117	177	54.5%	1.04 [0.90 , 1.20]
Subtotal (95% CI)		**348**		**362**	**100.0%**	**1.10 [0.99 , 1.23]**
Total events:	232		218			
Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.5.3 8 mg/day						
French 2012 (study 304)	117	133	100	121	25.6%	1.06 [0.96 , 1.18]
French 2013 (study 305)	112	129	93	136	22.2%	1.27 [1.11 , 1.45]
Krauss 2012	121	169	101	185	23.6%	1.31 [1.12 , 1.54]
Nishida 2018	129	177	117	177	28.6%	1.10 [0.96 , 1.27]
Subtotal (95% CI)		**608**		**619**	**100.0%**	**1.18 [1.10 , 1.26]**
Total events:	479		411			
Heterogeneity: Chi² = 7.54, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 4.73 (P < 0.00001)						
1.5.4 12 mg/day						
French 2012 (study 304)	123	134	100	121	33.8%	1.11 [1.01 , 1.22]
French 2013 (study 305)	104	121	93	136	28.2%	1.26 [1.10 , 1.44]
Nishida 2018	156	180	117	177	38.0%	1.31 [1.16 , 1.48]
Subtotal (95% CI)		**435**		**434**	**100.0%**	**1.23 [1.15 , 1.31]**
Total events:	383		310			
Heterogeneity: Chi² = 5.45, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
1.5.5 All doses						
French 2012 (study 304)	240	267	100	121	20.3%	1.09 [0.99 , 1.19]
French 2013 (study 305)	216	250	93	136	17.8%	1.26 [1.12 , 1.43]
Krauss 2012	343	521	101	185	22.0%	1.21 [1.04 , 1.39]
Krauss 2012 (study 206)	68	102	32	51	6.3%	1.06 [0.83 , 1.37]
Krauss 2012 (study 208)	32	38	8	10	1.9%	1.05 [0.75 , 1.48]
Lagae 2016	68	85	31	48	5.8%	1.24 [0.98 , 1.57]
Nishida 2018	406	533	117	177	25.9%	1.15 [1.03 , 1.29]
Subtotal (95% CI)		**1796**		**728**	**100.0%**	**1.17 [1.10 , 1.24]**
Total events:	1373		482			
Heterogeneity: Chi² = 5.28, df = 6 (P = 0.51); I² = 0%						
Test for overall effect: Z = 5.35 (P < 0.00001)						



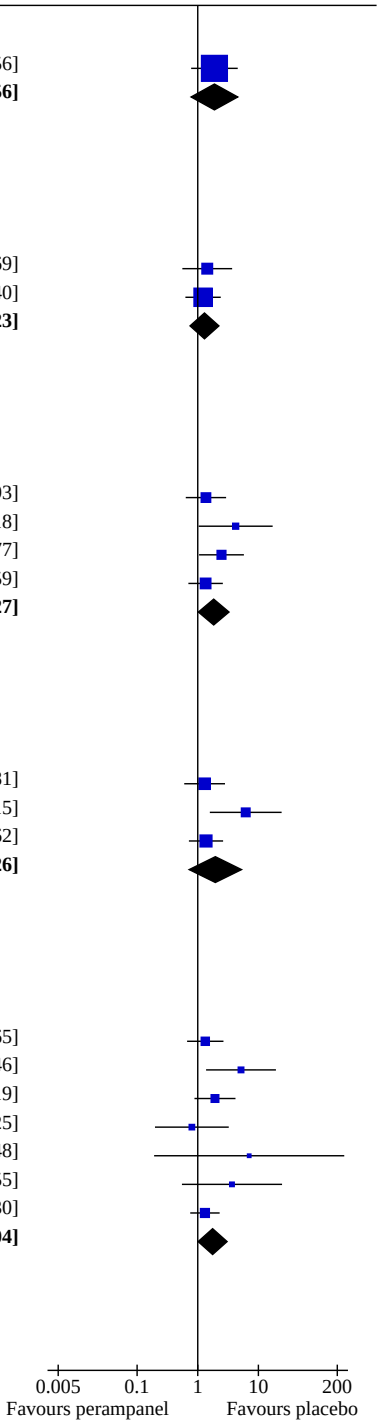
Analysis 1.6. Comparison 1: Perampanel versus placebo, Outcome 6: Dizziness

