National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[F] Add-on therapy for generalised tonic-clonic and focal onset seizures

Epilepsies in children, young people and adults

Evidence reviews underpinning recommendations 5.1.5-5.1.8 & 5.2.4-5.2.7 in the NICE guideline

November 2021

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Add-on therapy for generalised tonic-clonic seizures and focal onset seizures

Review question

This evidence report contains information on 2 reviews relating to add-on antiseizure therapies for generalised tonic-clonic seizures and focal onset seizures (with ot without evolution to bilateral tonic-clonic seizures).

- What add-on antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?
- What add-on antiseizure therapies are effective in the treatment of focal onset seizures?

Introduction

Focal onset seizures are defined as those that originate within a network limited to one hemisphere. They may be discretely localised or more widely distributed. Clinical manifestations will depend on the area of the brain involved in the seizure, and the function it subserves, for example, seizures from the occipital lobe will have visual manifestations. Focal seizures are also defined as to whether awareness is retained; if awareness of the event is impaired for any portion of the seizure, then the seizure is classified as a focal seizure with impaired awareness whereas if the awareness is retained throughout it is a focal aware seizure. Such seizures may evolve during the clinical course of the seizure to tonic clonic seizures – these are labelled as focal to bilateral tonic clonic seizures (previously called secondarily generalised tonic seizures).

Generalized from onset seizures are defined as originating at some point within, and rapidly engaging, bilaterally distributed networks. Tonic means there is generalised stiffening, and clonic repetitive jerking. In a generalised tonic clonic seizure there will be no warning, there will be sudden generalised stiffening of the body followed by repetitive jerking of all limbs. This seizure type is common amongst many different epilepsy types. The aim of this review is to determine which add-on antiseizure therapies improve outcomes in people with epilepsy who have focal onset or generalised tonic-clonic seizures.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• People with generalised tonic-clonic seizures for which one or more ASM has failed to respond, or refractory generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus) • People with focal onset epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus)
Intervention	The search for this review question will not restrict by treatment type but evidence on the following interventions is likely to be identified and/or is of most interest. • Brivaracetam • Carbamazepine • Clobazam • Clonazepam • Eslicarbazepine acetate • Ethosuximide • Gabapentin • Ketogenic diet • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Perampanel • Phenobarbitone • Phenytoin • Pregabalin • Sodium valproate • Topiramate • Zonisamide
Comparison	• Placebo • Any of the interventions outlined above

Outcome	Critical
	
	Outcomes in the NMA:
	• >50% reduction in seizure frequency during treatment or maintenance period
	• Seizure freedom during treatment or maintenance period
	
	Important
	
	Outcomes separate to the NMA:
	• Health-related quality of life (only validated scales will be included)
	• Adverse effects as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse effects)
	  ○ treatment cessation due to adverse event (dichotomous outcome only)
	  ○ mortality

ASM: antiseizure medication; NMA: network meta-analysis

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, the report of the network meta-analysis in appendix M and the methods supplement (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Network meta-analysis (NMA) for 50% reduction in seizure frequency in people with focal seizures: 99 randomised controlled trials (RCTs) reported across 97 articles involving 27,686 individuals were included in the NMA. Evidence for a total of 26 treatments were identified (25 active ASMs and placebo).

NMA for seizure freedom in people with focal seizures: 72 RCTs involving 20,826 individuals were included in the NMA. Evidence for 21 active ASMs and placebo were identified.

NMA for 50% reduction in seizure frequency in people with generalised tonic clonic seizures: 8 RCTs involving 1,218 individuals were included in the NMA. Evidence for 6 active ASMs and placebo were identified.

NMA for seizure freedom in people with generalised tonic clonic seizures: 8 RCTs involving 1,218 individuals were included in the NMA. Evidence for 6 active ASMs and placebo were identified.

A full list of included studies are available in appendix M. See also the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review, with reasons for their exclusion, are provided in appendix K.

1 Summary of studies included in the evidence review

2 Summaries of the NMAs that were created for this review are presented in Table 2.

3 **Table 2: Summary of included studies**

NMA	Population	Comparisons	Outcomes
NMA for 50% reduction in seizure frequency in people with focal seizures	People with focal onset epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus) Number of studies = 99 Number of participants = 27,686	• Brivaracetam • Carbamazepine • Carisbamate • Cenobamate • Eslicarbazepine Acetate • Retigabine • Gabapentin • Ganaxolone • Lacosamide • Lamotrigine • Levetiracetam • Loreclezole • Losigamone • Oxcarbazepine • Perampanel • Phenytoin • Placebo • Pregabalin • Primidone • Rufinamide • Selurampanel (BGG492) • Sodium valproate • Tiagabine • Topiramate • Vigabatrin • Zonisamide	• >50% reduction in seizure frequency during treatment or maintenance period • Seizure freedom during treatment or maintenance period • Health-related quality of life • Adverse effects as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event (dichotomous outcome only) ○ mortality
NMA for seizure freedom in people with focal seizures	People with focal onset epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus) Number of studies = 72 Number of participants = 20,826	• Brivaracetam • Carisbamate • Cenobamate • Eslicarbazepine Acetate • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Perampanel • Placebo • Pregabalin • Primidone • Retigabine	• >50% reduction in seizure frequency during treatment or maintenance period • Seizure freedom during treatment or maintenance period • Health-related quality of life • Adverse effects as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event (dichotomous outcome only) ○ mortality

NMA	Population	Comparisons	Outcomes
		• Rufinamide • Selurampanel (BGG492) • Sodium valproate • Tiagabine • Topiramate • Vigabatrin • Zonisamide	
NMA for 50% reduction in people with GTC seizures **&** **NMA for seizure freedom in people with GTC seizures**	People with generalised tonic-clonic seizures for which one or more ASM has failed to respond, or refractory generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus) Number of studies = 8 Number of participants = 1,218	• Brivaracetam • Lacosamide • Lamotrigine • Levetiracetam • Perampanel • Placebo • Topiramate	• >50% reduction in seizure frequency during treatment or maintenance period • Seizure freedom during treatment or maintenance period • Health-related quality of life • Adverse effects as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event (dichotomous outcome only) ○ mortality

ASM: Antiseizure medication; GTC: generalised tonic-clonic; IPD: individual patient data, NMA: network meta-analysis

See appendix M for a full list of included studies

Summary of the evidence

For focal seizures this analysis estimated that loreclezole and carbamazepine were the two ASMs which had the highest point estimate of relative effectiveness compared to placebo for 50% reduction in seizure frequency although both these estimates had wide 95% credible intervals. Cenobamate had the third highest point estimate of relative effectiveness compared to placebo and had relatively narrow credible intervals. The estimated effectiveness for cenobamate was also greater than that for lamotrigine, levetiracetam and gabapentin all drugs recommended in the previous NICE guideline for add-on treatment for focal seizures. Brivaracetam, carbamazepine, cenobamate, eslicarbazepine acetate lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregablin, topiramate, vigabatrin and zonisamide were all effective compared to placebo for 50% reduction in seizure frequency.

For GTC seizures all ASMs identified for the network had estimated relative effectiveness when compared to placebo with the only estimated difference in the relative effect between 2 active treatments being levetiracetam showing higher relative effectiveness than lacosamide for 50% reduction in seizure frequency.

For both focal and GTC seizures the NMAs for estimating seizure freedom showed large discrepancies between the values and credible intervals estimated and the observed data from the included RCTs. It was therefore difficult to lend weight to any of the conclusions from this NMA.

The percentage of patients with reported side effects, treatment cessation due to adverse event and mortality were reported inconsistently across studies and it was difficult to draw conclusions from them.

Quality assessment of studies included in the evidence review

See appendix F for GRADE tables. See appendix M for assessment of risk of bias for individual studies.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in supplementary material 2.

Summary of studies included in the economic evidence review

No economic evidence was identified which was applicable to this review question.

Economic model

One economic model was created to answer the review questions for both monotherapy and add-on therapy. See supplementary material 4. A summary of the model for add-on therapy for both focal and GTC seizures is presented below.

The economic model was a Markov model based upon the outcomes from the NMAs for this review question (Appendix M). For focal seizures the model estimated the cost effectiveness of brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenytoin, pregabalin, primidone, sodium valproate, tiagabine, topiramate, vigabatrin and zonisamide to a comparator of carbamazepine. For GTC seizures brivaracetam, lacosamide, levetiracetam, perampanel and topiramate were compared to lamotrigine.

Overview of methods

A decision-analytic model in the form of a Markov model based on the model from the previous NICE guideline was constructed to evaluate the relative cost effectiveness of the different add-on therapies. Short term effectiveness data was almost entirely taken from the relevant NMAs with longer term data coming from UK observational studies. The model cohort was based on a recent UK RCT. Quality of life was based on an individual's seizure status but was estimated using the EQ-5D and UK population preference weights. The perspective of the analysis was that of NHS and Personal and Social Services (PSS). National UK unit costs were used with a cost year of 2019/2020. All costs and outcomes were discounted at a rate of 3.5% per annum.

Results

<u>Add-on therapy for focal seizures</u>

In the base-case QALYs differ by only 0.03 across all interventions equivalent to 11 days in perfect health. Assuming a £20,000 per QALY threshold levetiracetam becomes the preferred option. Without levetiracetam, which is one of the preferred options for monotherapy (and therefore may not be an option for add-on therapy) topiramate becomes the preferred option under the base-case assumptions.

From the probabilistic sensitivity analysis carbamazepine is the preferred option at all values of willingness to pay per QALY up to £100,000. Carbamazepine had the highest point estimate for '50% reduction in seizure freedom' in the economic model with favourable but very wide confidence intervals. The direct evidence for carbamazepine in the accompanying NMA was based on two relatively old studies with a high risk of bias. Without carbamazepine no other ASM had more than a 15% probability of being the preferred option at a threshold of £20,000 per QALY. At the £20,000 per QALY threshold in the absence of carbamazepine, sodium valproate, gabapentin and levetiracetam were the preferred options.

Add-on therapy for GTC seizures

Under the base-case assumptions levetiracetam is the most effective intervention and the second least costly. It is the preferred option when a £20,000 per QALY threshold is assumed. The probabilistic sensitivity analysis shows at a threshold of £20,000 per QALY topiramate is the preferred option with a 57% probability of being the cost effective option. This is followed by perampanel (20.5%), levetiracetam (11.6%) and lacosamide (10.9%). Brivaracetam and lamotrigine had a zero probability of being the preferred option for all threshold values for a QALY.

Evidence statements

- There was evidence from the guideline economic analysis comparing the cost effectiveness of brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenytoin, pregabalin, primidone, sodium valproate, tiagabine, topiramate, vigabatrin and zonisamide to a comparator of carbamazepine in people with focal epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy. The model gave little clear indication of the prefered option for this patient group although carbamazepine had the highest probability during probalistic sensitivity analysis. Without carbamazepine no other ASM had more than a 15% probability of being the preferred option at a threshold of £20,000 per QALY. At the £20,000 per QALY threshold in the absence of carbamazepine, sodium valproate, gabapentin and levetiracetam were the preferred option. This evidence was directly applicable to the NICE decision-making context and had potentially serious limitations especially around the uncertainty of the key clinical evidence to inform the model.

- There was evidence from the guideline economic analysis levetiracetam to be the preferred option under the base-case assumptions with topiramate to the preffered option during sensitivity analysis with a probability of being the preferred option of 57% at a £20,000 per QALY threshold in people with GTC epilepsy for which one or more ASM has failed to respond, or refractory GTC epilepsy. This is followed by perampanel (20.5%), levetiracetam (11.6%) and lacosamide (10.9%). Brivaracetam and lamotrigine had a zero probability of being the preferred option for all threshold values for a QALY. This evidence was directly applicable to the NICE decision-making context and had potentially serious limitations especially around the uncertainty of the key clinical evidence to inform the model.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes greater than 50% reduction in seizure frequency during treatment or maintenance period and seizure freedom during treatment or maintenance period were identified as critical outcomes by the committee. Greater than 50% reduction in seizure frequency is widely reported in RCTs for the population considered in this review or can be easily calculated from other commonly reported outcomes. It also represents a change in seizure frequency which would likely improve quality of life and reduce contact with health services. Seizure freedom is a reasonably rare outcome in these people but is associated with large improvements in quality of life. Both outcomes are also recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE) as outcome measures for trials of add-on ASMs.

Important outcomes were identified as adverse events (disaggregated by percent of patients with reported side effects, treatment cessation due to adverse event and mortality) and health related quality of life, due to the importance both these outcomes have for people with epilepsy.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE-NMA. The certainty of outcomes were downgraded based on within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence (inconsistency).

For the outcome greater than 50% reduction in seizure frequency in focal seizures evidence was rated from very low to moderate. The main reason for downgrading was the indirectness of the results giving wide credible intervals. Lower quality ratings were predominantly for the older ASMs and for drugs not licensed for this indication. For seizure freedom the quality of the evidence was rated from low to moderate again predominantly as a result of indirectness.

For the outcome of greater than 50% reduction in seizure frequency for generalised tonic-clonic seizures the evidence was moderate for all outcomes apart from one which was downgraded to low for indirectness and with-in study bias. The quality of all outcomes for seizure freedom were rated as low predominantly as a result of indirectness.

The quality of the evidence for adverse events and quality of life outcomes were not formally assessed. These outcomes were reported narratively in the systematic review. Quality is likely to be limited for this evidence for a number of reasons in particular differences in reporting and definitions of adverse events between different studies, uncertainty around whether events had not occurred or had not been reported and the use of different scales for quality of life. These weaknesses are particularly important when making any comparison between ASMs based on adverse events or quality of life.

Benefits and harms

Add-on therapy for focal seizures

The committee considered the network meta-analysis for add-on therapies for people with focal epilepsy and used this evidence and their expertise to make recommendations. As over 90% of trials in this area compare active treatment to placebo it was hoped that a network meta-analysis would allow active treatments to be compared to other active treatments informing treatment decisions between them. However, no difference was identified for all of the ASMs which were effective (versus placebo) for either critical outcome and it was therefore difficult to highlight the

most effective ASMs. The committee therefore based their recommendations largely on the results of ASMs compared to placebo.

The committee agreed that, prior to starting antiseizure therapy there should be a discussion with the person, their family and carers, if appropriate, about an individualised antiseizure medication strategy according to their seizure type, treatment goals and the preferences of the person and their family or carers as appropriate. Treatment plans should be regularly reassessed, and its agreement should include a transparent explanation of the epilepsy type, severity and duration of adverse effects that the person with epilepsy may experience and how should these be managed. The person, their family and carers, should also be made aware that they should be taking the least amount of medicines as possible to be effective due to the side effects of being on numerous medications.

The committee emphasised that, monotherapy should be used in the first instance. When starting alternative antiseizure medications, the dose of the new antiseizure medication should be slowly increased, whilst the existing antiseizure medication is tapered off. When starting add-on antiseizure medications, the additional antiseizure medication should be carefully titrated, in line with the BNF guidance, adverse events monitored, and there should be a frequent treatment review.

Carisbamate, ezogabine/retigabine, ganaxolone, loreclezole, losigamine, and surampanel were not licensed or readily available in the UK at the time of the appraisal so the evidence for these drugs was not considered. Cenobamate was undergoing a separate health technology appraisal and therefore the committee did not review the evidence for this drug either.

Of the remaining drugs, carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate and zonisamide were estimated to be effective within the adjusted network meta-analysis for a 50% reduction in seizure frequency rate in the reduction of focal seizures when compared to placebo with relatively narrow credible intervals suggesting certainty around the estimate. These drugs were therefore recommended first line for add-on treatments for focal seizures, based on the evidence and the committee's expertise. Brivaracetam, eslicarbazepine, perampanel and pregablin were recommended second line as these were effective compared to placebo. Sodium valproate had wide 95% credible intervals in the network meta-analysis passing the line of no effect but based on committee expertise and that it is currently used in practice this drug was also recommended second line.

Phenobarbital, phenytoin, tiagibine and vigabatrin were recommended as third line add-on treatment based on the committee's opinion they can be effective treatments, whilst acknowledging their side effect profile of some of these drugs. Vigabatrin was effective compared to placebo in the NMA but with uncertainty around the estimate. Phenytoin had very wide credible intervals which and showed no difference to placebo. The credible intervals also passed the line of no effect for tiagabine. No evidence was identified for phenobarbital but it was recommended based on the committee's experience of its effectiveness and that it is currently used in practice.

Add-on therapy for generalised tonic-clonic seizures

For generalised tonic-clonic seizures all ASMs in the NMA had estimated relative effectiveness for the active treatment compared to placebo for the outcome of greater than 50% reduction in seizure frequency. Levetiracetam had relative effectiveness compared to lacosamide but there was no difference between any other active treatment. The committee recommended lacosamide, lamotrigine, levetiracetam, and topiramate as first line add-on therapies based on the evidence, as well as clobazam and sodium valproate based on their clinical experience and current use in practice.

Given the very wide 95% credible intervals for the evidence around brivaracetam for 50% reduction in seizure frequency, the committee recommended this drug as second line add-on treatment. Lacosamide was also included second line rather than first line based on it being less effective

than levetiracetam for 50% reduction in seizure frequency. The committee, based on their experience and that the ASMs are currently used in practice, also included phenobarbital, primidone and zonisamide for consideration as second line treatments.

Other considerations

The committee and economic analysis highlighted seizure freedom as an important outcome for people with focal and GTC seizures and was associated with large increases in quality of life and reductions in use of other medical resources. Seizure freedom is a reasonably rare event in this group and consequently, given the small event rates the 95% credible intervals around this outcome were extremely wide. A number of drugs showed effectiveness compared to placebo but given these wide credible intervals, for both focal and generalised tonic-clonic seizures, it was difficult to place confidence in these results.

Adverse events and quality of life were also considered by the committee for add-on therapy but it was difficult to place weight on these outcomes given the issues with the quality of the evidence discussed above.

The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children and, as a result, recommended that other antiseizure medications should be used as add-on treatment in this population. Nonetheless, the committee agreed that in some cases, for example, if women have tried other medication and it has not worked, sodium valproate should be available as an option. The committee agreed that sodium valproate should only be prescribed after a full and clear discussion with the girl or woman, ensuring she understands all the potential risks and benefits. If sodium valproate is prescribed, clinicians must follow MHRA guidance, which includes enrolment in a pregnancy prevention programme, if appropriate.

Based on their expertise the committee recommended against carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregablin, tiagabine and vigabatrin for people with co-existing absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected as they may exacerbate absence and myoclonic seizures.

The committee noted that, in line with the BNF, phenytoin should not be offered to people of Han Chinese or Thai family background and carbamazepine, oxcarbazepine and eslicarbazepine to people of European or Japanese family background because of the risks of serious complications, unless the person meets the pre-treatment screening advice for people from these groups. In addition, in line with the MHRA, the committee emphasised that long-term treatment with carbamazepine, phenytoin, primidone and sodium valproate can cause decreased bone mineral density and increased risk of osteomalacia. The committee noted that appropriate supplementation should be considered for those at risk.

Cost effectiveness and resource use

A bespoke economic model was created for this review question. The model compared all drugs for which there was evidence informing the NMAs and that were licensed for this indication. The model followed the NICE reference case. Similarly to the NMA, the economic model did not estimate any strong preferred option with no ASM having greater than a 15% probability of being the preferred option. This was because of wide 95% confidence intervals around the main clinical inputs to the model and the large cost savings and quality of life associated with seizure freedom.

The majority of the costs were not associated with the ASM prescribed, but with later costs for changing treatment or being hospitalised following a seizure. There was also limited difference between the costs of the various treatments. It is therefore likely that of the drugs considered in the model the most clinically effective would also be the most cost effective.

Other factors the committee took into account

The committee discussed that guidance on the use of cenobamate for focal onset seizures should be based on NICE's forthcoming technology appraisal on cenobamate for focal onset seizures in epilepsy.

Recommendations supported by this evidence review

This evidence review supports recommendations 5.1.5-5.1.8 & 5.2.4-5.2.7.