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 2 mg/day						
Krauss 2012	18	180	18	185	100.0%	1.03 [0.55 , 1.91]
Subtotal (99% CI)		**180**		**185**	**100.0%**	**1.03 [0.45 , 2.32]**
Total events:	18		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.6.2 4 mg/day						
Krauss 2012	28	172	18	185	52.2%	1.67 [0.96 , 2.91]
Nishida 2018	40	176	10	177	47.8%	4.02 [2.08 , 7.79]
Subtotal (99% CI)		**348**		**362**	**100.0%**	**2.55 [0.82 , 7.93]**
Total events:	68		28			
Heterogeneity: Tau^2 = 0.29; Chi^2 = 4.03, df = 1 (P = 0.04); I^2 = 75%						
Test for overall effect: Z = 2.12 (P = 0.03)						
1.6.3 8 mg/day						
French 2012 (study 304)	50	133	12	121	25.5%	3.79 [2.12 , 6.77]
French 2013 (study 305)	42	129	10	136	20.5%	4.43 [2.32 , 8.45]
Krauss 2012	45	169	18	185	33.5%	2.74 [1.65 , 4.54]
Nishida 2018	50	177	10	177	20.5%	5.00 [2.62 , 9.54]
Subtotal (99% CI)		**608**		**619**	**100.0%**	**3.71 [2.53 , 5.45]**
Total events:	187		50			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.53, df = 3 (P = 0.47); I^2 = 0%						
Test for overall effect: Z = 8.79 (P < 0.00001)						
1.6.4 12 mg/day						
French 2012 (study 304)	51	134	12	121	35.9%	3.84 [2.15 , 6.85]
French 2013 (study 305)	58	121	10	136	32.1%	6.52 [3.49 , 12.18]
Nishida 2018	76	180	10	177	32.0%	7.47 [4.00 , 13.97]
Subtotal (99% CI)		**435**		**434**	**100.0%**	**5.63 [3.29 , 9.64]**
Total events:	185		32			
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.71, df = 2 (P = 0.26); I^2 = 26%						
Test for overall effect: Z = 8.28 (P < 0.00001)						
1.6.5 All doses						
French 2012 (study 304)	101	267	12	121	16.6%	3.81 [2.18 , 6.67]
French 2013 (study 305)	100	250	10	136	16.0%	5.44 [2.94 , 10.07]
Krauss 2012	91	521	18	185	17.6%	1.80 [1.11 , 2.89]
Krauss 2012 (study 206)	14	102	8	51	13.8%	0.88 [0.39 , 1.95]
Krauss 2012 (study 208)	22	38	1	10	5.6%	5.79 [0.88 , 37.91]
Lagae 2016	26	85	7	48	14.4%	2.10 [0.99 , 4.47]
Nishida 2018	166	533	10	177	16.0%	5.51 [2.98 , 10.20]
Subtotal (99% CI)		**1796**		**728**	**100.0%**	**2.87 [1.45 , 5.70]**
Total events:	520		66			
Heterogeneity: Tau^2 = 0.34; Chi^2 = 23.82, df = 6 (P = 0.0006); I^2 = 75%						
Test for overall effect: Z = 3.97 (P < 0.0001)						



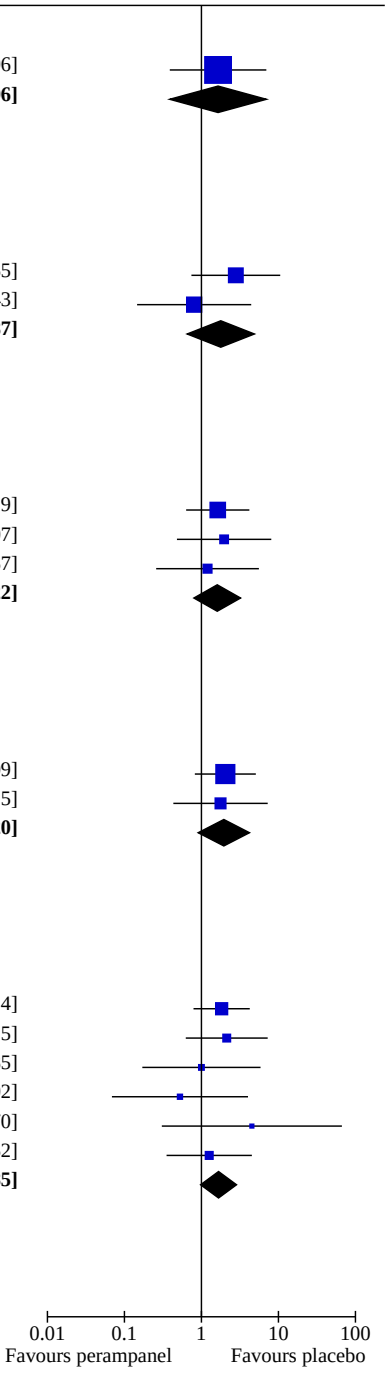
Analysis 1.7. Comparison 1: Perampanel versus placebo, Outcome 7: Somnolence

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 99% CI
1.7.1 2 mg/day						
Krauss 2012	22	180	12	185	100.0%	1.88 [0.78 , 4.56]
Subtotal (99% CI)		**180**		**185**	**100.0%**	**1.88 [0.78 , 4.56]**
Total events:	22		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.7.2 4 mg/day						
Krauss 2012	16	172	12	185	33.5%	1.43 [0.56 , 3.69]
Nishida 2018	28	176	23	177	66.5%	1.22 [0.63 , 2.40]
Subtotal (99% CI)		**348**		**362**	**100.0%**	**1.29 [0.75 , 2.23]**
Total events:	44		35			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.7.3 8 mg/day						
French 2012 (study 304)	24	133	16	121	28.5%	1.36 [0.63 , 2.93]
French 2013 (study 305)	16	129	4	136	13.1%	4.22 [1.04 , 17.18]
Krauss 2012	27	169	12	185	25.5%	2.46 [1.05 , 5.77]
Nishida 2018	31	177	23	177	32.9%	1.35 [0.70 , 2.59]
Subtotal (99% CI)		**608**		**619**	**100.0%**	**1.83 [1.03 , 3.27]**
Total events:	98		55			
Heterogeneity: Tau² = 0.09; Chi² = 5.48, df = 3 (P = 0.14); I² = 45%						
Test for overall effect: Z = 2.69 (P = 0.007)						
1.7.4 12 mg/day						
French 2012 (study 304)	23	134	16	121	36.3%	1.30 [0.60 , 2.81]
French 2013 (study 305)	22	121	4	136	24.8%	6.18 [1.58 , 24.15]
Nishida 2018	32	180	23	177	38.9%	1.37 [0.71 , 2.62]
Subtotal (99% CI)		**435**		**434**	**100.0%**	**1.95 [0.72 , 5.26]**
Total events:	77		43			
Heterogeneity: Tau² = 0.32; Chi² = 7.65, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.7.5 All doses						
French 2012 (study 304)	47	267	16	121	22.6%	1.33 [0.67 , 2.65]
French 2013 (study 305)	38	250	4	136	11.5%	5.17 [1.37 , 19.46]
Krauss 2012	65	521	12	185	20.6%	1.92 [0.88 , 4.19]
Krauss 2012 (study 206)	8	102	5	51	10.7%	0.80 [0.20 , 3.25]
Krauss 2012 (study 208)	12	38	0	10	2.2%	7.05 [0.19 , 260.48]
Lagae 2016	13	85	2	48	6.7%	3.67 [0.55 , 24.55]
Nishida 2018	91	533	23	177	25.8%	1.31 [0.75 , 2.30]
Subtotal (99% CI)		**1796**		**728**	**100.0%**	**1.76 [1.02 , 3.04]**
Total events:	274		62			
Heterogeneity: Tau² = 0.13; Chi² = 11.33, df = 6 (P = 0.08); I² = 47%						
Test for overall effect: Z = 2.65 (P = 0.008)						