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Appendix A – Review protocol

Review protocol for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

Field	Content
PROSPERO registration number	CRD42020176581
Review title	Pharmacological management (monotherapy or add-on therapy) of epileptic seizures and epilepsy syndromes
Review question	3.1 What antiseizure therapies (add-on) are effective in the treatment of generalised tonic clonic seizures? 3.2 What antiseizure therapies (add-on) are effective in the treatment of focal onset seizures?
Objective	To compare the effectiveness of antiseizure therapies used as add on therapy in children and adults with focal onset seizures or generalised tonic clonic seizures. This review will determine the effectiveness of antiseizure therapies given as add-ons (combination therapy). A separate review is being conducted for monotherapy treatment in these populations
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by: • Date: no date limit • English language studies • Human studies

Field	Content
	• RCT and systematic review study design filter The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Epilepsy
Population	Inclusion: • Children, young people and adults with generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus) that have failed to respond to one or more AEDs, or refractory generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus) • Children, young people and adults with focal onset epilepsy that have failed to respond to one or more AEDs, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus) Exclusion: • Newborn babies (under 28 days) with acute symptomatic seizures
Intervention	All AEDs (including combinations of) aimed at treating and managing epilepsy in the above patient group, will be considered by the NMA. The search for this review question will not restrict by treatment type but evidence on the following interventions is likely to be identified and/or is of most interest. • Brivaracetam • Carbamazepine • Clobazam • Clonazepam • Eslicarbazepine acetate • Ethosuximide • Gabapentin • Ketogenic diet • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Perampanel

Field	Content
	• Phenobarbitone • Phenytoin • Placebo • Pregabalin • Sodium valproate • Topiramate • Zonisamide Interventions which are not AEDs or combination interventions which include a component which is not an AED will only be considered in the NMA if they act as connectors of the interventions of interest in the network. Such interventions will be included in the NMA but will not form part of the decision problem when making recommendations. Trial arms with differing drug dose will be pooled together in the analysis as dose comparisons are outside of the scope of this review. A network diagram for all outcomes of interest will be constructed to explore whether all interventions are connected to the network. If more than one network is formed, then separate NMAs will be conducted for each network, as long as the network contains at least 3 interventions that are part of the decision problem. If pairs of interventions are not connected to a network, they will be analysed in pairwise meta-analysis. We assume that any individual that meets all inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set. For AEDs with teratogenic risk (i.e. sodium valproate) studies may exclude women of child bearing age even though this violates the 'randomised to all' assumption. For our outcomes we do not believe this relaxing of the assumption will influence the results and thus such studies are not excluded from the NMA. This however is explored during sensitivity analysis as discussed in section 16.
Comparator	• Any of the above
Types of study to be included	Included study designs: • Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • RCTs • RCTs will be included if they have at least one randomised pairwise comparison between two AEDs. RCTs will also be included if they include comparisons (whether AEDs or not) that act as connectors of interventions of interest in the network Excluded study designs: • Quasi-randomised or non-randomised controlled trials • Case-control studies

Field	Content
	• Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with a mixed population (i.e. including people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare setting (e.g. community, primary care, secondary care, tertiary care).
Primary outcomes (critical outcomes)	Outcomes in the NMA: • >50% reduction in seizure frequency during treatment or maintenance period • Seizure freedom during treatment or maintenance period Outcomes separate to the NMA: • Health-related quality of life (only validated scales will be included) • Adverse effects as assessed by: • % of patients with reported side effects (trial defined adverse and serious adverse effects) • Treatment cessation due to adverse event (dichotomous outcome only) • Mortality
Secondary outcomes (important outcomes)	• None
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Dual weeding and study selection will be undertaken for this question; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). All data extraction will be quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.

Field	Content
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	**Method of analysis** Network meta-analysis (NMAs) will be used to synthesise the selected outcomes for all eligible interventions that are connected to one or more networks of at least 3 interventions. It has been hypothesised that placebo response rates in RCTs relevant to this review have changed over time which may impact on the suitability of pooling all placebo interventions together. As we anticipate the majority of evidence for this review to come from placebo controlled trials we will investigate if this is likely to be the case and if so to control for it in our NMA. This will be investigated by firstly comparing placebo responders to non-responders to estimate an overall placebo response rate for all outcomes using the placebo arms of the identified studies and estimating a pooled placebo response rate using a random effects meta-analytical model. A Spearman's rank correlation coefficient will be calculated to identify and assess any changes in placebo or drug response rates overtime ("placebo drift") or any correlation between placebo outcomes and baseline seizure frequency. This will be done for all outcomes included in the NMA. If "placebo drift" or correlation between placebo outcomes and baseline characteristics is identified then this will be adjusted for in the NMA using meta-regression following NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment. The goodness of fit of the NMA with and without this adjustment will be explored as discussed below. NMA will be conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS Non-informative priors will be initially used, but if the data are sparse or there are convergence problems, then we will use evidence-based priors for the between studies standard deviation). To test whether prior estimates have an impact on the results, two chains with different initial values will be run simultaneously for each analysis. Convergence will be assessed by visually inspecting the mixing of the two chains in the history plots and the Brooks Gelman-Rubin diagram in WinBUGS. For the synthesis of the two outcomes (a binomial likelihood and logit link model will be used. The output of this analysis will be expressed as log-odds ratios (LORs) with 95% credible intervals (95% CrI) between all pairs of interventions assessed. We will also evaluate the ranking of each treatment and 95% CrI in each analysis, where a rank of 1 indicates

Field	Content
	best treatment. The goodness of fit of each model will be tested by comparing the posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, with the number of data points in the model. Smaller values of the residual deviance are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the analysis (each study arm contributes one data point). Models will also be compared using the deviance information criterion (DIC), a measure of model fit that is equal to the sum of the posterior mean deviance and the effective number of parameters, thus penalising model fit for model complexity; lower values are preferred and typically differences of at least 3 points are considered meaningful). The posterior median between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, will also be used to compare models. Inconsistency between direct and indirect evidence will be explored by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effects model). Deviance plots, in which the posterior mean deviance of the individual data points in the inconsistency model are plotted against their posterior mean deviance in the consistency model, will be inspected in order to identify studies which may have contributed to loops of evidence where inconsistency may be present. If these analyses identify potential inconsistency, further checks will be conducted using a node-split approach using the gemtc package in R. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared. If we find evidence of inconsistency, studies contributing to loops of evidence where there may be inconsistency will be checked for data accuracy and assessment of study inclusion will be revisited against inclusion/exclusion criteria. Baseline characteristics will be checked to identify any differences in effect modifiers across studies in loops identified as potentially inconsistent. Analyses will be repeated if corrections in the data extraction or study inclusion are made. If an important effect modifier is identified, then this may be explored in subgroup analyses if sufficient evidence is available. However, if evidence of inconsistency is still present following data corrections, revisiting inclusion criteria, exploring effect modification, no further studies will be excluded from the analysis, as their results cannot be considered as less valid than those of other studies solely because of the inconsistency findings. The presence of inconsistency in the NMA will be highlighted and results will be interpreted accordingly. A number of sensitivity analyses will also be performed (in addition to the subgroup analyses) which will restrict the inclusion criteria for studies in the NMA to see if this changes the results or conclusions: Studies with a high or unclear risk of bias will be excluded from the network. Studies which excluded women of childbearing aged due to teratogenic risk will be excluded from the network

Field	Content			
	For adverse events a non-comparative summary of those reported in the identified trials will be presented. Given we are expecting a large number of comparisons and variable reporting of this outcome comparative synthesis of evidence would be difficult and not helpful. For quality of life again we expect variance in reporting of this outcome using different time points and quality of life scales as well as a large number of comparisons. Again a non-comparative summary will be given.			
Analysis of sub-groups	If sufficient data is available, separate networks and analysis will be conducted on: • Previous treatment • Those with treatment resistant epilepsy (defined as "failure of two tolerated, appropriately chosen and used antiepileptic drug schedules") • Those with generalised tonic-clonic seizures (RQ 3.1) • Those with focal onset seizures (RQ 3.2)			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	1 May 2020			
Anticipated completion date	7 January 2021			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☐
	Piloting of the study selection process		☐	☐
	Formal screening of search results against eligibility criteria		☐	☐
	Data extraction		☐	☐
	Risk of bias (quality) assessment		☐	☐
	Data analysis		☐	☐
Named contact	5a. Named contact National Guideline Alliance			

Field	Content
	5b. Named contact e-mail Epilepsies@nice.org.uk. 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	NGA technical team
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=176581
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Generalised tonic clonic seizures Focal onset seizures?
Details of existing review of same topic by same authors	Not applicable
Current review status	☒ Ongoing

Field	Content	
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

1

Appendix B – Literature search strategies

Literature search strategies for review question: What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

Clinical

Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID

EMCare 1995 to February 03, 2021; Embase Classic+Embase 1947 to 2021 February 03; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 February 03, 2021
Date of last search: 03 February 2021

Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ use ppez, emczd, emcr or (epilep* or seizure* or convuls*).ti,ab.
2	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
3	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
4	or/1-3
5	brivaracetam/ use emczd, emcr or (brivaracetam or brivlera or nubriveo or rikelta).ti,ab.
6	carbamazepine/ use emczd, emcr or exp carbamazepine/ use ppez or carbamazepin*.sh. or (amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol).ti,ab.
7	clobazam/ use emczd, emcr or clobazam/ use ppez or (chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl).ti,ab.
8	clonazepam/ use emczd, emcr or clonazepam/ use ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.
9	exp eslicarbazepine/ use emczd, emcr or (eslicarbazepin* or aptiom or zebinix).ti,ab.
10	ethosuximide/ use emczd, emcr or ethosuximide/ use ppez or (emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethylsuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin).ti,ab.
11	gabapentin/ use emczd, emcr or gabapentin/ use ppez or gabapentin*.sh. or (apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin).ti,ab.
12	(diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycerides/) use ppez or (fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/) use emczd, emcr
13	((adequate adj3 protein*) or atkin* or keto* or kd* or (carbohydrate* adj5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) adj5 (index or treat* or modulat*)) or (high fat* adj5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or low glyc* index treatment* or lgit or (medium chain adj (tryglyceride* or triglyceride*)) or mct*).ti,ab.
14	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
15	lamotrigine/ use emczd, emcr, ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamitor* or amitrin* or lamodex or lamogine or lamotrin* or lamotrigin* or lamotrix or neurium).ti,ab.
16	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
17	oxcarbazepine/ use emczd, emcr or oxcarbazepine/ use ppez or oxcarbazepin*.sh. or (apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or

#	searches
	trileptin).ti,ab.
18	perampanel/ use emczd, emcr or (fycompa or perampanel).ti,ab.
19	phenobarbital/ use emczd, emcr or exp phenobarbital/ use ppez or (adonal or aephenal or agrypnal or alepsal or amylofene or andral or aparoxal or aphenylbarbit or aphenyletten or atrofen or austrominal or barbapil or barbellen or barbenyl or barbilettae or barbilixir or barbinal or barbiphen or barbiphenyl or barbivis or barbonal or barbonalett or barbophen or bardorm or bartol or bialminal or calmetten or calminal or carbronal or cardenal or cemalonal or codibarbital or coronaletta or cratecil or damoral or dezibarbitur or dormina or dormiral or dromural or ensobarb or ensodorm or epanal or epidorm or epilol or episedal or epsylone or eskabarb or etilfen or euneryl or fenbital or fenemal or fenobarbital or fenolbarbital or fenosed or fenylettae or gardenal* or gardepanyl or glysoletten or haplopan or haplos or helional or hennoletten or hypnaletten or hypno tablinetten or hypnogen fragner or hypnolone or hypno-tablinetten or hypnotal or hypnotalon or hysteps or hysteps or lefebar or leonal or leonal leo or lephebar or lepinal or lethyl or linasen or liquital or lixophen or lubergal or lubrokal or lumesettes or lumesyn or luminal or luminale or luminaletas or luminalette or luminaletten or luminalettes or luminalum or lumofridetten or luphenil or luramin or menobarb or molinal or monosodium salt or neurobarb or nirvonal or noptil or nova pheno or nunol or parkotal or pharmetten or phen bar or phenaemal or phenemal or phenethylbarbital sodium or phenobal or phenobarb or phenobarbital or phenobarbitol or phenobarbiton or phenobarbitone or phenobarbitural or phenobarbyl or phenonyl or phenotal or phenoturic or phenoyl or phenyl ethyl barbituric acid or phenylbarbital or phenylethyl barbituric acid or phenylethylbarbituric acid or phenylethylmalonyl urea or phenylethylmalonylurea or phenyletten or phenyral or polcominal or promptonal or seda tablinen or sedabar or sedicat or sedizorin or sedlyn or sedofen or sedonal or sedonettes or seneval or sevenal or sombutol mcclung or somnolens or somnoletten or somnosan or somonal or spasepilin or starifen or starilettae or stental or teolaxin or theolaxin or triabarb or tridezibarbitur or uni-feno or versomnal or wakobital or zadoletten or zadonal).ti,ab.
20	phenytoin/ use emczd, emcr or phenytoin/ use ppez or (alepsin or aleviatin or antilepsin or antisacer or auranile or cansoin or causoin or citrull?amon or comital or comitoina or convul or cumatil or danten or dantinal or dantoin* or denyl or fifenilhidantoin* or di hydan or difenin or difetoin or differenin or dihycon or difhydan* or dihydan or di-hydan or dilabid or dilantin* or di lan or dintoin or dintoina or diphantoin* or diphedal or diphedan or di-phen or di phetine or diphenat or diphenin* or diph?ntoin or diphentyn or diphenyl?hydantoin or diphenylan or diphenyldantoin or diphenylhydantoin* or diphenylhydatanoin* or diphenytoin or ditoin* or ditomed or ekko or elepsindon or enkelfel or epamin or epanutin or epasmir or epifenyl or epilantin or epinat or orepdantoin* or epelin or ephihydan or epilan or epilantin or epised or eptal or eptoin or felantin or fenantoin or fenatoin or fenidantoin or fenitoin* or fentoin or fenylepsin or fenytoin* or hidan or hindatal or hidanil or hidantal or hidantomin or hydant?in or hydantilo or hidantina or hydant?l or hydant?inal or h?dantoina* or hydantol or ictalis or idantoil or idantoin or iphenylhydantoin or kessodanten or labopal or lehydan or lepitoin or lepsin or mesantoin or minetoin or neosidantoina or novantoina or novophenytoin or omhidantoina or oxylan or phanantin or phanatine or phenat?ine or phenhydan or phenhydane or phenilep or phent?toin or phenybin or phenydan or phenydantin or phenytek or phenytex or phen?toin* or pyoredol or ritmenal or saceril or sanepil or silantin or sinergina or sodantoin or sodant?on or solant?in or solantyl or sylantoic or tacosal or thilophenyl or toin or vasilcon or zentronal or zentropil).ti,ab.
21	placebo*.ti,ab,sh. or double-blind method/ use ppez or double blind procedure/ use emczd, emcr
22	pregabalin/ use emczd, emcr, ppez or (lyrica or pregabalin).ti,ab.
23	valproic acid/ use emczd, emcr,ppez or (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetate sodium or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetate sodium or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim chrono or epilim chronosphere or epilim enteric or epilim or episenta or epival cr or ergenyl or ergenyl chrono or ergenyl chronosphere or ergenyl retard or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or n dipropylacetic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or semisodium valproate or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or sodium di n propylacetate or sodium dipropyl acetate or sodium dipropylacetate or sodium n dipropylacetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.
24	topiramate/ use emczd, emcr,ppez or (epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab.
25	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
26	or/5-25
27	clinical trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.

#	searches
28	27 use ppez
29	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
30	29 use ppez
31	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
32	31 use emczd, emcr
33	or/28,30,32
34	meta-analysis/
35	meta-analysis as topic/ or systematic reviews as topic/
36	"systematic review"/
37	meta-analysis/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43	(search* adj4 literature).ab.
44	(Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45	cochrane.jw.
46	((pool* or combined) adj2 (data or trials or studies or results)).ab.
47	(or/34-35,38,40-46) use ppez
48	(or/36-39,41-46) use emczd, emcr
49	or/47-48
50	or/33,49
51	4 and 26 and 50
52	limit 51 to english language
53	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
54	53 use emez
55	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)
56	55 use mesz
57	54 or 56
58	52 not 57

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 2 of 12, February 2021; Cochrane Central Register of Controlled Trials, Issue 2 of 12, February 2021

Date of last search 03 February 2021

#	searches
1	mesh descriptor: [epilepsy] explode all trees
2	(epilep* or seizure* or convuls*):ti,ab.
3	mesh descriptor: [epilepsy, tonic-clonic] this term only
4	mesh descriptor: [epilepsy, generalized] this term only
5	(((clonic or “grand mal” or tonic or (tonic near/3 clonic)) near/2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*))):ti,ab.
6	mesh descriptor: [epilepsies, partial] explode all trees
7	((focal or “focal onset” or local or partial or “simple partial”) adj3 (epileps* or seizure*)):ti,ab,kw
8	{or #1-#7}
9	((brivaracetam or brivlera or nubriveo or rikelta)):ti,ab,kw

#	searches
10	mesh descriptor: [carbamazepine] explode all trees
11	((amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol)):ti,ab,kw
12	mesh descriptor: [clobazam] explode all trees
13	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab,kw
14	mesh descriptor: [clonazepam] this term only
15	((aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril)):ti,ab,kw
16	((eslicarbazepin* or aptiom or zebinix)):ti,ab,kw
17	mesh descriptor: [ethosuximide] this term only
18	((emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethylsuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin)):ti,ab,kw
19	mesh descriptor: [vigabatrin] this term only
20	(("4 vinyl 4 aminobutyric acid" or "4 vinylaminobutyric acid" or "4 vinylgaba" or "gamma vinyl 4 aminobutyric acid" or "gamma vinyl gaba" or "gamma vinyl gamma aminobutyric acid" or "gamma vinylgaba" or "n vinyl 4 aminobutyric acid" or "n vinyl gaba" or "n vinyl gamma aminobutyric acid" or vigadrone or sabril or sabrilex or vigabatrin or "gamma vinyl gaba" or "gamma vinyl gamma aminobutyric acid")):ti,ab,kw (word variations have been searched)
21	mesh descriptor: [diet, carbohydrate-restricted] this term only
22	mesh descriptor: [dietary fats] explode all trees
23	mesh descriptor: [glycemic index] explode all trees
24	mesh descriptor: [diet, ketogenic] this term only
25	mesh descriptor: [triglycerides] explode all trees
26	(((adequate near/3 protein*) or atkin* or keto* or kd or (carbohydrate* near/5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulat*)) or ("high fat*" near/5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or "low carb*" or lchf or "low glyc* index treatment*" or lgit or ("medium chain" near/ (tryglyceride* or triglyceride*)) or mct*)):ti,ab,kw
27	mesh descriptor: [lacosamide] this term only
28	((erlosamide or harkoseride or lacosamide or vimpat)):ti,ab,kw
29	mesh descriptor: [lamotrigine] this term only
30	((crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
31	mesh descriptor: [levetiracetam] this term only
32	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
33	mesh descriptor: [oxcarbazepine] this term only
34	((apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin)):ti,ab,kw
35	((fycompa or perampanel)):ti,ab,kw
36	mesh descriptor: [phenobarbital] explode all trees
37	((adonal or aephenal or agrypnal or alepsal or amylofene or andral or aparoxal or aphenylbarbit or aphenyletten or atrofen or austrominal or barbapil or barbellen or barbenyl or barbilettae or barbilixir or barbinal or barbiphen or barbiphenyl or barbivis or barbonal or barbonalett or barbophen or bardorm or bartol or bialminal or calmetten or calminal or carbronal or cardenal or cemalonal or codibarbital or coronaletta or cratecil or damoral or dezibarbitur or dormina or dormiral or dromural or ensobarb or ensodorm or epanal or epidorm or epilol or episedal or epsylone or eskabarb or etilfen or euneryl or fenbital or fenemal or fenobarbital or fenolbarbital or fenosed or fenylettae or gardenal* or gardepanyl or glysoletten or haplopan or haplos or helional or hennoletten or hypnaletten or "hypno tablinetten" or "hypnogen fragner" or hypnolone or hypno-tablinetten or hypnotal or hypnotalon or hysteps or hysteps or lefebar or leonal or lephebar or lepinal or lethyl or linasen or liquital or lixophen or lubergal or lubrokal or lumesettes or lumesyn or luminal or luminale or luminaletas or luminalette or luminaletten or luminalettes or luminalum or lumofridetten or luphenil or luramin or menobarb or molinal or "monosodium salt" or neurobarb or nirvonal or noptil or "nova pheno" or nunol or parkotal or pharmetten or "phen bar" or phenaemal or phenemal or "phenethylbarbital sodium" or phenobal or phenobarb or phenobarbital or phenobarbitol or phenobarbiton or phenobarbitone or phenobarbitural or phenobarbyl or phenonyl or phenotal or phenoturic or phenoyl or "phenyl ethyl barbituric acid" or phenylbarbital or "phenylethyl barbituric acid" or "phenylethylbarbituric acid" or "phenylethylmalonyl urea" or phenylethylmalonylurea or phenyletten or phenyral or polcominal or promptonal or "seda tablinen" or sedabar or sedicat or sedizorin or sedlyn or sedofen or sedonal or sedonettes or seneval or sevenal or "sombutol mcclung" or somnolens or somnoletten or somnosan or somonal or spasepilin or starifen or starilettae or stental or teolaxin or theolaxin or triabarb or tridezibarbitur or uni-feno or versomnal or wakobital or zadoletten or zadonal)):ti,ab,kw
38	mesh descriptor: [phenytoin] this term only