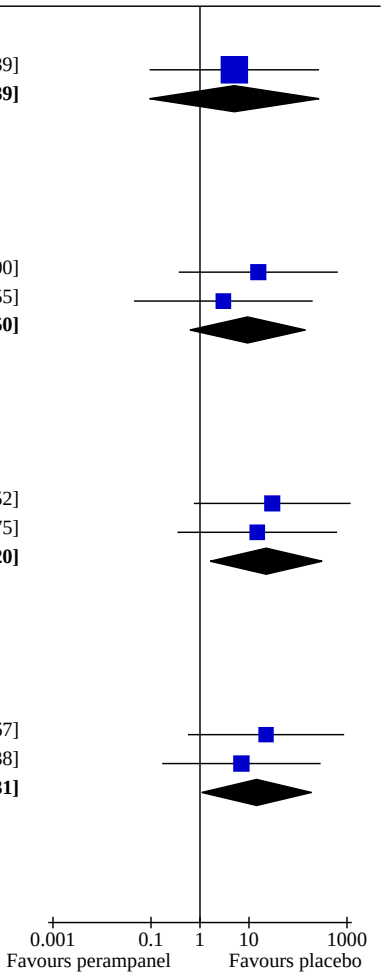
Analysis 1.8. Comparison 1: Perampanel versus placebo, Outcome 8: Fatigue

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 99% CI
1.8.1 2 mg/day						
Krauss 2012	8	180	5	185	100.0%	1.64 [0.39 , 6.96]
Subtotal (99% CI)		**180**		**185**	**100.0%**	**1.64 [0.39 , 6.96]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
1.8.2 4 mg/day						
Krauss 2012	13	172	5	185	49.1%	2.80 [0.74 , 10.55]
Nishida 2018	4	176	5	177	50.9%	0.80 [0.15 , 4.43]
Subtotal (99% CI)		**348**		**362**	**100.0%**	**1.78 [0.65 , 4.87]**
Total events:	17		10			
Heterogeneity: Chi² = 2.21, df = 1 (P = 0.14); I² = 55%						
Test for overall effect: Z = 1.48 (P = 0.14)						
1.8.3 8 mg/day						
French 2013 (study 305)	17	129	11	136	52.3%	1.63 [0.63 , 4.19]
Krauss 2012	9	169	5	185	23.3%	1.97 [0.48 , 8.07]
Nishida 2018	6	177	5	177	24.4%	1.20 [0.26 , 5.57]
Subtotal (99% CI)		**475**		**498**	**100.0%**	**1.60 [0.80 , 3.22]**
Total events:	32		21			
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.8.4 12 mg/day						
French 2013 (study 305)	20	121	11	136	67.3%	2.04 [0.82 , 5.09]
Nishida 2018	9	180	5	177	32.7%	1.77 [0.43 , 7.25]
Subtotal (99% CI)		**301**		**313**	**100.0%**	**1.95 [0.91 , 4.20]**
Total events:	29		16			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.8.5 All doses						
French 2013 (study 305)	37	250	11	136	37.9%	1.83 [0.79 , 4.24]
Krauss 2012	30	521	5	185	19.6%	2.13 [0.63 , 7.25]
Krauss 2012 (study 206)	6	102	3	51	10.6%	1.00 [0.17 , 5.85]
Krauss 2012 (study 208)	4	38	2	10	8.4%	0.53 [0.07 , 4.02]
Lagae 2016	8	85	1	48	3.4%	4.52 [0.31 , 66.70]
Nishida 2018	19	533	5	177	20.0%	1.26 [0.35 , 4.52]
Subtotal (99% CI)		**1529**		**607**	**100.0%**	**1.67 [0.98 , 2.85]**
Total events:	104		27			
Heterogeneity: Chi² = 4.26, df = 5 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.46 (P = 0.01)						



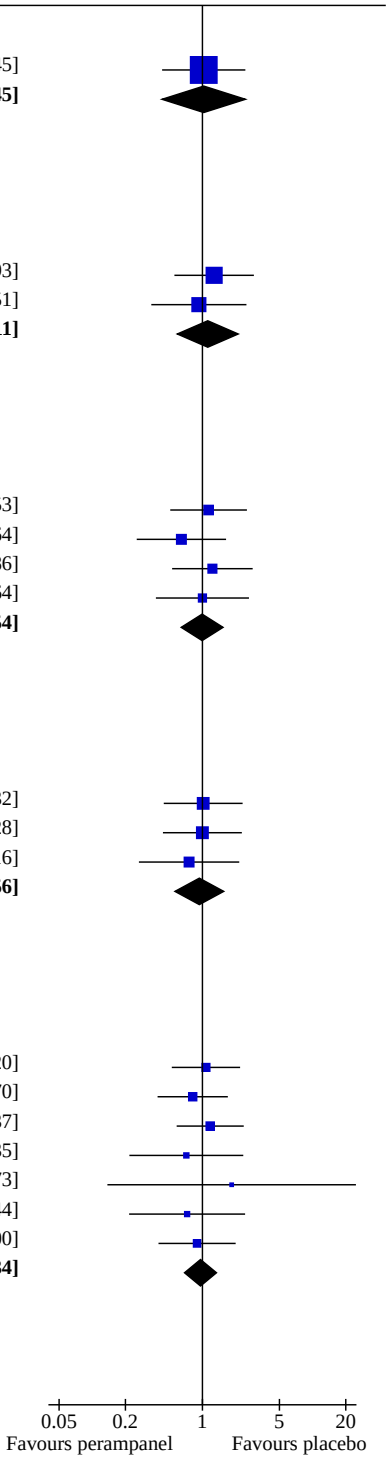
Analysis 1.9. Comparison 1: Perampanel versus placebo, Outcome 9: Ataxia

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 99% CI
1.9.1 4 mg/day						
Nishida 2018	2	176	0	177	100.0%	5.03 [0.09 , 269.39]
Subtotal (99% CI)		**176**		**177**	**100.0%**	**5.03 [0.09 , 269.39]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.9.2 8 mg/day						
French 2012 (study 304)	8	133	0	121	51.1%	15.48 [0.37 , 648.00]
Nishida 2018	1	177	0	177	48.9%	3.00 [0.05 , 199.55]
Subtotal (99% CI)		**310**		**298**	**100.0%**	**9.38 [0.62 , 141.50]**
Total events:	9		0			
Heterogeneity: Chi^2 = 0.61, df = 1 (P = 0.44); I^2 = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
1.9.3 12 mg/day						
French 2012 (study 304)	16	134	0	121	51.0%	29.82 [0.75 , 1186.52]
Nishida 2018	7	180	0	177	49.0%	14.75 [0.35 , 628.75]
Subtotal (99% CI)		**314**		**298**	**100.0%**	**22.44 [1.62 , 311.20]**
Total events:	23		0			
Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 = 0%						
Test for overall effect: Z = 3.05 (P = 0.002)						
1.9.4 All doses						
French 2012 (study 304)	24	267	0	121	47.8%	22.31 [0.57 , 874.67]
Nishida 2018	10	533	0	177	52.2%	7.00 [0.17 , 289.38]
Subtotal (99% CI)		**800**		**298**	**100.0%**	**14.32 [1.09 , 188.31]**
Total events:	34		0			
Heterogeneity: Chi^2 = 0.34, df = 1 (P = 0.56); I^2 = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						