#	searches
39	((alepsin or aleviatin or antilepsin or antisacer or cansoin or citrullamon or comital or cumatil or danten or dantoin or denyl or “di hydan” or difenin or difetoin or differenin or difhydan or dihydan or dilantin or dilantin or dintoin or dintoina or diphantoin* or diphedal or diphedan or “di-phen” or diphenin* or diphentoin or “diphenyl hydantoin” or diphenylan or diphenyldantoin or diphenylhydantoin* or diphenytoin or ditoin or ditomed or ekko or epamin or epanutin or epelin or epilan or epilantin or eptal or eptoin or felantin or fenantoin or fenatoin or fenidantoin or fenitoin or fenytoin* or hidanil or hidantal or hydantin or hydantinal or hydantoinal or hydantol or idantoin or lehydan or lepitoin or minetoin or neosidantoina or phenhydan or phenhydane or phenilep or phentytoin or phenybin or phenydan or phenydantin or phenytek or phenytex or phenytoin* or pyoredol or sanepil or sodantoin or sodanton or solantoin or solantyl or tacosal or vasilcon or zentropil)):ti,ab,kw
40	mesh descriptor: [placebox] this term only
41	mesh descriptor: [double-blind method] this term only
42	placebo*.:ti,ab,kw.
43	mesh descriptor: [pregabalin] this term only
44	((lyrica or pregabalin)):ti,ab,kw
45	mesh descriptor: [valproic acid] this term only
46	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or “di n propylacetate” or “di n propylacetate sodium” or “di n propylacetic acid” or diplexil or “dipropyl acetate” or “dipropyl acetic acid” or dipropylacetate or “dipropylacetate sodium” or “dipropylacetatic acid” or “dipropylacetic acid” or diprosin or divalproex or epilam or epilex or “epilim chrono” or “epilim chromosphere” or “epilim enteric” or epilim or episenta or “epival cr” or ergenyl or “espa valept” or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or “myproic acid” or “n dipropylacetic acid” or orfil or orfiril or orlept or petilin or “propylisopropylacetic acid” or propymal or “semisodium valproate” or “sodium 2 propylpentanoate” or “sodium 2 propylvalerate” or “sodium di n propyl acetate” or “sodium di n propylacetate” or “sodium dipropyl acetate” or “sodium dipropylacetate” or “sodium n dipropylacetate” or stavzor or “valberg pr” or valcote or valepil or valeptol or valerin or “valhel pr” or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or “valproic acid” or valprosid or valprotek or valsup or vupral)):ti,ab,kw
47	mesh descriptor: [topiramate] this term only
48	((epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)):ti,ab,kw
49	mesh descriptor: [zonisamide] this term only
50	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
51	{or #9-#50}
52	#8 and #51

Database(s): DARE; HTA database - CRD
Date of last search: 03 February 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor epilepsy, tonic-clonic this term only
3	mesh descriptor epilepsy, generalized this term only
4	mesh descriptor epilepsies, partial explode all trees
5	(epilep* or seizure* or convuls*):ti,ab.
6	(((clonic or “grand mal” or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
7	((focal or “focal onset” or local or partial or “simple partial”) near2 (epileps* or seizure*))
8	#1 or #2 or #3 or #4 or #5 or #6 or #7

Economic

Database(s): MEDLINE & Embase (Multifile) - OVID
Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021
Date of last search: 31 March 2021

Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab.
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab.
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.

#	searches
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD

Date of last search: 31 March 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or ("continous spike wave of slow sleep" or "infant* spasm*")
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or "petit mal*" or pyknolepsy or "typical absence*")
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or "brief seizure" or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only
10	(bcects or bects or brec or "benign epilepsy" or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or "temporal-central focal") near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or "myoclonic astatic" or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 "eyelid myoclonia") or (ige near2 phantom absenc*) or "impulsive petit mal" or (janz near3 (epilep* or "petit mal")) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or "perioral myoclon*")
13	mesh descriptor spasms, infantile this term only
14	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal"or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or "lennox gastaut" or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	("child* epileptic encephalopath*" or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or "progressive familial epilep*" or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or "muscle jerk")
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or "doose* syndrome" or mae or "generali?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or "focal onset" or local or partial or "simple partial") near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or "grand mal" or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

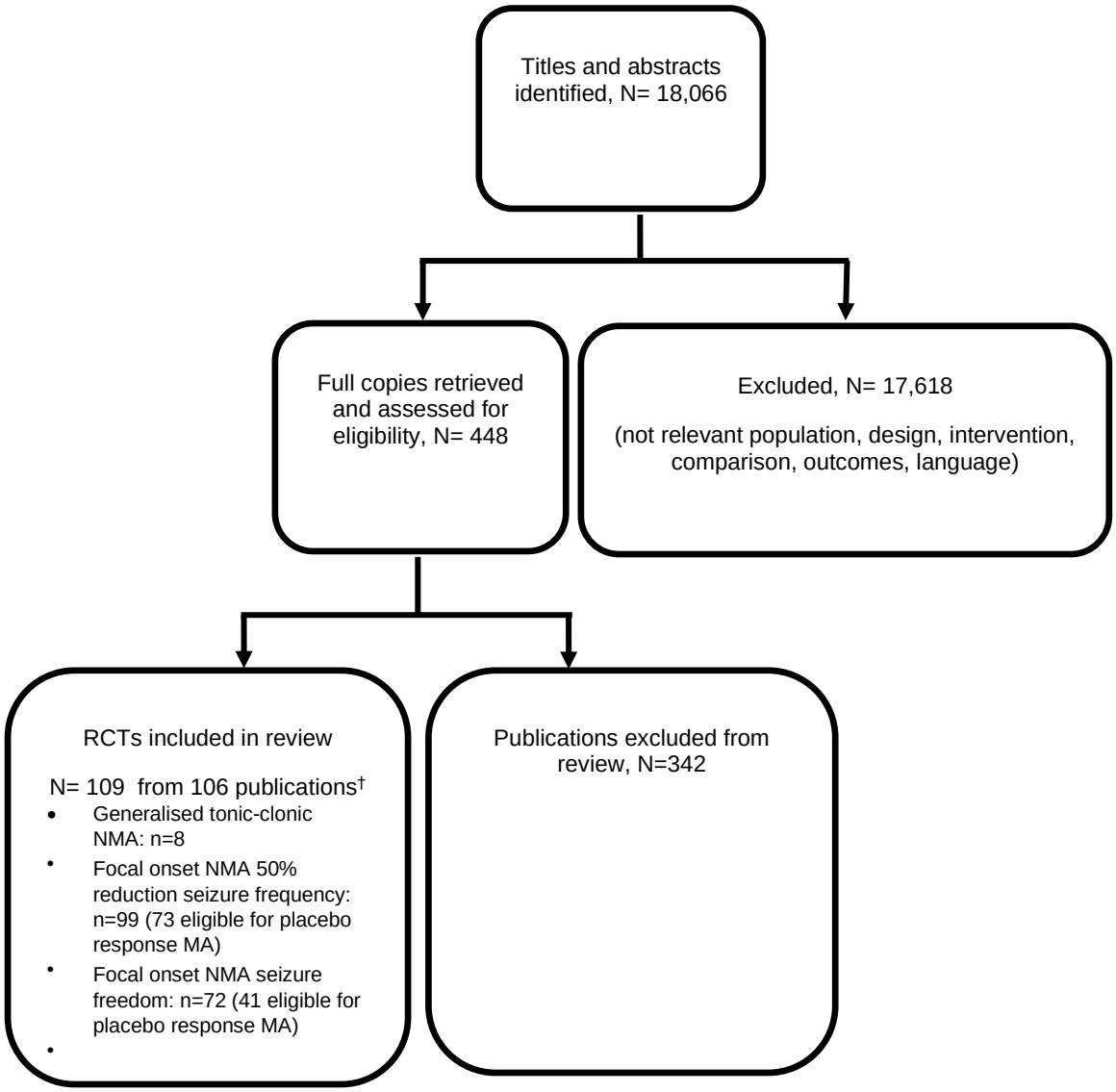
1
2
3
4

Appendix C – Clinical evidence study selection

Study selection for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?



MA: meta-analysis; NMA: network Meta-analysis; RCT: randomised controlled trial
†*study (Kwan 2014) reported outcomes in a disaggregated form for both focal and generalised tonic-clonic seizures*

1 Appendix D – Clinical evidence tables

2 Evidence tables for review questions:

3 What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

4 What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

5 **Table 3: Clinical evidence table for the focal seizures network meta-analyses**

Study	Intervention	Control	Number trial participant		50% reduction in seizure frequency		Seizure Freedom	
			Intervention	Control	Intervention	Control	Intervention	Control
Klein 2015	Brivaracetam	Placebo	505	263	192	56	23	2
Biton 2014	Brivaracetam	Placebo	301	99	77	16	6	0
Kwan 2014	Brivaracetam	Placebo	323	108	98	18	5	0
Ryvlin 2014	Brivaracetam	Placebo	298	100	90	20	6	0
Van Paesschen 2013	Brivaracetam	Placebo	105	52	35	9	8	1
French 2010	Brivaracetam	Placebo	154	54	68	9	12	1
Halford 2011	Carisbamate	Placebo	362	185	116	48	19	4
Sperling (Study1) 2010	Carisbamate	Placebo	379	186	86	39	NR	NR
Sperling (Study2) 2010	Carisbamate	Placebo	373	188	110	33	NR	NR
Chung 2020	Cenobamate	Placebo	113	108	63	23	32	10
Krauss 2020	Cenobamate	Placebo	329	102	157	26	35	1
Kirkham 2020	Eslicarbazepine Acetate	Placebo	134	129	41	40	NR	NR
Jozwiak 2018	Eslicarbazepine Acetate	Placebo	83	40	42	10	18	2

Sperling 2015	Eslicarbazepine Acetate	Placebo	427	224	153	51	9	2
Ben-Menachem 2010	Eslicarbazepine Acetate	Placebo	295	100	92	13	13	1
Elger 2009	Eslicarbazepine Acetate	Placebo	300	102	98	20	14	2
Gil-Nagel 2009	Eslicarbazepine Acetate	Placebo	165	87	58	19	7	1
French 2016	Gabapentin	Pregabalin	242	242	140	134	NR	NR
Yamauchi 2006	Gabapentin	Placebo	127	82	20	5	0	0
Appleton 1999	Gabapentin	Placebo	119	128	24	21	3	1
Anhut 1994	Gabapentin	Placebo	163	109	36	10	NR	NR
Sivenius 1991	Gabapentin	Placebo	27	18	5	3	NR	NR
UK Gabapentin Study Group 1990	Gabapentin	Placebo	61	66	14	6	NR	NR
Sperling 2017	Ganaxolone	Placebo	98	49	26	6	1	1
Farkas 2019	Lacosamide	Placebo	171	172	90	56	23	15
Hong 2016	Lacosamide	Placebo	363	184	158	36	18	0
Chung 2010	Lacosamide	Placebo	301	104	117	19	9	0
Halász 2009	Lacosamide	Placebo	322	163	120	41	8	3
Ben-Menachem 2007	Lacosamide	Placebo	321	97	120	21	7	0
Baulac 2010	Lamotrigine	Pregabalin	141	152	34	54	4	6
		Placebo		141		30		1
Labiner 2009	Lamotrigine	Levetiracetam	132	136	NR	NR	29	28
Naritoku 2007	Lamotrigine	Placebo	121	122	61	31	20	6
Blum 2006	Lamotrigine	Topiramate	96	96	NR	NR	39	55
Matsuo 1993	Lamotrigine	Placebo	143	73	33	12	12	1

Lee 2019	Levetiracetam	Topiramate	177	166	120	112	62	37
Inoue 2015	Levetiracetam	Placebo	281	70	59	8	6	0
Zaccara 2014	Levetiracetam	Pregabalin	255	254	139	130	38	19
Levisohn 2009	Levetiracetam	Placebo	64	34	40	14	30	3
Peltola 2009	Levetiracetam	Placebo	79	79	34	23	8	1
Piña-Garza 2009	Levetiracetam	Placebo	60	56	25	10	7	3
Wu 2009	Levetiracetam	Placebo	103	103	57	26	11	2
Xiao 2009	Levetiracetam	Placebo	28	28	13	11	3	2
Zhou 2008	Levetiracetam	Placebo	14	14	8	2	1	0
Glauser 2006	Levetiracetam	Placebo	101	97	45	19	7	1
Tsai 2006	Levetiracetam	Placebo	47	47	20	5	4	0
Ben-Menachem 2000	Levetiracetam	Placebo	181	105	76	18	15	1
Betts 2000	Levetiracetam	Placebo	80	39	21	5	6	1
Cereghino 2000	Levetiracetam	Placebo	199	95	70	10	11	0
Shorvon 2000	Levetiracetam	Placebo	212	112	53	11	7	1
Rentmeester 1991	Loreclezole	Placebo	32	30	6	0	NR	NR
Bauer 2001	Losigamone	Placebo	99	104	22	15	NR	NR
Fujiwara 2019	Oxcarbazepine	Placebo	48	51	11	2	NR	NR
French 2014	Oxcarbazepine	Placebo	245	121	94	34	20	4
Barcs 2000	Oxcarbazepine	Placebo	521	173	205	22	61	1
Glauser 2000	Oxcarbazepine	Placebo	138	129	57	28	5	1
Nishida 2018	Perampanel	Placebo	531	176	181	34	20	1

French 2013	Perampanel	Placebo	250	136	84	20	9	2
French 2012	Perampanel	Placebo	266	121	98	32	5	0
Krauss 2012	Perampanel	Placebo	521	184	145	33	19	2
Krauss (study 206) 2012	Perampanel	Placebo	102	51	31	11	NR	NR
Krauss (study 208) 2012	Perampanel	Placebo	38	10	15	2	NR	NR
Antinew 2019	Pregabalin	Placebo	201	94	69	21	NR	NR
French 2014	Pregabalin	Placebo	215	110	88	39	NR	NR
Lee 2009	Pregabalin	Placebo	119	59	55	19	5	2
Beydoun 2005	Pregabalin	Placebo	215	98	98	9	17	0
Elger 2005	Pregabalin	Placebo	268	73	101	6	8	1
Arroyo 2004	Pregabalin	Placebo	191	97	54	6	NR	NR
French 2003	Pregabalin	Placebo	355	100	121	14	NR	NR
Sun 2009	Primidone	Sodium Valproate	68	68	23	35	11	18
Lim 2016	Retigabine	Placebo	50	25	14	1	4	0
French 2011	Retigabine	Placebo	153	152	68	27	3	0
Brodie 2010	Retigabine	Placebo	359	179	131	31	12	2
Porter 2007	Retigabine	Placebo	301	96	88	15	0	0
Biton 2011	Rufinamide	Placebo	176	181	52	25	NR	NR
Elger 2010	Rufinamide	Placebo	514	133	60	12	NR	NR
Brodie 2009	Rufinamide	Placebo	156	157	44	29	6	3
Palhagen 2001	Rufinamide	Placebo	25	25	9	3	NR	NR
Elger 2017	Selurampanel	Placebo	68	25	19	4	4	1

	(BGG492)							
Willmore 1996	Sodium Valproate	Placebo	74	63	28	12	6	1
Fritz 2005	Tiagabine	Topiramate	21	20	4	7	1	2
CramerA 2001	Tiagabine	Phenytoin	105	101	23	28	NR	NR
CramerB 2001	Tiagabine	Carbamazepine	67	76	14	33	NR	NR
Kalviainen 1998	Tiagabine	Placebo	77	77	11	5	NR	NR
Uthman 1998	Tiagabine	Placebo	206	91	38	4	NR	NR
Sachdeo 1997	Tiagabine	Placebo	211	107	54	9	NR	NR
Chung 2014	Topiramate	Placebo	124	125	47	29	4	2
Zhang 2011	Topiramate	Placebo	46	40	22	3	8	1
Kerr 2005	Topiramate	Placebo	37	35	11	9	NR	NR
Guberman 2002	Topiramate	Placebo	171	92	75	22	NR	NR
Elterman 1999	Topiramate	Placebo	41	45	16	9	2	0
Lee 1999	Topiramate	Placebo	91	86	45	11	7	1
Faught 1996	Topiramate	Placebo	136	45	54	8	NR	NR
Privitera 1996	Topiramate	Placebo	143	47	58	4	NR	NR
Sharief 1996	Topiramate	Placebo	23	24	8	2	2	0
Bruni 2000	Vigabatrin	Placebo	58	53	28	14	5	2
Dean 1999	Vigabatrin	Placebo	129	45	55	3	9	0
Grunewald 1994	Vigabatrin	Placebo	22	23	9	4	NR	NR
Lu 2011	Zonisamide	Placebo	53	51	29	18	3	1
Brodie 2005	Zonisamide	Placebo	231	120	88	20	6	2
Sackellares 2004	Zonisamide	Placebo	78	74	21	12	NR	NR

Faught 2001 *NR: not reported*	Zonisamide	Placebo	118	85	41	16	6	2	

Table 4: Clinical evidence tables for the generalised tonic-clonic seizure network meta-analyses

Study	Intervention	Control	Number trial participant		50% reduction in seizure frequency		Seizure Freedom	
			Intervention	Control	Intervention	Control	Intervention	Control
Kwan(2014)	Brivaracetam	Placebo	36	13	16	2	2	0
Vossler(2020)	Lacosamide	Placebo	121	121	82	63	43	26
Biton(2010)	Lamotrigine	Placebo	76	77	57	32	15	7
Biton(2005)	Lamotrigine	Placebo	58	59	37	23	12	10
Wu(2018)	Levetiracetam	Placebo	126	125	91	31	32	3
Berkovic(2007)	Levetiracetam	Placebo	80	84	54	37	13	2
French(2015)	Perampanel	Placebo	81	81	52	31	26	10
Biton(1999)	Topiramate	Placebo	41	39	18	7	2	0

For a full discussion of the clinical evidence see appendix M.

Appendix E – Forest plots

Forest plots for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

The below forest plots are for the network meta-analysis which was considered by the committee to provide the best fit for the identified evidence. Full forest plots are available in appendix M.

Figure 1: Forest plot of effect estimates and 95% credible intervals for 50% reduction in seizure frequency compared to placebo in focal seizures in the adjusted NMA

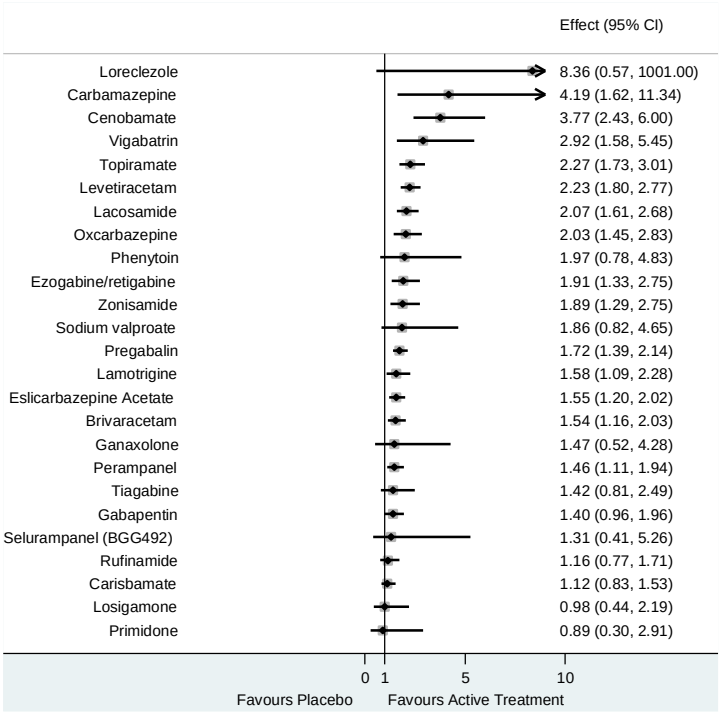
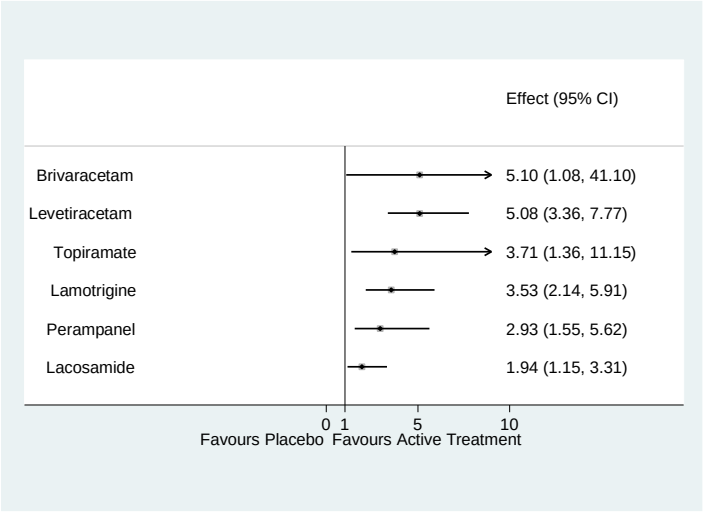


Figure 2: Forest plot of effect estimates and 95% credible intervals for 50% reduction in seizure frequency compared to placebo in GTC seizures fixed effects NMA



Appendix F – GRADE tables

GRADE tables for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

No assessments using GRADE were done for outcomes included in this review. For discussion of the strength of outcomes from the network meta-analyses please see appendix M.

Appendix G – Economic evidence study selection

Economic evidence study selection for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

One economic model was created to answer the review questions for both monotherapy and add-on therapy. See supplementary material 4.

Appendix K – Excluded studies

Excluded studies for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

Study	Reason for Exclusion
Absence seizures: ethosuximide versus valproic acid versus lamotrigine, Archives of Disease in Childhood, 95, 599â€• , 2010	No outcomes of interest
Adjunctive eslicarbazepine acetate: a pooled analysis of three phase III trials, Epilepsy & Behavior, 72, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Comparative Clinical Trial of Gabapentin and Sodium Valproate as Add-on Therapy in Refractory Partial Epilepsies: open Randomized Multicenter Trial, Journal of korean epilepsy society, 4, 19â€• 26, 2000	Article in Korean
Tolerability of adjunctive eslicarbazepine acetate according to concomitant lamotrigine or carbamazepine use: a subgroup analysis of three phase III trials in adults with focal (partial-onset) seizures, Epilepsy Research, 147, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Abou-Khalil, B., Rogin, J. B., Biraben, A., Andrea Galimberti, C., Kowacs, P., Hong, S. B., Blum, D., Nunes, T., Da Silva, P. S., Grinnell, T., et al.,, Eslicarbazepine acetate as adjunctive therapy in patients with refractory partialonset seizures: safety results of a 12-week randomized placebo-controlled study <after the author list please add: >, on behalf of the 304 study team, Epilepsy currents., 14, 210â€• 211, 2014	Conference abstract
Abril Jaramillo, Javier, Estevez Maria, Jose Carlos, Giron Ubeda, Juan Miguel, Vega Lopez, Oscar, Calzado Rivas, Maria Elena, Perez Diaz, Hernando, Garcia Martin, Guillermina, Vila Herrero, Elena, Chamorro-Munoz, M., Vazquez, F., De la Fuente, C., Redondo, L., Pelaez, N., Santagueda, Patricia, Rodriguez Uranga, Juan Jesus, Effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal seizures in the routine clinical practice: Spain prospective study (PERADON), Epilepsy & behavior : E&B, 102, 106655, 2020	No a RCT
Ahadi, P., Nasiri, J., Ghazavi, M., Mosavian, T., Mansouri, V., A comparative study on the efficacy of levetiracetam and carbamazepine in the treatment of rolandic seizures in children: An open-label randomized controlled trial, Journal of Research in Pharmacy Practice, 9, 68-72,	No add-on therapy

Study	Reason for Exclusion
2020	
Al-Bachari,S., Pulman,J., Hutton,J.L., Marson,A.G., Gabapentin add-on for drug-resistant partial epilepsy, Cochrane Database of Systematic Reviews, -, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Aldenkamp, A. P., Baker, G., Mulder, O. G., Chadwick, D., Cooper, P., Doelman, J., Duncan, R., Gassmann-Mayer, C., de Haan, G. J., Hughson, C., et al.,, A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures, Epilepsia, 41, 1167â€• 1178, 2000	No outcomes of interest
Allen, J. W., Oxley, J., Robertson, M. M., Clobazam as adjunctive treatment in refractory epilepsy, British Medical Journal, 286, 1246-1247, 1983	Cross-over study design
Alsaad, A. M. S., Koren, G., Exposure to rufinamide and risks of CNS adverse events in drug-resistant epilepsy: A meta-analysis of randomized, placebo-controlled trials, British Journal of Clinical Pharmacology, 78, 1264-1271, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Alving, J., Kristensen, O., Tsiropoulos, I., Mondrup, K., Double-blind placebo-controlled evaluation of flunarizine as adjunct therapy in epilepsy with complex partial seizures, Acta Neurologica Scandinavica, 79, 128-132, 1989	Cross-over study design
Anonymous,, Correction to Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial (The Lancet Neurology (2020) 19(1) (38-48), (S1474442219303990), (10.1016/S1474-4422(19)30399-0)), The Lancet Neurology, 19, e3, 2020	No RCT
Antinew, J., Pitrosky, B., Knapp, L., Almas, M., Farkas, V., Farkas, M. K., Adjunctive treatment with pregabalin for partial onset seizures in paediatric patients: a randomized controlled trial, Epilepsia, 58, S79â€• , 2017	Conference Abtract
Arnold, S., Laloyaux, C., Schulz, A. L., Elmoufti, S., Yates, S., Fakhoury, T., Long-term safety and efficacy of brivaracetam in adults with focal seizures: Results from an open-label, multinational, follow-up trial, Epilepsy Research, 166, 106404, 2020	No add-on therapy
Bacia, T., Purska-Rowinska, E., Okuszko, S., Clonazepam in the treatment of drug-resistant epilepsy: a clinical short and long term follow-up study, Monographs in Neural Sciences, 5, 153-9, 1980	No a RCT
Battaglia, A., Ferrari, A. R., Guerrini, R., Double-blind placebo-controlled trial of flunarizine as add-on therapy in refractory childhood epilepsy, Brain & Development, 13, 217â€• 222, 1991	No population (of the 12 people included in trial, 6 (50%) had Lennox-Gastaut syndrome)

Study	Reason for Exclusion
Benbadis, S., Carreno, M., Striano, S., Sousa, R., Rocha, F., Blum, D., Cheng, H., Lack of exacerbation of partial-onset seizures during adjunctive treatment with eslicarbazepine acetate: a pooled analysis of three phase iii controlled trials, Epilepsy currents., 15, 151, 2015	Conference abstract
Ben-Menachem, E., Baulac, M., Hong, S. B., Cleveland, J. M., Reichel, C., Schulz, A. L., Wagener, G., Brandt, C., Safety, tolerability, and efficacy of brivaracetam as adjunctive therapy in patients with focal seizures, generalized onset seizures, or Unverricht-Lundborg disease: An open-label, long-term follow-up trial, Epilepsy Research, 170, 106526, 2021	No RCT (extension trial of a RCT)
Ben-Menachem, E., Gunning, B., Arenas Cabrera, C. M., Van Landingham, K., Crockett, J., Taylor, L., Critchley, D., Tayo, B., Morrison, G., Toledo, M., A phase 2 trial to explore the potential for a pharmacokinetic drug-drug interaction with valproate when in combination with cannabidiol in adult epilepsy patients, Epilepsia, 59 (Supplement 3), S51, 2018	No outcome of interest
Ben-Menachem, E., Mameniskiene, R., Quarato, P. P., Klein, P., Gamage, J., Schiemann, J., Johnson, M. E., Whitesides, J., McDonough, B., Eckhardt, K., Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies, Neurology, 87, 314-23, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ben-Menachem, E., MameniÅ¡kienÄ—, R., Quarato, P. P., Klein, P., Gamage, J., Schiemann, J., Johnson, M. E., Whitesides, J., McDonough, B., Eckhardt, K., Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies, Neurology, 87, 314â€• 323, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bensch, J., Blennow, G., Ferngren, H., Gamstorp, I., Herrlin, K. M., Kubista, J., Arvidsson, A., Dahlstrom, H., A double-blind study of clonazepam in the treatment of therapy-resistant epilepsy in children, Developmental Medicine & Child Neurology, 19, 335-42, 1977	Cross-over study design
Beran, R. G., Berkovic, S. F., Buchanan, N., Danta, G., Mackenzie, R., Schapel, G., Sheean, G., Vajda, F., Cooper, B., A double-blind, placebo-controlled crossover study of vigabatrin 2 g/day and 3 g/day in uncontrolled partial seizures, Seizure, 5, 259-265, 1996	Cross-over study design
Beran, R. G., Berkovic, S. F., Dunagan, F. M., Vajda, F. J. E., Danta, G., Black, A. B., Mackenzie, R., Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy, Epilepsia, 39, 1329-1333, 1998	Cross-over study design
Beran,, Rg,, Berkovic, S. F., Dunagan, F. M., Vajda, F. J. E., Danta, G., Black, A. B., Double-blind placebo-controlled cross-over study of	Conference abstract

Study	Reason for Exclusion
lamotrigine in treatment-resistent epilepsy, Journal of Clinical Neuroscience, 4, 384, 1997	
Bergqvist, A. G. C., Schall, J. I., Gallagher, P. R., Cnaan, A., Stallings, V. A., Fasting versus gradual initiation of the ketogenic diet: A prospective, randomized clinical trial of efficacy, Epilepsia, 46, 1810-1819, 2005	no add-on therapy
Binnie, C. D., Beintema, D. J., Debets, R. M. C., Van Emde Boas, W., Meijer, J. W. A., Meinardi, H., Peck, A. W., Westendorp, A. M., Yuen, W. C., Seven day administration of lamotrigine in epilepsy: Placebo-controlled add-on trial, Epilepsy Research, 1, 202-208, 1987	Cross-over study design
Binnie, C. D., Debets, R. M., Engelsman, M., Meijer, J. W., Meinardi, H., Overweg, J., Peck, A. W., Van Wieringen, A., Yuen, W. C., Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy, Epilepsy Research, 4, 222â€• 229, 1989	Cross-over study design
Biraben, A., Beaussart, M., Josien, E., Pestre, M., Savet, J. F., Schaff, J. L., Tourniaire, D., Sevestre, M., Renault-Djouadi, J., Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study, Epileptic Disorders, 3, 91â€• 100, 2001	No relevant to PICO (the aim was to compare two dose regimens of tiagabine: two times daily versus three times daily)
Birket-Smith, E., Lund, M., Mikkelsen, B., Vestermark, S., Olsen, P. Z., Holm, P., A controlled trial on Ro 5-4023 (clonazepam) in the treatment of psychomotor epilepsy, Acta Neurologica Scandinavica. Supplementum, 53, 18-25, 1973	Cross-over study design
Biton, V., Gil-Nagel, A., Isojarvi, J., Doty, P., Hebert, D., Fountain, N. B., Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials, Epilepsy & Behavior, 52, 119-27, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Biton, V., Krauss, G., Blum, D., Sousa, R., Grinnell, T., Efficacy of eslicarbazepine acetate in patients with refractory partial onset seizures: a pooled analysis of three phase iii controlled studies, Epilepsy currents., 14, 209â€• 210, 2014	Conference abstract
Blatt, I., Chung, S. S., Hogan, R. E., Clark, A., Anders, B., Halvorsen, M., Efficacy and safety of usl255, once-daily extended-release topiramate, in adults with partial onset seizures: the prevail study, Epilepsia, 55, 42â€• 43, 2014	Conference abstract
Blatt, I., Nagaraddi, V. N., Anders, B., Clark, A. M., Halvorsen, M. B., Hogan, R. E., USL255 is efficacious across all partial-onset seizure types and with a variety of concomitant antiepileptic drugs: results from subgroup analyses of the phase 3 prevail clinical trial, Epilepsy Currents,	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
14, 204, 2014	
Boas, J., Dam, M., Friis, M. L., Kristensen, O., Pedersen, B., Gallagher, J., Controlled trial of lamotrigine (Lamictal) for treatment-resistant partial seizures, Acta Neurologica Scandinavica, 94, 247-252, 1996	Cross-over study design
Boon, P., Chauvel, P., Pohlmann-Eden, B., Otoul, C., Wroe, S., Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy, Epilepsy Research, 48, 77-89, 2002	Cross-over study design
Borges, K., Kaul, N., Germaine, J., Carrasco-Pozo, C., Kwan, P., O'Brien, T. J., Open-label long-term treatment of add-on triheptanoin in adults with drug-resistant epilepsy, Epilepsia Open., 2020	No RCT (extension trial of a RCT)
Borghs, S., Elmoufti, S., Health-related quality of life in double-blind phase iii studies of brivaracetam as adjunctive therapy of partial-onset seizures, Value in Health, 18, A762â€• A763, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bourgeois, B., Leppik, I. E., Sackellares, J. C., Laxer, K., Lesser, R., Messenheimer, J. A., Kramer, L. D., Kamin, M., Rosenberg, A., Felbamate: A double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures, Neurology, 43, 693-696, 1993	No outcome of interest
Brandt, C., Klein, P., Badalamenti, V., Gasalla, T., Whitesides, J., Safety and tolerability of adjunctive brivaracetam in epilepsy: In-depth pooled analysis, Epilepsy and Behavior, Part A. 103 (no pagination), 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brandt, C., Sanchez, J. C., Steinhoff, B., Serratosa, J., Milanov, I., Efficacy and safety of cenobamate in european epilepsy patients with uncontrolled focal-onset seizures, European Journal of Neurology, 27, 148, 2020	Conference abstract
Bresnahan, R., Atimâ€• Oluk, M., Marson, A. G., Oxcarbazepine addâ€• on for drugâ€• resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Hounsome, J., Jette, N., Hutton, J. L., Marson, A. G., Topiramate add-on therapy for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2019 (10) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Martin-McGill, K. J., Hutton, J. L., Marson, A. G., Tiagabine add-on therapy for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2019 (10) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Martin-McGill, K. J., Milburn-McNulty, P., Powell, G., Sills, G. J., Marson, A. G., Sulthiame add-on therapy for epilepsy, Cochrane Database of Systematic Reviews, 2019 (8) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Martin-Mcgill, K. J., Williamson,	Systematic review/meta-analysis of randomised

Study	Reason for Exclusion
J., Michael, B. D., Marson, A. G., Clobazam add-on therapy for drug-resistant epilepsy, Cochrane Database of Systematic Reviews, 2019 (10) (no pagination), 2019	controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Panebianco, M., Marson, A. G., Brivaracetam add-on therapy for drug-resistant epilepsy, Cochrane Database of Systematic Reviews, 2019 (3) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Bresnahan, R., Panebianco, M., Marson, A. G., Lamotrigine add-on therapy for drug-resistant generalised tonic-clonic seizures, Cochrane Database of Systematic Reviews, 2020 (7) (no pagination), 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Brickel, N., Derossett, S., McDonald, S., Cyr, T., Nohria, V., Adams, B., Evaluation of the tolerability of adjunctive retigabine/ezogabine during the recommended titration schedule in adults with partial-onset seizures, Epilepsia, 53, 195â€• 196, 2012	Conference abstract
Brigo, F., Bragazzi, N. L., Nardone, R., Trinka, E., Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs, Seizure, 42, 29-37, 2016	Network meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Del Felice, A., Melatonin as add-on treatment for epilepsy, Cochrane database of systematic reviews (Online), 6, CD006967, 2012	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Igwe, S. C., Bragazzi, N. L., Stiripentol addâ€• on therapy for drugâ€• resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Brigo, F., Igwe, S. C., Bragazzi, N. L., Stiripentol add-on therapy for focal refractory epilepsy, Cochrane Database of Systematic Reviews, 2018 (5) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Igwe, S. C., Del Felice, A., Melatonin as addâ€• on treatment for epilepsy, Cochrane Database of Systematic Reviews, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Lattanzi, S., Igwe, S. C., Behzadifar, M., Bragazzi, N. L., Zonisamide add-on therapy for focal epilepsy, Cochrane Database of Systematic Reviews, 2018 (10) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Lattanzi, S., Igwe, S. C., Behzadifar, M., Bragazzi, N. L., Zonisamide add-on therapy for focal epilepsy, Cochrane Database of Systematic Reviews, 2020, CD001416, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Brodie, M. J., French, J. A., McDonald, S. A., Lee, W. J., Adams, B., Scott, A., Nohria, V., DeRossett, S., Adjunctive use of ezogabine/retigabine with either traditional sodium channel blocking antiepileptic drugs (AEDs) or AEDs with other mechanisms of	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
action: Evaluation of efficacy and tolerability, Epilepsy Research, 108, 989-994, 2014	
Brodie, M. J., Larkin, J. G., Cox, A., Besag, F. M., A double-blind, crossover, placebo-controlled trial of adjuvant nifedipine in refractory epilepsy, British Journal of Clinical Pharmacology, 29, 592Pâ€• 593P, 1990	Conference abstract
Brodie, M. J., Whitesides, J., Schiemann, J., D'Souza, J., Johnson, M. E., Tolerability, safety, and efficacy of adjunctive brivaracetam for focal seizures in older patients: A pooled analysis from three phase III studies, Epilepsy Research, 127, 114-118, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Buckley, C. T., Waters, O. R., DeMaagd, G., Cenobamate: A New Adjunctive Agent for Drug-Resistant Focal Onset Epilepsy, The Annals of pharmacotherapy, 1060028020941113, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Callaghan, N., Goggin, T., Adjunctive therapy in resistant epilepsy, Epilepsia, 29 Suppl 1, S29-35, 1988	No RCT
Carmichael, K., Pulman, J., Lakhan, S. E., Parikh, P., Marson, A. G., Zonisamide add-on for drug-resistant partial epilepsy, Cochrane Database of Systematic Reviews, 2013 (12) (no pagination), 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Cereghino, J. J., Brock, J. T., Van Meter, J. C., Penry, J. K., Smith, L. D., White, B. G., Carbamazepine for epilepsy. A controlled prospective evaluation, Neurology, 24, 401-10, 1974	No RCT
Chang, X. C., Yuan, H., Wang, Y., Xu, H. Q., Hong, W. K., Zheng, R. Y., Eslicarbazepine acetate addâ€• on for drugâ€• resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Chang, X. C., Yuan, H., Wang, Y., Xu, H. Q., Zheng, R. Y., Eslicarbazepine acetate add-on for drug-resistant partial epilepsy, Cochrane database of systematic reviews (Online), 12, CD008907, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Chappell, A. S., Sander, J. W., Brodie, M. J., Chadwick, D., Lledo, A., Zhang, D., Bjerke, J., Kiesler, G. M., Arroyo, S., A crossover, add-on trial of talampanel in patients with refractory partial seizures, Neurology, 58, 1680-1682, 2002	Cross-over study design
Charokopou, M., Harvey, R., Srivastava, K., Brandt, C., Borghs, S., Relative performance of brivaracetam as adjunctive treatment of focal seizures in adults: a network meta-analysis, Current Medical Research and Opinion, 35, 1345-1354, 2019	Network meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Chen, D., Bian, H., Zhang, L., A meta-analysis of levetiracetam for randomized placebo-controlled trials in patients with refractory epilepsy, Neuropsychiatric Disease and	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
Treatment, 15, 905-917, 2019	
Chen, D., Chen, T., Zhang, Q., Lin, Y., Si, Y., Zhang, W. W., Xu, D., Liu, L., Dose effects of lacosamide as add-on therapy for partial-onset seizure in adult, Neurological Sciences, 37, 907-920, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Chen, H., He, H., Xiao, Y., Luo, M., Luo, H., Wang, J., Losigamone add-on therapy for focal epilepsy, Cochrane Database of Systematic Reviews, 2019 (12) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Cheng, H., Tosiello, R., Blum, D., Determination of the minimal clinically important difference (MCID) in seizure frequency in three phase iii trials of adjunctive eslicarbazepine acetate (ESL) for partial-onset (focal) seizures (POS), Neurology, 90, 2018	Conference abstract
Chiron, C., Tran, A., Rey, E., d'Athis, P., Vincent, J., Tonnelier, S., Marchand, M. C., Dulac, O., Pons, G., Stiripentol in childhood partial epilepsy: a placebo-controlled trial, Epilepsia, 41 Suppl 7, 191, 2000	Conference abstract
Chung, S. S., A review of the efficacy and safety of extended-release topiramate in the adjunctive treatment for refractory partial-onset seizures, Therapeutic Advances in Neurological Disorders, 8, 131-136, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Chung, S. S., Fakhoury, T. A., Anders, B., Laine, D., Arnold, S., Halvorsen, M. B., Usl255, a once-Daily, extended-Release topiramate, is efficacious as an adjunctive therapy for refractory partial-onset seizures: results from the randomized phase 3 prevail clinical trial, Epilepsy Currents, 14, 104, 2014	Conference abstract
Chung, S., Fakhoury, T., Arnold, S., Lawson, B., Blatt, I., Clark, A., Halvorsen, M., Nagaraddi, V., Anders, B., Efficacy, safety, and impact on quality of life of USL255 in patients with refractory partial-onset seizures: the prevail study, Neurology, 82, 2014	Conference abstract
Chung, S., Hogan, R. E., Blatt, I., Lawson, B., Halvorsen, M., Efficacy and safety of USL255, Qudexy® XR (Topiramate) extended-release capsules, and second-generation AEDs, Neurology, 88, 2017	Conference abstract
Coppola, G., Iervolino, G., Mastrosimone, M., La Torre, G., Ruiu, F., Pascotto, A., Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial, Brain & Development, 26, 373-6, 2004	Cross-over study design
Coppola, G., Pascotto, A., Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy, Brain and Development, 18, 50-52, 1996	Cross-over study design