Analysis 1.10. Comparison 1: Perampanel versus placebo, Outcome 10: Headache

Study or Subgroup	Perampanel Events	Perampanel Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 99% CI
1.10.1 2 mg/day						
Krauss 2012	16	180	16	185	100.0%	1.03 [0.43 , 2.45]
Subtotal (99% CI)		**180**		**185**	**100.0%**	**1.03 [0.43 , 2.45]**
Total events:	16		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.10.2 4 mg/day						
Krauss 2012	19	172	16	185	54.3%	1.28 [0.56 , 2.93]
Nishida 2018	12	176	13	177	45.7%	0.93 [0.34 , 2.51]
Subtotal (99% CI)		**348**		**362**	**100.0%**	**1.12 [0.59 , 2.11]**
Total events:	31		29			
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.10.3 8 mg/day						
French 2012 (study 304)	20	133	16	121	26.8%	1.14 [0.51 , 2.53]
French 2013 (study 305)	11	129	18	136	28.0%	0.64 [0.25 , 1.64]
Krauss 2012	18	169	16	185	24.4%	1.23 [0.53 , 2.86]
Nishida 2018	13	177	13	177	20.8%	1.00 [0.38 , 2.64]
Subtotal (99% CI)		**608**		**619**	**100.0%**	**0.99 [0.64 , 1.54]**
Total events:	62		63			
Heterogeneity: Chi² = 2.05, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.10.4 12 mg/day						
French 2012 (study 304)	18	134	16	121	35.9%	1.02 [0.45 , 2.32]
French 2013 (study 305)	16	121	18	136	36.2%	1.00 [0.44 , 2.28]
Nishida 2018	10	180	13	177	28.0%	0.76 [0.27 , 2.16]
Subtotal (99% CI)		**435**		**434**	**100.0%**	**0.94 [0.56 , 1.56]**
Total events:	44		47			
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.10.5 All doses						
French 2012 (study 304)	38	267	16	121	20.3%	1.08 [0.53 , 2.20]
French 2013 (study 305)	27	250	18	136	21.5%	0.82 [0.39 , 1.70]
Krauss 2012	53	521	16	185	21.8%	1.18 [0.58 , 2.37]
Krauss 2012 (study 206)	10	102	7	51	8.6%	0.71 [0.22 , 2.35]
Krauss 2012 (study 208)	7	38	1	10	1.5%	1.84 [0.14 , 24.73]
Lagae 2016	9	85	7	48	8.3%	0.73 [0.22 , 2.44]
Nishida 2018	35	533	13	177	18.0%	0.89 [0.40 , 2.00]
Subtotal (99% CI)		**1796**		**728**	**100.0%**	**0.96 [0.69 , 1.34]**
Total events:	179		78			
Heterogeneity: Chi² = 2.28, df = 6 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.75)						



APPENDICES

Appendix 1. CRS Web search strategy

1. (E2007 OR Fycompa OR Perampanel*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

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

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

4. #2 OR #3 AND CENTRAL:TARGET

5. #1 AND #4

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

7. #5 NOT #6

Appendix 2. MEDLINE Ovid search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2022).

1. (E2007 or perampanel$ or fycompa).mp.

2. exp Epilepsies, Partial/

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

4. 2 or 3

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

6. clinical trials as topic.sh.

7. trial.ti.

8. 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

11. 1 and 4 and 10

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

13. 11 not 12

14. remove duplicates from 13

HISTORY

Protocol first published: Issue 2, 2014

CONTRIBUTIONS OF AUTHORS

RB was primarily responsible for the final version of this review.

RH provided support for the review and screened the results from the searches conducted in August 2018, September 2019, June 2021, and October 2022.

JW was responsible for the screening of search results for searches conducted in June 2017 and November 2015, and arbitrated any disagreements.

DECLARATIONS OF INTEREST

RB: none.

RH: none.

JW: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute of Health Research (NIHR), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We changed the electronic search methods between the publication of the protocol (Huang 2014), and the conduct of the review. CRS Web includes randomised or quasi-randomised controlled trials from Specialised Registers of Cochrane Review Groups, including Epilepsy; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; Embase; ClinicalTrials.gov; and the World Health Organization International Clinical Trials Registry Platform (ICTRP). Thus, it is no longer necessary to search the additional databases listed in the protocol.
- We added methods for summarising and interpreting results since the publication of the protocol. These methods mainly concern the GRADE approach to assessing the evidence, and the construction of summary of findings tables, which are now methodological standards expected by Cochrane.
- We listed 50% or greater reduction in seizure frequency and seizure freedom as primary outcomes in the protocol. However, we only considered 50% or greater reduction in seizure frequency a primary outcome in the review; seizure freedom was considered a secondary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects]; *Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination; *Drug-Related Side Effects and Adverse Reactions; *Epilepsies, Partial [chemically induced] [drug therapy]; Randomized Controlled Trials as Topic; Seizures [drug therapy]

MeSH check words

Aged; Humans