Study	Reason for Exclusion
Cosi, V., Callieco, R., Galimberti, C. A., Tartara, A., Lanzi, G., Balottin, U., Perucca, E., Effect of Vigabatrin (gamma-vinyl-GABA) on visual, brainstem auditory and somatosensory evoked potentials in epileptic patients, European Neurology, 28, 42-46, 1988	Cross-over study design
Craig, D., Rice, S., Paton, F., Fox, D., Woolacott, N., Retigabine for the adjunctive treatment of adults with partial-onset seizures in epilepsy with and without secondary generalization: A NICE single technology appraisal, PharmacoEconomics, 31, 101-110, 2013	Review (NICE technology appraisal) of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Crawford, P., Meinardi, H., Brown, S., Rentmeester Th, W., Pedersen, B., Pedersen, P. C., Lassen, L. C., Tiagabine: Efficacy and safety in adjunctive treatment of partial seizures, Epilepsia, 42, 531-538, 2001	Cross-over study design
Cretin, B., Hirsch, E., Adjunctive antiepileptic drugs in adult epilepsy: how the first add-on could be the last, Expert Opinion on Pharmacotherapy, 11, 1053-67, 2010	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Cross, J. H., Auvin, S., Patten, A., Giorgi, L., Safety and tolerability of zonisamide in paediatric patients with epilepsy, European Journal of Paediatric Neurology, 18, 747-758, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Dahlin, M., Knutsson, E., Amark, P., Nergardh, A., Reduction of epileptiform activity in response to low-dose clonazepam in children with epilepsy: A randomized double-blind study, Epilepsia, 41, 308-315, 2000	Cross-over study design
Dalla Bernardina, B., Fontana, E., Vigevano, F., Fusco, L., Torelli, D., Galeone, D., Buti, D., Cianchetti, C., Gnanasakthy, A., Iudice, A., Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study, Epilepsia, 36, 687-91, 1995	No RCT
Dalziel, S. R., Borland, M. L., Furyk, J., Bonisch, M., Neutze, J., Donath, S., Francis, K. L., Sharpe, C., Harvey, A. S., Davidson, A., et al.,, Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial, Lancet (london, england), 393, 2135â€• 2145, 2019	No relevant to PICO (the aim was to determine whether phenytoin or levetiracetam is the superior second-line treatment for paediatric convulsive status epilepticus.)
Dasari, A., Bansal, D., Gudala, K., Brivaracetam add-on therapy for epilepsy: Evidence based meta-analysis and meta-regression of randomized controlled trials, Journal of Neurological Sciences, 34, 1-15, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
De Goede, C. G., Gupta, R., Antiepileptic drugs versus no treatment or placebo for children with benign epilepsy with centro temporal spikes, Cochrane Database of Systematic Reviews, (4) (no pagination), 2007	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
de Pasquet, E. G., Scaramelli, A., de Caceres, M. P., L'Heritier, C., Feldman, S., Santana, R., Aguilar, J., Musch, B., Morselli, P. L., Double-blind, placebo-controlled, cross-over trial of progabide as add-on therapy in epileptic patients, Epilepsia, 32, 133-9, 1991	Cross-over study design
Dincheva, S., Baykoushev, S., Chalukova-Atanassova, N., The effect and side-effects of treatment with antelepsin, Folia Medica (Plovdiv), 26, 38-43, 1984	No a RCT
Dreifuss, F., Cereghino, J., Debrabandere, L., Johnscher, G., Multicenter, double-blind, placebo-controlled trial of ucbL059 (500mg b.i.d. and 1500mg b.i.d.) as add-on therapy in patients with refractory partial epilepsy, Epilepsia, 37 Suppl 5, 204, 1996	Conference abstract
D'Souza, J., Constantine, S., Wamil, A., McCague, K., Improved seizure control when oxcarbazepine is added to sodium channel blockers or other antiepileptic drugs, Epilepsia, 45 Suppl 7, 307â€• 308, 2004	Conference abstract
Elger, C., Koepp, M., Trinka, E., Villanueva, V., Chaves, J., Ben-Menachen, E., Kowacs, P. A., Gil-Nagel, A., Moreira, J., Gama, H., et al.,, Pooled efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: data from four double-blind placebo-controlled pivotal phase III clinical studies, CNS Neuroscience & Therapeutics, 23, 961â€• 972, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Elliott, J., van Katwyk, S., McCoy, B., Clifford, T., Potter, B. K., Skidmore, B., Wells, G. A., Coyle, D., Decision Models for Assessing the Cost Effectiveness of Treatments for Pediatric Drug-Resistant Epilepsy: A Systematic Review of Economic Evaluations, PharmacoEconomics., 2019	No a RCT, Systematic review, references checked
El-Rashidy, O. F., Nassar, M. F., Abdel-Hamid, I. A., Shatla, R. H., Abdel-Hamid, M. H., Gabr, S. S., Mohamed, S. G., El-Sayed, W. S., Shaaban, S. Y., Modified Atkins diet vs classic ketogenic formula in intractable epilepsy, Acta Neurologica Scandinavica, 128, 402â€• 408, 2013	No outcomes of interest
Farkas, V., Steinborn, B., Flamini, J., Dilley, D., Bozorg, A., Daniels, T., Scheffer, I., Efficacy and tolerability of adjunctive lacosamide in children and adolescents with uncontrolled focal seizures: a randomized, double-blind, placebo-controlled trial, Annals of Neurology, 82, S287â€• S290, 2017	Conference Abstract
Feldman, R. G., Hayes, M. K., Browne, T. R., A double-blind comparison of clonazepam with placebo for refractory tonic-clonic seizures, Neurology, 31, 159, 1981	Conference abstract
Fisher, R. S., Sachdeo, R. C., Pellock, J., Penovich, P. E., Magnus, L., Bernstein, P., Rapid initiation of gabapentin: A randomized,	No relevant to PICO (The aim was to compare the tolerability of two different dose-initiation regimens of gabapentin for the adjunctive

Study	Reason for Exclusion
controlled trial, Neurology, 56, 743-748, 2001	treatment of partial seizures)
Fogarasi, Andras, Flamini, Robert, Milh, Mathieu, Phillips, Steven, Yoshitomi, Shinsaku, Patten, Anna, Takase, Takao, Laurenza, Antonio, Ngo, Leock Y., Open-label study to investigate the safety and efficacy of adjunctive perampanel in pediatric patients (4 to <12 years) with inadequately controlled focal seizures or generalized tonic-clonic seizures, Epilepsia, 61, 125-137, 2020	No a RCT
French, J. A., Brodsky, A., von Rosenstiel, P., Efficacy and tolerability of 5, 20 and 50 mg/day brivaracetam (UCB 34714) as adjunctive treatment in adults with refractory partial-onset seizures, Epilepsia, 48 Suppl 6, 400, 2007	Conference abstract
French, J. A., Costantini, C., Brodsky, A., von Rosenstiel, P., Adjunctive brivaracetam for refractory partial-onset seizures, Neurology, 75, 519â€• 525, 2010	Duplicate of star id:1211271
French, J. A., Elger, C., Goldberg-Stern, H., Thomson, A., Krauss, G. L., Squillacote, D., Yang, H., Kumar, D., Perampanel randomized controlled trials in epilepsy: a global phase III program, Epilepsy Currents, 11, 2011	Conference abstract
French, J. A., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T. J., Laurenza, A., Patten, A., et al.,, Adjunctive perampanel (PER) for treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients (PTS) with idiopathic generalized epilepsy (IGE): a double-blind, randomized, placebo-controlled phase III trial, Epilepsy currents., 15, 367, 2015	Conference abstract
French, J. A., Malicsi, M. J. R., Kugler, A. R., Knapp, L. E., Bockbrader, H. N., Garofalo, E. A., Pregabalin adjunctive therapy in patients with partial seizures, Epilepsia, 40 Suppl 7, 106, 1999	Conference abstract
French, J., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T. J., Laurenza, A., Patten, A., et al.,, Adjunctive perampanel for the treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients with idiopathic generalized epilepsy (IGE): a double-blind randomized placebo-controlled phase III trial, Neurology, 84, 2015	Conference Abstract
French, J., Sperling, M., Perucca, E., Losey, T., Shneker, B., DiVentura, B. Y., Belkin, M. I., Hua, L., Paskavitz, J., A randomized, double-blind, placebocontrolled study to evaluate the efficacy, safety and tolerability of VX-765 in patients with treatment-resistant focal seizures, Epilepsy Currents, 14, 440â€• 441, 2014	Conference abstract
French, J., von Rosenstiel, P., Efficacy and tolerability of brivaracetam as adjunctive treatment for adults with refractory partial-onset	Conference abstract

Study	Reason for Exclusion
seizures, Epilepsia, 48 Suppl 7, 78, 2007	
Froscher, W., Bulau, P., Burr, W., Penin, H., Rao, M. L., De Beukelaar, F., Double-blind placebo-controlled trial with flunarizine in therapy-resistant epileptic patients, Clinical Neuropharmacology, 11, 232-240, 1988	Cross-over study design
Gao, L., Xia, L., Zhao, F. L., Li, S. C., Clinical efficacy and safety of the newer antiepileptic drugs as adjunctive treatment in adults with refractory partial-onset epilepsy: A meta-analysis of randomized placebo-controlled trials, Epilepsy Research, 103, 31-44, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Garza-Morales, S. J., Pizarro-Castellanos, M., Sitges-Berrondo, M., Briceno-Gonzalez, E., Ceja-Moreno, H., Rodriguez-Leyva, I., Alonso-Rivera, C., Gongora-Rivera, F., Ruiz-Sandoval, L., Multicenter, double-blind, randomized, placebo-controlled trial of sustainedrelease vinpocetine as adjunctive treatment of focal-onset seizures, Epilepsia., 56, 12, 2015	Conference abstract
Gaston, T. E., Szaflarski, J. P., Cannabis for the Treatment of Epilepsy: an Update, Current Neurology and Neuroscience Reports, 18 (11) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Gericke, C. A., Picard, F., de Saint-Martin, A., Strumia, S., Marescaux, C., Hirsch, E., Efficacy of lamotrigine in idiopathic generalized epilepsy syndromes: a video-EEG-controlled, open study, Epileptic Disorders, 1, 159-65, 1999	No RCT
Gil-Nagel, A., Burdette, D., Hammond, J., VanLandingham, K., Shaikh, S., Seizure-free patients and seizure-free days with retigabine 600-1200 mg/day compared with placebo in adults with drug-resistant epilepsy, Proceedings of the 64th annual meeting of the american epilepsy society, 2010	Conference abstract
Gil-Nagel, A., Elger, C., Ben-Menachem, E., Halasz, P., Lopes-Lima, J., Gabbai, A. A., Nunes, T., Falcao, A., Almeida, L., Da-Silva, P. S., Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies, Epilepsia, 54, 98-107, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Gil-Nagel, A., Zaccara, G., Baldinetti, F., Leon, T., Add-on treatment with pregabalin for partial seizures with or without generalisation: Pooled data analysis of four randomised placebo-controlled trials, Seizure, 18, 184-192, 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Glauser, T. A., Sachdeo, R. C., Bebin, M., Wheless, J. W., D'Souza, J., Two-year long-term safety and efficacy data of oxcarbazepine in children with refractory partial epilepsy, Epilepsia, 43 Suppl 7, 57â€• 58, 2002	Conference abstract
Glauser, T. A., Sfikas, N., Oxcarbazepine adjunctive therapy in children with inadequately controlled partial seizures: an analysis of	Conference abstract

Study	Reason for Exclusion
seizure-free rates, Epilepsia, 44 Suppl 9, 266, 2003	
Glauser, T., Kluger, G., Sachdeo, R., Krauss, G., Perdomo, C., Arroyo, S., Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome, Neurology, 70, 1950-1958, 2008	No population (This study was focused on people with Lennoxâ□“Gastaut syndrome)
Goldberg-Stern, H., Oren, H., Peled, N., Garty, B. Z., Effect of melatonin on seizure frequency in intractable epilepsy: A pilot study, Journal of Child Neurology, 27, 1524-1528, 2012	Cross-over study design
Gowda, V. K., Romana, A., Shivanna, N. H., Benakappa, N., Benakappa, A., Levetiracetam versus Phenobarbitone in Neonatal Seizures - A Randomized Controlled Trial, Indian Pediatrics, 56, 643-646, 2019	No add-on therapy
Gupta, M., Aneja, S., Kohli, K., Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: A randomized, double-blind, placebo-controlled trial, Epilepsy and Behavior, 5, 316-321, 2004	No outcome of interest
Gupta, M., Gupta, Y. K., Agarwal, S., Aneja, S., Kalaivani, M., Kohli, K., Effects of add-on melatonin administration on antioxidant enzymes in children with epilepsy taking carbamazepine monotherapy: A randomized, double-blind, placebo-controlled trial, Epilepsia, 45, 1636-1639, 2004	No outcomes of interest
Gupta, M., Gupta, Y. K., Agarwal, S., Aneja, S., Kohli, K., A randomized, double-blind, placebo controlled trial of melatonin add-on therapy in epileptic children on valproate monotherapy: effect on glutathione peroxidase and glutathione reductase enzymes, British Journal of Clinical Pharmacology, 58, 542â€• 547, 2004	No outcomes of interest
Gupta,, M,, Gupta,, Y, K., Aneja,, S,, Kohli,, K,, Add-on melatonin improves quality of life in epileptic children on valproate/carbamazepine monotherapy: a randomized double blind placebo controlled trial, Quality of Life Research, 14, 2048, 2005	Conference abstract
Harris, J. A., Murphy, J. A., Lacosamide: An adjunctive agent for partial-onset seizures and potential therapy for neuropathic pain, Annals of Pharmacotherapy, 43, 1809-1817, 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Harvey, J., Andermann, E., Chung, S., Trinka, E., Cendes, F., Passarell, J., Fiedler-Kelly, J., Ludwig, E., Sunkaraneni, S., Sousa, R., et al.,, Relationship between eslicarbazepine exposure and efficacy of eslicarbazepine acetate adjunctive therapy, Epilepsy currents., 15, 149, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Hirsch, E. R. W., Edrich, P., Tassinari, C. A., Benbadis, S., Levetiracetam as an add-on therapy for idiopathic generalised epilepsy syndromes with onset during adolescence: analysis of two randomised, double-blind,	Conference abstract

Study	Reason for Exclusion
placebo-controlled studies, European jounral of neurology, 15, 83, Abstract no: P1200, 2008	
Hogan, R. E., Arnold, S., Fakhoury, T. A., Anders, B., Laine, D., Todd, W. M., Lawson, B., Safety and tolerability of usl255 in subjects with refractory partial-onset seizures: results from the randomized, phase 3 prevail clinical trial, Epilepsy Currents, 14, 103, 2014	Conference abstract
Hogan, R., Arnold, S., Fakhoury, T., Anders, B., Adverse event profile of usl255 in patients with refractory partial-onset seizures: the prevail study, Neurology, 82, 2014	Conference abstract
Houtkooper, M. A., Lammertsma, A., Meyer, J. W., Goedhart, D. M., Meinardi, H., van Oorschot, C. A., Blom, G. F., Höppener, R. J., Hulsman, J. A., Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine?, Epilepsia, 28, 693â€• 698, 1987	Cross-over study design
Hoy, S. M., Lacosamide: A review of its use as adjunctive therapy in the management of partial-onset seizures, CNS Drugs, 27, 1125-1142, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Hoy, S. M., Zonisamide: A review of its use as adjunctive therapy in the management of partial seizures in pediatric patients aged >=6 years, Pediatric Drugs, 16, 235-246, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Hu, T. Y., Wang, H. Q., Zhang, W. P., Tian, R. F., Lei, G. S., Deng, Y. C., Xing, J. L., Network meta-analysis of antiepileptic drugs in focal drug-resistant epilepsy, Epilepsy Research, 167, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Hufnagel, A., Ben-Menachem, E., Gabbai, A. A., Falcao, A., Almeida, L., Soares-da-Silva, P., Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: Results of a 1-year open-label extension study, Epilepsy Research, 103, 262-269, 2013	No RCT (extension trial of a RCT)
Husain, A., Chung, S., Faught, E., Isojarvi, J., McShea, C., Doty, P., Long-term safety and efficacy in patients with uncontrolled partial-onset seizures treated with adjunctive lacosamide: Results from a phase III open-label extension trial, Epilepsia, 53, 521-528, 2012	No RCT (extension trial of a RCT)
Iivanainen, M., Waltimo, O., Tokola, O., Parantainen, J., Tamminen, M., Allonen, H., Neuvonen, P. J., A controlled study with taltrimide and sodium valproate: valproate effective in partial epilepsy, Acta Neurologica Scandinavica, 82, 121-125, 1990	Cross-over study design
Jain, S. V., Horn, P. S., Simakajornboon, N., Beebe, D. W., Holland, K., Byars, A. W., Glauser, T. A., Melatonin improves sleep in children with epilepsy: A randomized, double-blind, crossover study, Sleep Medicine, 16, 637-644, 2015	Cross-over study design

Study	Reason for Exclusion
Jawad, S., Richens, A., Goodwin, G., Yuen, W. C., Controlled trial of lamotrigine (Lamictal) for refractory partial seizures, Epilepsia, 30, 356â€• 363, 1989	Cross-over study design
Jedrzejczak, J., Tiagabine as add-on therapy may be more effective with valproic acid--open label, multicentre study of patients with focal epilepsy, European Journal of Neurology, 12, 176-80, 2005	No RCT
Jones, M. W., Blume, W., Guberman, A., Lee, M., Pillay, N., Weaver, D., Veloso, F., Remacemide hydrochloride (300mg, 600mg, 800mg/day) efficacy and safety versus placebo in patients with refractory epilepsy, Epilepsia, 37 Suppl 5, 166, 1996	Conference abstract
Kappes, J. A., Hayes, W. J., Strain, J. D., Farver, D. K., Brivaracetam: An Adjunctive Treatment for Partial-Onset Seizures, Journal of Clinical Pharmacology, 57, 811-817, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Kaur, G., Andriola, M., Manganas, L., Efficacy of cannabidiol in children with intractable epilepsy, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Keating, G. M., Eslicarbazepine acetate: a review of its use as adjunctive therapy in refractory partial-onset seizures, CNS Drugs, 28, 583-600, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Keene, D. L., Whiting, S., Humphreys, P., Clobazam as an add-on drug in the treatment of refractory epilepsy of childhood, Canadian Journal of Neurological Sciences, 17, 317-319, 1990	Cross-over study design
Khan, N., Shah, D., Tongbram, V., Verdian, L., Hawkins, N., The efficacy and tolerability of perampanel and other recently approved anti-epileptic drugs for the treatment of refractory partial onset seizure: A systematic review and Bayesian network meta-analysis, Current Medical Research and Opinion, 29, 1001-1013, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Kim, Ji Hyun, Kim, Dong Wook, Lee, Sang Kun, Seo, Dae Won, Lee, Ji Woong, Park, Hae Joon, Lee, Sang Ahm, First add-on perampanel for focal-onset seizures: An open-label, prospective study, Acta Neurologica Scandinavica, 141, 132-140, 2020	No a RCT
Kirkham, F., Auvin, S., Rocha, F., Moreira, J., Soares-da-Silva, P., A placebo-controlled trial of eslicarbazepine acetate add-on therapy for focal seizures in children, European Journal of Paediatric Neurology, 21, e38â€• , 2017	Conference abstract
Klein, P., Biton, V., Dilley, D., Barnes, M., Schiemann, J., Lu, S., Safety and tolerability of adjunctive brivaracetam as intravenous infusion or bolus in patients with epilepsy, Epilepsia, 57, 1130-1138, 2016	No outcome of interest

Study	Reason for Exclusion
Klein, P., McLachlan, R., Foris, K., Nondonfaz, X., Elmoufti, S., Dimova, S., Brandt, C., Effect of lifetime antiepileptic drug treatment history on efficacy and tolerability of adjunctive brivaracetam in adults with focal seizures: Post-hoc analysis of a randomized, placebo-controlled trial, Epilepsy Research, 167, 106369, 2020	No a RCT (Post-hoc analysis of data from Klein 2015 - already included in the guideline for this topic)
Klein, P., Tyrlikova, I., Mathews, G. C., Dietary treatment in adults with refractory epilepsy: A review, Neurology, 83, 1978-1985, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ko, D., Ramsay, R. E., Perampanel: Expanding therapeutic options for patients with medically refractory secondary generalized convulsive seizures, Acta Neurologica Scandinavica, 127, 36-43, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ko, D., Yang, H., Williams, B., Xing, D., Laurenza, A., Pooled perampanel phase iii trials: time to onset and duration for most common adverse events, Epilepsy currents., 14, 67, 2014	Conference abstract
Koeppen, D., Baruzzi, A., Capozza, M., Chauvel, P., Courjon, J., Favel, P., Harmant, J., Lorenz, H., Oller, F. V., Procaccianti, G., Clobazam in therapy-resistant patients with partial epilepsy: a double-blind placebo-controlled crossover study, Epilepsia, 28, 495â€• 506, 1987	Cross-over study design
Kossoff, E. H., Turner, Z., Bluml, R. M., Pyzik, P. L., Vining, E. P. G., A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet, Epilepsy and Behavior, 10, 432-436, 2007	Cross-over study design
Kramer, L. D., Satlin, A., Krauss, G. L., French, J., Perucca, E., Ben-Menachem, E., Kwan, P., Shih, J. J., Laurenza, A., Yang, H., et al.,, Perampanel for adjunctive treatment of partial-onset seizures: a pooled dose-response analysis of phase III studies, Epilepsia, 55, 423â€• 431, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Kramer, L. D., Satlin, A., Krauss, G. L., French, J., Perucca, E., Ben-Menachem, E., Kwan, P., Shih, J. J., Laurenza, A., Yang, H., Zhu, J., Squillacote, D., Perampanel for adjunctive treatment of partial-onset seizures: A pooled dose-response analysis of phase III studies, Epilepsia, 55, 423-431, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Krauss, G. L., Elger, C., Marson, A. G., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., Phase III study of perampanel as adjunctive therapy in patients with refractory partial seizures: seizure freedom and exploratory endpoints, Epilepsy Currents, 12, 2012	Conference abstract
Krauss, G. L., Perucca, E., Ben-Menachem, E., Kwan, P., Shih, J. J., Squillacote, D., Yang, H., Gee, M., Zhu, J., Laurenza, A., Perampanel, a selective, noncompetitive alpha-amino-3-	No RCT (extension trial of a RCT)

Study	Reason for Exclusion
hydroxy-5-methyl-4- isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: Interim results from phase III, extension study 307, Epilepsia, 54, 126-134, 2013	
Krauss, G., Biton, V., Harvey, J. H., Elger, C., Trinka, E., Soares da Silva, P., Gama, H., Cheng, H., Grinnell, T., Blum, D., Influence of titration schedule and maintenance dose on the tolerability of adjunctive eslicarbazepine acetate: An integrated analysis of three randomized placebo-controlled trials, Epilepsy Research, 139, 1-8, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Krauss, G., Biton, V., Harvey, J., Blum, D., Sousa, R., Grinnell, T., Adverse event profile of eslicarbazepine acetate during dose titration in phase III controlled studies of patients with refractory partial-onset seizures, Epilepsy currents., 14, 392â€• 393, 2014	Conference abstract
Krauss, G., Biton, V., Klapper, J., Bar, M., Rektor, I., Vaiciene-Magistris, N., Liigant, A., Kumar, D., Squillacote, D., Determination of tolerability, safety, and efficacy of perampanel, a selective AMPA receptor antagonist, as adjunctive therapy in subjects with refractory partial seizures, Epilepsia, 50 Suppl 10, 103, Abstract no: p476, 2009	Conference abstract
Krauss, G., Kamin, M., Efficacy and tolerability of adjunctive cenobamate therapy in different types of partial-onset seizures, Neurology, 90, 2018	Conference abstract
Krauss, G., Yang, J., Biton, V., Klapper, J., Bar, M., Rektor, I., Determination of maximum tolerated dose (MTD), safety, efficacy, and pharmacokinetic (PK) of perampanel, a selective AMPA receptor antagonist, as adjunctive therapy in subjects with refractory partial seizures, Epilepsia, 49 Suppl 7, 46â€• 47, 2008	Conference abstract
Kuzmanovski, I., Nikodijevic-Kedeva, D., Petrovska, D., Cvetkovska, E., Pashu, M., Vaskov, T., Babinkostova, Z., Tegretol versus lamotrigine in patients with partial refractory epilepsy: a 6 month clinical study, Epilepsia, 45 Suppl 3, 134â€• 135, Abstract no: p316, 2004	Conference abstract
Kverneland, M., Molteberg, E., Iversen, P. O., Veierod, M. B., Tauboll, E., Selmer, K. K., Nakken, K. O., Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial, Epilepsia, 59, 1567-1576, 2018	No outcomes of interest
Kwan, P., Lim, S. H., Chinvarun, Y., Cabral-Lim, L., Aziz, Z. A., Lo, Y. K., Tonner, F., Beh, K., Edrich, P., N. Investigator Group, Efficacy and safety of levetiracetam as adjunctive therapy in adult patients with uncontrolled partial epilepsy: the Asia SKATE II Study, Epilepsy & Behavior, 18, 100-5, 2010	No RCT

Study	Reason for Exclusion
Lambrechts, D. A. J. E., de Kinderen, R. J. A., Vles, J. S. H., de Louw, A. J. A., Aldenkamp, A. P., Majoie, H. J. M., A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta Neurologica Scandinavica, 137, 152-154, 2018	No RCT
Lambrechts, D. A., de Kinderen, R. J., Vles, J. S., de Louw, A. J., Aldenkamp, A. P., Majoie, H. J., A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta Neurologica Scandinavica, 135, 231â€• 239, 2017	no add-on therapy
Lappalainen, J., Tsai, J., Amerine, W., Patroneva, A., A Multicenter, Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial to Determine the Efficacy and Safety of Ganaxolone as Adjunctive Therapy for Adults with Drug-Resistant Focal-Onset Seizures, Neurology, 88, 2017	Conference abstract
Larkin, J. G., Besag, F. M. C., Cox, A., Williams, J., Brodie, M. J., Nifedipine for epilepsy? A double-blind, placebo-controlled trial, Epilepsia, 33, 346-352, 1992	Cross-over study design
Larkin, J. G., McKee, P. J. W., Blacklaw, J., Thompson, G. G., Morgan, I. C., Brodie, M. J., Nimodipine in refractory epilepsy: A placebo-controlled, add-on study, Epilepsy Research, 9, 71-77, 1991	Cross-over study design
Latini, F., Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial, Neurologia argentina, 3, 75â€• 76, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Lattanzi, S., Brigo, F., Cagnetti, C., Verrotti, A., Zaccara, G., Silvestrini, M., Eslicarbazepine acetate in the treatment of adults with partial-onset epilepsy: An evidence-based review of efficacy, safety and place in therapy, Core Evidence, 13, 21-31, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Lattanzi, S., Brigo, F., Grillo, E., Cagnetti, C., Verrotti, A., Zaccara, G., Silvestrini, M., Adjunctive Eslicarbazepine Acetate in Pediatric Patients with Focal Epilepsy: A Systematic Review and Meta-Analysis, CNS Drugs, 32, 189-196, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Lattanzi, S., Cagnetti, C., Foschi, N., Provinciali, L., Silvestrini, M., Brivaracetam add-on for refractory focal epilepsy: A systematic review and meta-analysis, Neurology, 86, 1344-1352, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Lattanzi, S., Trinka, E., Zaccara, G., Striano, P., Del Giovane, C., Silvestrini, M., Brigo, F., Adjunctive Cenobamate for Focal-Onset Seizures in Adults: A Systematic Review and Meta-Analysis, CNS Drugs, 34, 1105-1120, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Laurenza, A., Yang, H., Squillacote, D., Kumar, D., Satlin, A., Kramer, L. D., Adjunctive	Conference abstract

Study	Reason for Exclusion
perampanel does not increase the risk of cardiac adverse events compared with placebo: a pooled analysis of three phase III trials, Epilepsia., 54, 70, 2013	
Leach, J. P., Girvan, J., Jamieson, V., Jones, T., Richens, A., Brodie, M. J., Mutual interaction between remacemide hydrochloride and phenytoin, Epilepsy Research, 26, 381-388, 1997	Cross-over study design
Leach, J. P., Girvan, J., Paul, A., Brodie, M. J., Gabapentin and cognition: A double blind, dose ranging, placebo controlled study in refractory epilepsy, Journal of Neurology Neurosurgery and Psychiatry, 62, 372-376, 1997	Cross-over study design
Lee, B. I., Double-blind placebo-controlled randomized clinical trial of topiramate add-on therapy in medically intractable partial epilepsies, Journal of the korean neurological association, 16, 809â€• 819, 1998	Article in Korean
Lee, B., Loesch, C., Osakabe, T., Lee, J., A randomized, open-label, parallel group, multi-center comparative trial of levetiracetam and topiramate as adjunctive treatment in refractory focal epilepsy, Epilepsia, 57, 165â€• 166, 2016	Conference abstract
Lee, S. K., Nam, H. W., Chang, I. J., Comparative add-on trial of vigabatrin and valproic acid on intractable partial seizures with carbamazepine monotherapy, Journal of the korean neurological association, 15, 754â€• 761, 1997	Article in Korean
Leppik, I. E., Dreifuss, F. E., Pledger, G. W., Graves, N. M., Santilli, N., Drury, I., Tsay, J. Y., Jacobs, M. P., Bertram, E., Cereghino, J. J., Felbamate for partial seizures: results of a controlled clinical trial, Neurology, 41, 1785â€• 1789, 1991	No outcome of interest
Li-na, Z., Deng, C., Hai-jiao, W., Da, X., Ge, T., Ling, L., Indirect comparison of third-generation antiepileptic drugs as adjunctive treatment for uncontrolled focal epilepsy, Epilepsy Research, 139, 60-72, 2018	NMA, no relevant data could be extracted for inclusion. References checked for inclusion
Liu, H., Xu, X., Influence of adjunctive lacosamide in patients with seizures: a systematic review and meta-analysis, International Journal of Neuroscience, 128, 670-676, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Liu, Z., Li, J., Yang, F., Hu, Y., Liu, J., Hu, H., Su, W., Sodium valproate combined with levetiracetam in pediatric epilepsy and its influence on NSE, IL-6, hs-CRP and electroencephalogram improvement, Experimental and Therapeutic Medicine, 20, 2043-2048, 2020	No outcomes of interest
Loiseau, P., Bossi, L., Guyot, M., Orofiamma, B., Morselli, P. L., Double-blind crossover trial of progabide versus placebo in severe epilepsies, Epilepsia, 24, 703-715, 1983	Cross-over study design

Study	Reason for Exclusion
Loiseau, P., Hardenberg, J. P., Pestre, M., Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy, Epilepsia, 27, 115-120, 1986	Cross-over study design
Loiseau, P., Yuen, A. W. C., Duche, B., Menager, T., Arne-Bes, M. C., A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures, Epilepsy Research, 7, 136-145, 1990	Cross-over study design
Lozsadi, D., Hemming, K., Marson, A. G., Pregabalin add-on for drug-resistant partial epilepsy, The Cochrane database of systematic reviews, CD005612, 2008	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ma, J., Huang, S., You, C., Adjunctive brivaracetam for patients with refractory partial seizures: A meta-analysis of randomized placebo-controlled trials, Epilepsy Research, 114, 59-65, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Mann, D., Antinew, J., Knapp, L., Almas, M., Liu, J., Scavone, J., Yang, R., Modequillo, M., Makedonska, I., Ortiz, M., Kyrychenko, A., Nordli, D., Farkas, V., Farkas, M. K., Shalkevich, L., Jansen, A., Ivanov, I., Nedkova, V., Fang, F., Wang, Y., Pinard, J. M., Brandl, U., Zafeiriou, D., Altmann, A., Berenyi, M., Bessenyei, M., Fogaras, A., Szabo, G., Fattal-Valevski, A., Kim, K. J., Beydoun, A., Hmaimess, G., Yahaya, N. A., Barlaan-Lukban, M., Bolanos, M., De la Calzada, J. J., Estrella Ibe, M., Valencia, M. A. A., Craiu, D., Diaconu, G., Antonova, T., Belousova, E., Karakulova, Y., Khaletskaya, O., Lvova, O., Strachunskaya, M., Kravljanac, R., Nikolic, D., Lopez Pison, F., Chang, Y. C., Chou, I. C., Lee, W. T., Nabangchang, C., Sanmaneechai, O., Dundar, N. O., Gencpinar, P., Chomolyak, Y., Delva, D., Martyniuk, V., Davis, R., Ferreira, J., Tomasovic, J., Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age: A double-blind, placebo-controlled, video-electroencephalographic trial, Epilepsia, 61, 617-626, 2020	No outcomes of interest
Mann, D., Liu, J., Chew, M., Bockbrader, H., Alvey, C. W., Zegarac, E., Pellock, J., Pitman, V., A placebo-controlled, escalating dose, multiple dose study to evaluate the safety, tolerability and pharmacokinetics of pregabalin in pediatric patients with partial onset seizures, Epilepsy currents., 14, 437â€• 438, 2014	Conference abstract
Marson, A. G., Kadir, Z. Z., Hutton, J. L., Chadwick, D. W., Gabapentin add-on for drug-resistant partial epilepsy, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Marson, A., Burnside, G., Appleton, R., Leach, J. P., Sills, G., Tudur-Smith, C., Plumpton, C., Hughes, D., Williamson, P., Baker, G., et al.,, The SANAD II study of effectiveness of	Conference Abstract

Study	Reason for Exclusion
valproate or levetiracetam in generalised and unclassifiable epilepsy: an un-blinded randomised controlled trial, Epilepsia, 60, 25â€• , 2019	
Marson, A., Smith, D., Tudur Smith, C., Williamson, P., Jacoby, A., Chadwick, D., Carbamazepine versus gabapentin, lamotrigine, oxcarbazepine and topiramate for epilepsy: results from arm A of the SANAD trial, Epilepsia, 47, 272, Abstract no: 3.200, 2006	Conference abstract
Martin-Mcgill, K. J., Jackson, C. F., Bresnahan, R., Levy, R. G., Cooper, P. N., Ketogenic diets for drug-resistant epilepsy, Cochrane Database of Systematic Reviews, 2018 (11) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Martyn-St James, M., Glanville, J., McCool, R., Duffy, S., Cooper, J., Hugel, P., Lane, P. W., The efficacy and safety of retigabine and other adjunctive treatments for refractory partial epilepsy: A systematic review and indirect comparison, Seizure, 21, 665-678, 2012	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Masland, R. L., A controlled trial of clonazepam in temporal lobe, epilepsy, Acta Neurologica Scandinavica. Supplementum, 60, 49-54, 1975	No RCT
Mbizvo, G. K., Chandrasekar, B., Nevitt, S. J., Dixon, P., Hutton, J. L., Marson, A. G., Levetiracetam add-on for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2020, CD001901, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Mbizvo, G. K., Dixon, P., Hutton, J. L., Marson, A. G., Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review, Cochrane database of systematic reviews (Online), 9, CD001901, 2012	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
McKee, P. J., Blacklaw, J., Friel, E., Thompson, G. G., Gillham, R. A., Brodie, M. J., Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients?, Epilepsia, 34, 937â€• 943, 1993	Cross-over study design
McLean, M. J., Ramsay, R. E., Leppik, L. E., Rowan, A. J., Shellenberger, M. K., Wallace, J., Gabapentin as add-on therapy in refractory partial epilepsy: A double- blind, placebo-controlled, parallel-group study, Neurology, 43, 2292-2298, 1993	Duplicate. This study has been already been included in the analysis
Meador, K. J., Loring, D. W., Hulihan, J. F., Kamin, M., Karim, R., Differential cognitive and behavioral effects of topiramate and valproate, Neurology, 60, 1483-1488, 2003	No outcome of interest
Meng, Y., Wu, J., Shi, J., Weng, W., Zhou, Z., Comparison of the safety of brivaracetam at various doses among patients with epilepsy: A network meta-analysis of randomized controlled trials, Experimental and Therapeutic Medicine, 20, 9262, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Messenheimer, J., Ramsay, R. E., Willmore, L. J., Leroy, R. F., Zielinski, J. J., Mattson, R.,	Cross-over study design

Study	Reason for Exclusion
Pellock, J. M., Valakas, A. M., Womble, G., Risner, M., Lamotrigine therapy for partial seizures: A multicenter, placebo- controlled, double-blind, cross-over trial, Epilepsia, 35, 113-121, 1994	
Michael, B., Marson, A. G., Clobazam as an add-on in the management of refractory epilepsy, Cochrane Database of Systematic Reviews, (2) (no pagination), 2008	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Michelucci, R., Cavaciocchi, P., Riguzzi, P., Passarelli, D., Parmeggiani, L., Santangelo, M., Zamagni, M., Iudice, A., Tassinari, C. A., Single-blind, placebo-controlled dose-modification study of vigabatrin in refractory epileptic patients, Journal of Epilepsy, 5, 248-252, 1992	No RCT
Minecan, D., Beydoun, A., Sachdeo, R., D'Souza, J., Safety and efficacy of oxcarbazepine after 2 years' treatment in patients with inadequately controlled partial-onset seizures, Epilepsia, 43 Suppl 7, 196, 2002	Conference abstract
Mintz, M., Pina-Garza, J. E., Wolf, S. M., McGoldrick, P. E., Jozwiak, S., Grinnell, T., Cantu, D., Costa, R., Moreira, J., Li, Y., et al.,, Safety and Tolerability of Adjunctive Eslicarbazepine Acetate in Pediatric Patients (Aged 4-17 Years) With Focal Seizures, Journal of Child Neurology, 35, 265â€• 273, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Mintzer, S., French, J., Williams, B., Patten, A., Laurenza, A., Extrapolation of Adjunctive Efficacy and Safety Data from Phase III Partial Epilepsy Trials to Evaluate Perampanel as Monotherapy, Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN, 90, 2018	Conference abstract
Moglia, A., Bergamasco, B., Di Perri, R., Mancia, D., Flunarizine as add-on therapy in epilepsy. Crossover study vs placebo, Functional Neurology, 1, 547-50, 1986	Cross-over RCT
Mohd-Tahir, N. A., Li, S. C., Meta-analyses of newer antiepileptic drugs as adjunct for treatment of focal epilepsy in children, Epilepsy Research, 139, 113-122, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Morrell, M. J., Leppik, I., French, J., Ferrendelli, J., Han, J., Magnus, L., The KEEPER trial: levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study, Epilepsy Research, 54, 153-61, 2003	No RCT
Moseley, B. D., Sperling, M. R., Asadi-Pooya, A. A., Diaz, A., Elmouft, S., Schiemann, J., Whitesides, J., Efficacy, safety, and tolerability of adjunctive brivaracetam for secondarily generalized tonic-clonic seizures: Pooled results from three Phase III studies, Epilepsy Research, 127, 179-185, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Moseley, B., Diaz, A., Elmoufti, S., Whitesides, J., Efficacy of adjunctive brivaracetam in	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could

Study	Reason for Exclusion
patients with secondarily generalized tonic-clonic seizures at baseline: Pooled results from long-term follow-up studies, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	be extracted for inclusion. References checked for inclusion
Naritoku, D. K., Hulihan, J. F., Schwarzman, L. K., Kamin, M., Olson, W. H., Effect of cotherapy reduction on tolerability of epilepsy add-on therapy: A randomized controlled trial, Annals of Pharmacotherapy, 39, 418-423, 2005	No outcome of interest
Neal,E.G., Chaffe,H., Schwartz,R.H., Lawson,M.S., Edwards,N., Fitzsimmons,G., Whitney,A., Cross,J.H., The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial, Lancet Neurology, 7, 500-506, 2008	No study design. This study use a waiting list control group: [..] were randomly assigned to receive a ketogenic diet, either immediately or after a 3-month delay, with no other changes to treatment (control group) [..].
Noachtar, S., Andermann, E., Meyvisch, P., Andermann, F., Gough, W. B., Schiemann-Delgado, J., Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures, Neurology, 70, 607-616, 2008	No relevant to the PICO (This RCT evaluates the use adjunctive antiepileptic therapy in idiopathic generalized epilepsy with myoclonic seizures)
Nordli, D. R., Bagiella, E., Arzimanoglou, A., Wang, J., Kumar, D., Laurenza, A., French, J., Meta-analysis of drug efficacy in adult vs pediatric trials of patients with PGTC seizures, Neurology, 94, E1845-E1852, 2020	ystematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
O'Brien, T. J., Borghs, S., He, Q., Schulz, A. L., Yates, S., Biton, V., Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: An up to 11-year, open-label, follow-up trial, Epilepsia, 61, 636-646, 2020	No RCT (extension trial of 3 RCTs included in this guideline's topic: French 2010; Ryvlin 2014; and Biton 2014)
O'Connell, B. K., Gloss, D., Devinsky, O., Cannabinoids in treatment-resistant epilepsy: A review, Epilepsy and Behavior, Part B. 70, 341-348, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
O'Donoghue, M. F., Sander, Jwas, Eeg-Olofsson, O., Reynolds, E. H., Brodie, M. J., Richens, A., Yuen, A. W. C., Duval, X., Chosidow, O., Semah, F., et al.,, Lamotrigine versus carbamazepine in epilepsy, Lancet, 345, 1300â€• 1302, 1995	No RCT
Ogunmekan, A. O., Hwang, P. A., A randomized, double-blind, placebo-controlled, clinical trial of D-alpha-tocopheryl acetate (vitamin E), as add-on therapy, for epilepsy in children, Epilepsia, 30, 84-89, 1989	No outcome of interest
Owen, R. T., Eslicarbazepine acetate: A novel agent for the adjunctive treatment of epilepsy, Drugs of Today, 46, 23-31, 2010	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Pack, A. M., Perampanel: Another choice for patients with idiopathic generalized epilepsy who have tonic-clonic seizures, Epilepsy Currents, 16, 27-28, 2016	No RCT
Panebianco, M., Al-Bachari, S., Weston, J.,	Systematic review/meta-analysis of randomised

Study	Reason for Exclusion
Hutton, J. L., Marson, A. G., Gabapentin add-on treatment for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2018 (10) (no pagination), 2018	controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Panebianco, M., Bresnahan, R., Hemming, K., Marson, A. G., Pregabalin add-on for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 7, CD005612, 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Panebianco, M., Prabhakar, H., Marson, A. G., Rufinamide add-on therapy for refractory epilepsy, Cochrane Database of Systematic Reviews, 2018 (4) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Pathak, G., Upadhyay, A., Pathak, U., Chawla, D., Goel, S. P., Phenobarbitone versus phenytoin for treatment of neonatal seizures: An open-label randomized controlled trial, Indian Pediatrics, 50, 753-757, 2013	No add-on therapy
Perucca, E., Krauss, G. L., Kwan, P., Ben-Menachem, E., Wang, X. F., Shih, J., Williams, B., Laurenza, A., Yang, H., Marked reduction in secondarily generalized seizures in patients treated with perampanel for 3 and 4 years, Epilepsia, 57 (Supplement 2), 6-7, 2016	Conference abstract
Piña-Garza, J. E., Espinoza, R., Nordli, D., Bennett, D. A., Spirito, S., Stites, T. E., Tang, D., Sturm, Y., Oxcarbazepine adjunctive therapy in infants and young children with partial seizures, Neurology, 65, 1370â€• 1375, 2005	No relevant to the PICO (This RCT evaluates the use adjunctive Oxcarbazepine in patients receiving either high-dose (60 mg/kg/day) or low-dose (10 mg/kg/day) oxcarbaz-epine as oral suspension.)
Pledger, G. W., Sackellares, J. C., Treiman, D. M., Pellock, J. M., Wright, F. S., Mikati, M., Sahlroot, J. T., Tsay, J. Y., Drake, M. E., Olson, L., Handforth, C. A., Garnett, W. R., Schachter, S., Kupferberg, H. J., Ashworth, M. R., McCormick, C., Leiderman, D., Kapetanovic, I. M., Driscoll, S., Flunarizine for treatment of partial seizures: Results of a concentration-controlled trial, Neurology, 44, 1830-1836, 1994	No outcome of interest
Porter, R. J., Gil-Nagel, A., Burdette, D., Hammond, J., DeRossett, S. E., Tolerability of retigabine as adjunctive therapy in adults with drug-resistant partial-onset seizures during titration and maintenance phases, Epilepsy Currents, 11, 2011	Conference abstract
Privitera, M., Efficacy of levetiracetam: A review of three pivotal clinical trials, Epilepsia, 42, 31-35, 2001	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Pulman, J., Hemming, K., Marson, A. G., Pregabalin add-on for drug-resistant partial epilepsy, Cochrane Database of Systematic Reviews, 2014 (3) (no pagination), 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Pulman, J., Jette, N., Dykeman, J., Hemming, K., Hutton, J. L., Marson, A. G., Topiramate add-on for drug-resistant partial epilepsy, Cochrane Database of Systematic Reviews, 2014 (2) (no pagination), 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Pulman, J., Marson, A. G., Hutton, J. L.,	Systematic review/meta-analysis of randomised

Study	Reason for Exclusion
Tiagabine add-on for drug-resistant partial epilepsy, Cochrane database of systematic reviews (Online), 5, CD001908, 2012	controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Quarato, P. P., Whitesides, J., D'Souza, J., Johnson, M. E., Schiemann, J., Efficacy and safety of adjunctive brivaracetam for partial-onset (focal) seizures: pooled results from three fixeddose, randomised, double-blind, placebocontrolled phase III studies, Epilepsia, 56, 208â€• 209, 2015	Conference abstract
Raju, G. B., Behari, M., Prasad, K., Ahuja, G. K., Randomized, double-blind, placebo-controlled, clinical trial of D-alpha- tocopherol (vitamin E) as add-on therapy in uncontrolled epilepsy, Epilepsia, 35, 368-372, 1994	Cross-over study design
Ramaratnam, S., Panebianco, M., Marson, A. G., Lamotrigine addâ€• on for drugâ€• resistant partial epilepsy, Cochrane Database of Systematic Reviews, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ramsay, R. E., Perucca, E., Robbins, J., Barrett, J. A., Spiegel, K., Rapid onset of seizure suppression with pregabalin adjunctive treatment in patients with partial seizures, Epilepsia, 50, 1891â€• 1898, 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Rascol, O., Squalli, A., Montastruc, J. L., Garat, A., Houin, G., Lachau, S., Tor, J., Blehaut, H., Rascol, A., A pilot study of stiripentol, a new anticonvulsant drug, in complex partial seizures uncontrolled by carbamazepine, Clinical Neuropharmacology, 12, 119-23, 1989	No RCT
Rektor, I., Krauss, G. L., Bar, M., Biton, V., Klapper, J. A., Vaiciene-Magistris, N., Kuba, R., Squillacote, D., Gee, M., Kumar, D., Perampanel Study 207: Long-term open-label evaluation in patients with epilepsy, Acta Neurologica Scandinavica, 126, 263-269, 2012	No RCT (extension trial of a RCT)
Rektor, I., Krauss, G. L., Inoue, Y., Kaneko, S., Williams, B., Patten, A., Bibbiani, F., Laurenza, A., Wechsler, R. T., Assessment of the long-term efficacy and safety of adjunctive perampanel: Pooled analyses of four open-label extension studies, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Rektor, I., Krauss, G. L., Inoue, Y., Kaneko, S., Williams, B., Patten, A., Malhotra, M., Laurenza, A., Wechsler, R. T., Assessment of the long-term efficacy and safety of adjunctive perampanel in tonic-clonic seizures: Analysis of four open-label extension studies, Epilepsia, 61, 1491-1502, 2020	No RCT (extension trial of 4 RCTs included in this guideline's topic: Krauss 2012; French 2012; French 2013; and Nishida 2018)
Renfroe, B., Lagae, L., Williams, B., Yang, H., Kumar, D., Laurenza, A., Adjunctive perampanel in adolescents with inadequately controlled partial-onset seizures: efficacy and safety results from study 235 (phase II), Journal of the american pharmacists association., 55, e173,	Conference abstract

Study	Reason for Exclusion
2015	
Renfroe, B., Yang, H., Williams, B., Huang, S., Laurenza, A., Interim efficacy and safety analysis of adjunctive perampanel in the adolescent population from the extension phase of 3 double-blind, placebo-controlled, phase 3 (CORE) studies in patients with refractory partial-onset seizures, Annals of neurology., 74, S172, 2013	Conference Abstract
Resnick, T., Grinnell, T., Cantu, D., Li, Y., Graca, J., Gama, H., Blum, D., Analysis of allergic reactions in clinical trials of eslicarbazepine acetate in children (aged 4-17 years) with focal seizures, Neurology, 92, 2019	Conference abstract
Reynolds, E. H., Heller, A. J., Chadwick, D., Valproate versus carbamazepine for seizures, New England Journal of Medicine, 328, 207â€• 8; author reply 209, 1993	No RCT
Rheims, S., Cucherat, M., Arzimanoglou, A., Ryvlin, P., Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy, PLoS Medicine, 5, 1223-1237, 2008	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Richens, A., Chadwick, D. W., Duncan, J. S., Dam, M., Gram, L., Mikkelsen, M., Morrow, J., Mengel, H., Shu, V., McKelvy, J. F., Pierce, M. W., Adjunctive treatment of partial seizures with tiagabine: A placebo-controlled trial, Epilepsy Research, 21, 37-42, 1995	Cross-over study design
Richens, A., Mawer, G., Crawford, P., Harrison, B., A placebo-controlled, double-blind cross-over trial of adjunctive one month remacemide hydrochloride treatment in patients with refractory epilepsy, Seizure, 9, 537â€• 543, 2000	Cross-over study design
Rocha, J., Moreira, P., Pinto, R., Soares-Da-Silva, P., A placebo-controlled trial of eslicarbazepine acetate add-on therapy for partial seizures in children, Journal of the neurological sciences., 357, e439â€• e440, 2015	Conference abstract
Rogawski, M. A., Yang, H., Fant, R. V., Williams, B., Xing, D., Dobrinsky, C., Laurenza, A., Perampanel discontinuation is not associated with self-reported withdrawal symptoms in patients completing phase III clinical studies, Epilepsy currents., 15, 317, 2015	Conference abstract
Rogin, J., Abou-Khalil, B., Blum, D., Sousa, R., Grinnell, T., Eslicarbazepine acetate as adjunctive treatment for refractory partial-onset seizures: pooled analysis of safety data from three phase III controlled trialS, Epilepsy currents., 14, 209, 2014	Conference abstract
Rogin, J., Resnick, T., Strom, L., Ben-Menachem, E., Kochen, S., Blum, D., Gama, H., Soares-Da-Silva, P., Grinnell, T., Incidence of allergic reaction adverse events during	Conference abstract

Study	Reason for Exclusion
adjunctive treatment with eslicarbazepine acetate in patients with refractory partial-onset seizures: a pooled analysis of three phase III placebo-controlled studies, Neurology, 82, 2014	
Rogin, J., Resnick, T., Strom, L., Ben-Menachem, E., Kochen, S., Blum, D., Gama, H., Soares-da-Silva, P., Li, Y., Grinnell, T., Analysis of cutaneous allergic reactions in clinical trials of eslicarbazepine acetate, Acta Neurologica Scandinavica., 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Rosati, A., Giorgi, L., Bradshaw, K., Guerrini, R., Efficacy of long-term adjunctive zonisamide therapy in paediatric patients with partial epilepsy: results of an open-label extension study of a Phase III, randomised, double-blind, placebocontrolled trial, Developmental Medicine and Child Neurology, 56, 23, 2014	Conference Abstract
Rosati, A., Segieth, J., Giorgi, L., Guerrini, R., Results from the catz study: a phase III, double-blind, randomized, placebo-controlled trial to assess the efficacy and safety of adjunctive zonisamide in pediatric patients with partial-onset seizures, Neurology, 78, 2012	Conference Abstract
Rosenfeld, W. E., Benbadis, S., Edrich, P., Tassinari, C. A., Hirsch, E., Levetiracetam as add-on therapy for idiopathic generalized epilepsy syndromes with onset during adolescence: Analysis of two randomized, double-blind, placebo-controlled studies, Epilepsy Research, 85, 72-80, 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Rosenfeld, W., Abou-Khalil, B., Morrell, M., Reife, R., Pledger, G., Hayden, R., Double-blind placebo controlled trial of topiramate adjunctive therapy for partial-onset epilepsy, Epilepsia, 37 Suppl 4, 5, 1996	Conference abstract
Rosenfeld, W., Conry, J., Lagae, L., Rozentals, G., Yang, H., Fain, R., Williams, B., Kumar, D., Zhu, J., Laurenza, A., Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a combined extension study, European Journal of Paediatric Neurology, 19, 435-45, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Ryvlin, P., Cucherat, M., Rheims, S., Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: A meta-analysis of placebo-controlled randomised trials, The Lancet Neurology, 10, 961-968, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Sackellares, J. C., Wilder, B. J., Ramsay, R. E., Browne, T. R., Abou-Khalil, B. W., Berent, S., Guterman, A., Howard, G. F., Wagner, J., Double-blind, placebo-controlled clinical trial of zonisaminde in complex partial seizures, Neurology, 36, 85, 1986	Conference abstract
Sake, J. K., Hebert, D., Isojrvi, J., Doty, P., De	Systematic review/meta-analysis of randomised

Study	Reason for Exclusion
Backer, M., Davies, K., Eggert-Formella, A., Zackheim, J., A Pooled Analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs, CNS Drugs, 24, 1055-1068, 2010	controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Sander, J. W. A. S., Patsalos, P. N., Oxley, J. R., Hamilton, M. J., Yuen, W. C., A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy, Epilepsy Research, 6, 221-226, 1990	Cross-over study design
Sankar, R., Kirkham, F. J., Holmes, G. L., Pina-Garza, J. E., Wheless, J., Gama, H., Moreira, J., Cantu, D., Tosiello, R., Blum, D., Grinnell, T., Long-term safety and tolerability of adjunctive eslicarbazepine acetate in children with focal seizures, Epilepsy and Behavior, 112 (no pagination), 2020	No RCT (extension trial of 2 RCTs included in this guideline's topic: Joswack 2018; Kirkham 2020)
Sato, S., White, B. G., Penry, J. K., Dreifuss, F. E., Sackellares, J. C., Kupferberg, H. J., Valproic acid versus ethosuximide in the treatment of absence seizures, Neurology, 32, 157â€• 163, 1982	Cross-over study design
Sawh, S. C., Newman, J. J., Deshpande, S., Jones, P. M., Lacosamide adjunctive therapy for partial-onset seizures: A meta-analysis, PeerJ, 2013 (1) (no pagination), 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Saxena, P., Singh, A., Upadhyay, A., Gupta, P., Sharma, S., Vishnubatla, S., Effect of Withholding Phenobarbitone Maintenance in Neonatal Seizures: A Randomized Controlled Trial, Indian Pediatrics, 53, 1069-1073, 2016	No add-on therapy
Schachter, S. C., Leppik, I. E., Matsuo, F., Messenheimer, J. A., Faught, E., Moore, E. L., Risner, M. E., Lamotrigine: A six-month, placebo-controlled, safety and tolerance study, Journal of Epilepsy, 8, 201-209, 1995	No outcome of interest
Schachter, S., Vazquez, B., D'Souza, J., Two-year, long-term, open-label extension study of efficacy and safety of oxcarbazepine in patients with uncontrolled partial-onset seizures, Epilepsia, 43 Suppl 7, 200, 2002	Conference abstract
Schapel, G. J., Beran, R. G., Vajda, F. J. E., Berkovic, S. F., Mashford, M. L., Dunagan, F. M., Yuen, W. C., Davies, G., Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures, Journal of Neurology Neurosurgery and Psychiatry, 56, 448-453, 1993	Cross-over study design
Schiemann-Delgado, J., Yang, H., Loge Cde, L., Stalvey, T. J., Jones, J., Legoff, D., Mintz, M., A long-term open-label extension study assessing cognition and behavior, tolerability, safety, and efficacy of adjunctive levetiracetam in children aged 4 to 16 years with partial-onset seizures, Journal of Child Neurology, 27, 80â€• 89, 2012	No RCT (extension trial of a RCT)
Schmidt, D., Rohde, M., Wolf, P., Roeder-Wanner, U., Clobazam for refractory focal	No outcome of interest

Study	Reason for Exclusion
epilepsy. A controlled trial, Archives of Neurology, 43, 824-826, 1986	
Schmidt, D., Utech, K., Progabide for refractory partial epilepsy: A controlled add-on trial, Neurology, 36, 217-221, 1986	Cross-over study design
Seo,J.H., Lee,Y.M., Lee,J.S., Kang,H.C., Kim,H.D., Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios--comparison of 3:1 with 4:1 diet, Epilepsia, 48, 801-805, 2007	No population (of the 76 people included in trial, more than half (n=47, 61%) had infantile spasms or Lennox-Gastaut syndrome)
Sharma, S., Sankhyan, N., Gulati, S., Agarwala, A., Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial, Epilepsia, 54, 481-486, 2013	this was an economic evaluation conducted no population (most of the children in this study had Lennox-Gastaut syndrome and West syndrome)
Shi, L. L., Bresnahan, R., Martin-McGill, K. J., Dong, J., Ni, H., Geng, J., Felbamate add-on therapy for drug-resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2019 (8) (no pagination), 2019	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Shi, L. L., Dong, J., Ni, H., Geng, J., Wu, T., Felbamate as an add-on therapy for refractory epilepsy, Cochrane database of systematic reviews (Online), 1, CD008295, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Simoens, S., Lacosamide as adjunctive therapy for partial-onset epileptic seizures: A review of the clinical and economic literature, Current Medical Research and Opinion, 27, 1329-1338, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Sivenius, J., Kalviainen, R., Ylinen, A., Riekkinen, P., Double-blind study of Gabapentin in the treatment of partial seizures, Epilepsia, 32, 539-542, 1991	No outcome of interest
Slater, J., Chung, S., Huynh, L., Duh, M. S., Gorin, B., McMicken, C., Ziemann, A., Isojarvi, J., Efficacy of antiepileptic drugs in the adjunctive treatment of refractory partial-onset seizures: Meta-analysis of pivotal trials, Epilepsy Research, 143, 120-129, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Smith, D., Baker, G., Davies, G., Dewey, M., Chadwick, D. W., Outcomes of add-on treatment with lamotrigine in partial epilepsy, Epilepsia, 34, 312-322, 1993	Cross-over study design
Sobaniec, W., KuÅ‚ak, W., Smigielska-Kuzia, J., BoÄ‡kowski, L., Majkowski, J., Jedrzejczak, J., A multicenter, placebo-controlled, double-blind study of efficacy of a new form of carbamazepine (Carbatrol) in refractory epileptic patients, Polish Journal of Pharmacology, 56, 195â€• 201, 2004	No outcome of interest
Sondhi, V., Agarwala, A., Pandey, R. M., Chakrabarty, B., Jauhari, P., Lodha, R., Toteja, G. S., Sharma, S., Paul, V. K., Kossoff, E., Gulati, S., Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet among Children with Drug-Resistant Epilepsy: A Randomized Clinical Trial, JAMA	No add-on therapy

Study	Reason for Exclusion
Pediatrics, 174, 944-951, 2020	
Song, L., Liu, F., Liu, Y., Zhang, R., Ji, H., Jia, Y., Clonazepam add-on therapy for drug-resistant epilepsy, Cochrane Database of Systematic Reviews, 2020 (4) (no pagination), 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Song, L., Liu, F., Liu, Y., Zhang, R., Ji, H., Jia, Y., Clonazepam add-on therapy for refractory epilepsy in adults and children, Cochrane Database of Systematic Reviews, 2018 (5) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Sourbron, J., Klinkenberg, S., van Kuijk, S. M. J., Lagae, L., Lambrechts, D., Braakman, H. M. H., Majoie, M., Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis, Child's Nervous System, 36, 1099-1109, 2020	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for included studies
Sperling, M., Harvey, J., Biraben, A., Andrea Galimberti, C., Kowacs, P., Hong, S. B., Cheng, H., Blum, D., Nunes, T., Soares-Da-Silva, P., Adjunctive eslicarbazepine acetate in patients with refractory partial-onset seizures: efficacy results of a 12 week randomized placebo-controlled study <after the author list please add: > On behalf of the 3 04 study team, Epilepsy currents., 14, 393â€• 394, 2014	Conference abstract
Sperling, Michael R., Klein, Pavel, Aboumatar, Sami, Gelfand, Michael, Halford, Jonathan J., Krauss, Gregory L., Rosenfeld, William E., Vossler, David G., Wechsler, Robert, Borchert, Leona, Kamin, Marc, Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study, Epilepsia, 61, 1099-1108, 2020	No a RCT
Squillacote, D., Krauss, G., Vaiciene-Magistris, N., Kumar, D., A phase II study evaluating the safety, tolerability and efficacy of perampanel, a selective AMPA receptor antagonist, in patients with refractory partial seizures, Epilepsy Currents, 11, 2011	Conference abstract
Steinhoff, B. J., Ben-Menachem, E., Ryvlin, P., Shorvon, S., Kramer, L., Satlin, A., Squillacote, D., Yang, H., Zhu, J., Laurenza, A., Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analysis of three phase III studies, Epilepsia, 54, 1481-1489, 2013	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Steinhoff, B. J., Sanchez-Alvarez, J., Majkowska-Zwolinska, B., Maciejowski, M., Villanueva, V., Brandt, C., Efficacy and safety of cenobamate as adjunctive therapy in patients with uncontrolled focal seizures: Results from two double-blind, placebocontrolled, international studies, European Journal of Neurology, 27, 60, 2020	Conference Abstract
Steinhoff, B. J., Somerville, E. R., Van Paesschen, W., Ryvlin, P., Schelstraete, I., The	No RCT

Study	Reason for Exclusion
SKATE study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy, Epilepsy Research, 76, 6-14, 2007	
Steinhoff, B. J., Trinka, E., Wieser, H. G., Dach-Lev Study Group, Levetiracetam in patients with refractory epilepsy: results of the SKATE trial in Austria, Germany and Switzerland, Seizure, 14, 490-6, 2005	No RCT
Stockings, E., Zagic, D., Campbell, G., Weier, M., Hall, W. D., Nielsen, S., Herkes, G. K., Farrell, M., Degenhardt, L., Evidence for cannabis and cannabinoids for epilepsy: A systematic review of controlled and observational evidence, Journal of Neurology, Neurosurgery and Psychiatry, 89, 741-753, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Sveinbjornsdottir, S., Sander, J. W. A. S., Patsalos, P. N., Upton, D., Thompson, P. J., Duncan, J. S., Neuropsychological effects of tiagabine, a potential new antiepileptic drug, Seizure, 3, 29-35, 1994	Cross-over study design
Szaflarski, J. P., Sadek, A., Greve, B., Williams, P., Varner, J. A., Moseley, B. D., Randomized open-label trial of intravenous brivaracetam versus lorazepam for acute treatment of increased seizure activity, Epilepsy and Behavior, 109 (no pagination), 2020	No add-on therapy
Tabrizi, N., Zarvani, A., Rezaei, P., Cheraghmakani, H., Alizadeh-Navaei, R., Levetiracetam in genetic generalized epilepsy: A prospective unblinded active-controlled trial, Epilepsy Research, 157 (no pagination), 2019	No add-on therapy
Taghdiri, M. M., Bakhshandeh Bali, M. K., Karimzadeh, P., Ashrafi, M. R., Tonekaboni, S. H., Ghofrani, M., Comparative efficacy of zonisamide and pregabalin as an adjunctive therapy in children with refractory epilepsy, Iranian Journal of Child Neurology, 9, 49-55, 2015	No outcome of interest
Tartara, A., Manni, R., Galimberti, C. A., Vigabatrin in the treatment of epilepsy: A double-blind, placebo-controlled study, Epilepsia, 27, 717-723, 1986	Cross-over study design
Theodore, W. H., Raubertas, R. F., Porter, R. J., Nice, F., Devinsky, O., Reeves, P., Bromfield, E., Ito, B., Balish, M., Felbamate: A clinical trial for complex partial seizures, Epilepsia, 32, 392-397, 1991	Cross-over study design
Thilothammal, N., Banu, K., Ratnam, R. S., Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study, Indian Pediatrics, 33, 549â€• 555, 1996	No add-on therapy
Tian, X., Yuan, M., Zhou, Q., Wang, X., The efficacy and safety of brivaracetam at different doses for partial-onset epilepsy: a meta-analysis of placebo-controlled studies, Expert Opinion on Pharmacotherapy, 16, 1755-67, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
Titre-Johnson, S. T. J., Schoeler, N. S., Eltze, C. E., Williams, R. W., Vezyroglou, K. V., McCullagh, M. C., Freemantle, N. F., Heales, S. H., Kneen, R. K., Marston, L. M., et al.,, Ketogenic diet in the treatment of epilepsy in children under the age of two years, Developmental Medicine and Child Neurology, 59, 119â€• , 2017	Conference abstract
Tjia-Leong, E., Leong, K., Marson, A., Lamotrigine add-on for refractory generalized tonic-clonic seizures, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Tjiaâ€• Leong, E., Leong, K., Marson, A. G., Lamotrigine adjunctive therapy for refractory generalized tonicâ€• clonic seizures, Cochrane Database of Systematic Reviews, 2010	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Togha, M., Akhondzadeh, S., Motamedi, M., Ahmadi, B., Razeghi, S., Allopurinol as Adjunctive Therapy in Intractable Epilepsy: A Double-blind and Placebo-controlled Trial, Archives of Medical Research, 38, 313-316, 2007	No outcomes of interest
Toledo, M., Whitesides, J., Schiemann, J., Johnson, M. E., Eckhardt, K., McDonough, B., Borghs, S., Kwan, P., Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures, Epilepsia, 57, 1139-1151, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
TomoviÄ‡, M., IliÄ‡, T., MihajloviÄ‡, M., JoviciÄ‡, A., Gabapentin as adjuvant therapy in the treatment of refractory partial epilepsy, Vojnosanitetski Pregled, 56, 151â€• 156, 1999	Article in Serbian
Trinka, E., Straub, H., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., Analysis of seizure frequency reduction by concomitant antiepileptic drug (aed) use with adjunctive perampanel: pooled phase iii results, Epilepsia, 53, 194â€• 195, 2012	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Uijl, S. G., Uiterwaal, C. S., Aldenkamp, A. P., Carpay, J. A., Doelman, J. C., Keizer, K., Vecht, C. J., de Krom, M. C., van Donselaar, C. A., Adjustment of treatment increases quality of life in patients with epilepsy: a randomized controlled pragmatic trial, European journal of neurology, 16, 1173â€• 1177, 2009	no add-on therapy
Upadhyay, A., Perween, S., Lal, P., Jaiswal, V., Gulati, I., Comparison of Phenobarbitone and Levetiracetam in the Treatment of Seizures in Term and Near Term Neonates: a Randomised Controlled Trial, Pediatric academic societies annual meeting; 2012 april 28 - may 1; boston ma, united states, 2012	Conference abstract
Uthman, B. M., Bazil, C. W., Beydoun, A., Schulze-Bonhage, A., Benabou, R., Whalen, E., Emir, B., Griesing, T., Leon, T., Long-term add-on pregabalin treatment in patients with partial-onset epilepsy: Pooled analysis of open-label	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
clinical trials, Epilepsia, 51, 968-978, 2010	
Vaz da Silva, M., Costa, R., Soares, E., Maia, J., Falcão, A., Almeida, L., Soares da Silva, P., Effect of eslicarbazepine acetate on the pharmacokinetics of digoxin in healthy subjects, Fundamental & Clinical Pharmacology, 23, 509â€• 514, 2009	Cross-over study design
Velez, F. F., Bond, T. C., Anastassopoulos, K. P., Wang, X., Sousa, R., Blum, D., Cramer, J. A., Impact of seizure frequency reduction on health-related quality of life among clinical trial subjects with refractory partial-onset seizures: A pooled analysis of phase III clinical trials of eslicarbazepine acetate, Epilepsy and Behavior, 68, 203-207, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Viraraghavan, V. R., Seth, A., Aneja, S., Singh, R., Dhanwal, D., Effect of high dose vitamin d supplementation on vitamin d nutrition status of pre-pubertal children on anti-epileptic drugs - A randomized controlled trial, Clinical Nutrition ESPEN, 29, 36-40, 2019	No outcomes of interest
Viteva, E., Zahariev, Z., Comparative effectiveness of add-on therapy with newer-generation antiepileptic drugs in Bulgarian patients with refractory epilepsy, Epilepsy & Behavior, 87, 137-145, 2018	No RCT
Vossler, D. G., Zonisamide as adjunctive therapy for adults with partial- onset epileptic seizures: An efficacy and safety review, Clinical Medicine Insights: Therapeutics, 2, 331-339, 2010	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Wechsler, R. T., French, J., Trinka, E., Brandt, C., O'Brien, T., Bibbiani, F., Patten, A., Laurenza, A., Long-term safety and efficacy outcomes of adjunctive perampanel: an open-label extension (OLEx) of a Phase III study in patients with drug-resistant primary generalized tonic-clonic (PGTC) seizures in idiopathic generalized epilepsy (IGE), Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Weston, J., Shukralla, A., McKay, A. J., Marson, A. G., Lacosamide add-on therapy for partial epilepsy, The Cochrane database of systematic reviews, 6, CD008841, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Wijnen, B. F. M., de Kinderen, R. J. A., Lambrechts, D. A. J. E., Postulart, D., Aldenkamp, A. P., Majoie, M. H. J. M., Evers, S. M. A. A., Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy, Epilepsy Research, 132, 91-99, 2017	this was an economic evaluation conducted alongside a RCT (Lambrechts 2017: already been excluded [no add-on therapy]).
Wu, T., Chuang, Y. C., Huang, H. C., Lim, S. N., Hsieh, P. F., Lee, W. T., Cheng, M. Y., Tsai, M. H., Jou, S. B., Chang, C. W., Hsieh, H. Y., Du, X., Hellot, S., McClung, C., Hung, C., A	No a RCT

Study	Reason for Exclusion
prospective, multicenter, noninterventional study in Taiwan to evaluate the safety and tolerability of lacosamide as adjunctive therapy for epilepsy in clinical practice, Epilepsy and Behavior, 113 (no pagination), 2020	
Wu, X., Wu, L. W., Wang, Y. P., Hong, Z., Zhao, Z. X., Huang, Y. G., Zhou, D., Wang, X. F., A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of zonisamide as adjunctive treatment in patients with refractory partial seizures, Chinese journal of neurology, 43, 459â€• 463, 2010	Article no in English
Xiao, Y., Luo, M., Wang, J., Luo, H., Losigamone add-on therapy for partial epilepsy, Cochrane database of systematic reviews (Online), 6, CD009324, 2012	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Xiao, Y., Luo, M., Wang, J., Luo, H., Losigamone add-on therapy for focal epilepsy, Cochrane Database of Systematic Reviews, 2018 (1) (no pagination), 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Xu, Z., Zhao, H., Chen, Z., The efficacy and safety of rufinamide in drug-resistant epilepsy: A meta-analysis of double-blind, randomized, placebo controlled trials, Epilepsy Research, 120, 104-110, 2016	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Yagi, K., Kameyama, S., Kaneko, S., Murasaki, M., Yamauchi, T., Multicenter, double-blind, randomized, placebo-controlled study of levetiracetam as add-on therapy in Japanese patients with uncontrolled partial seizures, Journal of the japan epilepsy society, 28, 3â€• 16, 2010	Article in Japanese
Yagi, K., Takeda, A., Kawai, I., The clinical efficacy of nh-15 (clobazam) for the treatement refractory epilepsy by the double-blind comparative study with inactive placebo, Igakunoayumi, 174, 229â€• 241, 1995	Artcicle in Japenese.
Yamada, M., Yoshida, K., Suzuki, A., Adjunctive therapy of levetiracetam in adult Japanese patients with uncontrolled partial-onset seizures: pooled data from two double-blind, placebo-controlled, randomized trials, Therapeutic research, 36, 787â€• 797, 2015	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Yuen, A. W. C., Sander, J. W., Fluegel, D., Patsalos, P. N., Browning, L., Bell, G. S., Johnson, A. L., Dogherty, C., Cunningham, C., Koepp, M. J., Double-blind, placebo-controlled parallel-group trial of omega-3 fatty acid supplementation in patients with chronic epilepsy, Epilepsia, 45 Suppl 7, 151, 2004	Conference abstract
Yuen, A. W. C., Sander, J. W., Fluegel, D., Patsalos, P. N., Browning, L., Bell, G. S., Johnson, A. L., Koepp, M. J., Double-blind placebo-controlled parallel-group trial of omega-3 fatty acid supplementation in patients with chronic epilepsy, Epilepsia, 46 Suppl 6, 194, 2005	Conference abstract

Study	Reason for Exclusion
Zaccara, G., Giovannelli, F., Franco, V., Cincotta, M., Tramacere, L., Verrotti, A., Adverse events, placebo and nocebo effects in placebo-treated paediatric patients with refractory focal epilepsies. Analysis of double-blind studies, Epilepsy Research, 108, 1685-1693, 2014	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Zadeh, W. W., Escartin, A., Byrnes, W., Tennigkeit, F., Borghs, S., Li, T., Dedeken, P., De Backer, M., Efficacy and safety of lacosamide as first add-on or later adjunctive treatment for uncontrolled partial-onset seizures: a multicentre open-label trial, Seizure, 31, 72â€• 79, 2015	No RCT
Zagnoni, P. G., Bianchi, A., Zolo, P., Canger, R., Cornaggia, C., D'Alessandro, P., DeMarco, P., Pisani, F., Gianelli, M., Verze, L., Viani, F., Zaccara, G., Allopurinol as add-on therapy in refractory epilepsy: A double-blind placebo-controlled randomized study, Epilepsia, 35, 107-112, 1994	Cross-over study design
Zare, M., Okhovat, A. A., Esmaillzadeh, A., Mahvary, J., Najafi, M. R., Saadatnia, M., Modified atkins diet in adult patients with refractory epilepsy: a controlled randomized clinical trial, Epilepsia, 56, 12, 2015	Conference abstract
Zhang, L., Li, S., Li, H., Zou, X., Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison, Seizure, 39, 28-33, 2016	Network meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Zhang, L., Liu, Y., Ding, C., Shi, S., Lin, W., Chen, T., Sun, H., Xu, Y., Dong, W., Chen, Q., et al.,, The efficacy and safety of zonisamide as adjunctive therapy in patients with partial seizure: a multicenter, randomized, double-blinded, placebo-controlled trial, Chinese journal of contemporary neurology and neurosurgery, 11, 408â€• 412, 2011	Article in Chinese
Zhang, L., Wang, C., Li, W., A meta-analysis of randomized controlled trials on levetiracetam in the treatment of pediatric patients with epilepsy, Neuropsychiatric Disease and Treatment, 14, 769-779, 2018	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Zhang, Y., Zhang, Y. X., Li, D., Lin, H. H., Song, Y. J., Meta-analysis of adjunctive levetiracetam in refractory partial seizures, Chinese journal of contemporary neurology and neurosurgery, 12, 542â€• 551, 2012	Article in Chinese
Zhang,L.L., Zeng,L.N., Li,Y.P., Side effects of phenobarbital in epilepsy: A systematic review, Epileptic Disorders, 13, 349-365, 2011	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Zhu, L. N., Chen, D., Xu, D., Tan, G., Wang, H. J., Liu, L., Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: An indirect comparison, Seizure, 51, 121-132, 2017	Network meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
Zis, P., Shafiq, F., Mitsikostas, D. D., Nocebo effect in refractory partial epilepsy during pre-surgical monitoring: Systematic review and meta-analysis of placebo-controlled clinical trials, Seizure, 45, 95-99, 2017	Systematic review/meta-analysis of randomised controlled trials (RCTs), no relevant data could be extracted for inclusion. References checked for inclusion
Zou, X., Yuan, T., Wu, B., Efficacy of progabide add-on for refractory epilepsy, Epilepsia, 53, 117â€• , 2012	Conference Abstract

Economic studies

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix L – Research recommendations

Research recommendations for review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

No research recommendations were made for this review question.

Appendix M – Network Meta-analysis full methods, results and discussion

Network Meta-analysis full methods, results and discussion for review review questions:

What (add-on) antiseizure therapies are effective in the treatment of generalised tonic-clonic seizures?

What (add-on) antiseizure therapies are effective in the treatment of focal onset seizures?

Objective

To estimate the relative effectiveness and summarise adverse events for ASMs for treating or managing focal seizures and generalised tonic-clonic seizures.

Methods

Study selection

Literature search

The literature search strategies for these review questions are presented in appendix B. The following databases were searched for randomised controlled trial (RCT) evidence on antiseizure therapies for focal seizures and generalised tonic-clonic (GTC) seizures.

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Embase
- MEDLINE

References from any identified systematic reviews were explored to identify any references not picked-up by the literature search.

Evidence was searched for up until the 3rd February 2021. No lower date limit was selected. Only studies reported in the English language were eligible for inclusion in the review. The literature search strategy was deliberately composed so as not to limit the results by type of ASM so any published RCT of ASM would be identified and be eligible for inclusion in the review.

Population

Network meta-analyses (NMAs) were conducted for 2 different populations: people with focal seizures and people with GTC seizures. RCTs, which involved children, young people or adults (or combinations of), were eligible for inclusion in the review and NMAs. Only new born babies (under 28 days old) with acute symptomatic seizures were excluded from the review based on age. RCTs of people with focal seizures and GTC seizures with or without other generalised seizure types (absence, myoclonus, and etcetera) were eligible for inclusion in the review and NMA. Add-on therapy was defined for this review as antiseizure therapy prescribed to people that have failed to respond to one or more ASM or had refractory epilepsy.

Interventions

The protocols for the NMAs did not explicitly include or exclude any specific type of ASM. All ASMs (and combinations of) aimed at treating or managing epileptic seizure in the above population were eligible for inclusion. Non-pharmacological interventions (or combinations of pharmacological and non-pharmacological) were eligible for the review and NMAs if they provided indirect evidence (that is, as a common comparator to two antiseizure medications) for the network. Such interventions were included in the NMA but did not form part of the decision problem when making recommendations. This includes placebo, which is the predominant comparator intervention in RCTs of add-on ASMs.

Trial arms with differing dosage of the same drug will be pooled together in the analysis as dose comparisons are outside of the scope of this review and guideline. The committee also highlighted that dosage was often fluid with dosage up or down titrated based on the impact on seizure frequency and the associated adverse events.

Outcome measures

Two primary outcomes of interest were identified for the review, which were considered likely to form a connected network and be reported sufficiently, similarly across different trials so as not to break the assumption of homogeneity across pooled interventions. RCTs were included in the NMA if they reported either or both outcome measures. These two outcome measures were:

- >50% reduction in seizure frequency during treatment or maintenance period
- Seizure freedom during treatment or maintenance period

Two other outcomes of interest were identified, but it was considered that these would be reported too heterogeneously to make pooling or direct comparison between interventions useless and would not be reported in a sufficient number of studies to form a network. These outcome measures were:

- Health-related quality of life
- Adverse events

These outcomes were only collected for studies which reported one of primary outcomes above. Given the issues identified above, especially heterogeneity about how such outcomes are collected and reported, these two outcomes were presented in a non-comparative summary.

Data, where reported, was collected and presented for adverse events for the following ways:

- The percentage of trial participants who reported adverse events or serious adverse events as defined by the trial
- The percentage of trial participants who ceased treatment as a result of adverse events
- The number of deaths reported regardless of cause

Other exclusion criteria

RCTs with a cross-over design, where all trial participants received all treatments of interest consecutively were excluded from the NMAs. Cross-over designs are associated with a higher proportion of drop-outs, unblinding whilst patients crossed into other treatment and the potential for carry-over effects. Such designs are no longer recommended for clinical trials in epilepsy (Nevitt 2017).

Studies with a mixed population (that is, including people with epilepsy and others with a condition different to epilepsy) were excluded from the review unless subgroup analysis for

those with epilepsy was reported or was able to be calculated from the published evidence. For mixed populations of people with focal onset and GTC seizures, where the individual seizure types were not reported separately, the study was included in the focal onset NMAs but not the GTC NMA. It was considered by the committee that the majority of participants in such studies would have focal onset seizures given this is the most prevalent seizure type.

Data Extraction

10% of the literature identified for this topic was dual weeded by 2 independent reviewers for potentially relevant studies. Any discrepancies were resolved by discussion between the 2 reviewers and where necessary with a third reviewer. Following discussion, the final 90% of literature was weeded by a sole reviewer. The full text of potentially relevant studies were retrieved and assessed for inclusion in the NMA based on the criteria listed above. All outcome measures plus other potentially relevant information was dual extracted by the 2 reviewers who performed the weeding. Data was extracted into an Excel spreadsheet following the Data extraction for complex meta-analysis (DECiMAL) guidance (Pedder 2016). Any discrepancies between reviewers in extraction were resolved through discussion with referral to a third reviewer where necessary.

Placebo response rate was also calculated from the extracted data for both primary outcomes where possible so placebo response rate could be adjusted for in the analyses if appropriate. Data for the 2 primary outcomes was collected in count form both for trial participants and for a positive outcome. The denominator in the NMA was the total number of people randomised to the treatment. Missing data was treated as a negative result (that is, a reduction in seizure frequency of 50% or seizure freedom had not been achieved). This was considered the most conservative assumption. It was also considered that people who did not make it to the final follow-up were more likely to have had a negative experience with the medication either through adverse events or lack of effectiveness in controlling seizures. Where the studies did not report the total number randomised other figures were used for example ‘per protocol’. Where multiple other total numbers were reported by a study the largest value was used for the analyses. All data was analysed under intention-to-treat principles.

‘Median seizure frequency at baseline over 28-days’ was also extracted for all studies so baseline placebo response rate could be adjusted for in the analyses. Where baseline seizure frequency was reported ‘over one month’ this was assumed to be 28 days unless the published paper stated otherwise. Where baseline response rate was reported over shorter or longer periods these were adjusted to a 28-day period assuming perfect correlation (that is,frequency over a 7-day period would be multiplied by 4).

Risk of bias

The risk of bias for individual studies was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Higgins 2019). RoB 2 assesses the risk of bias of individual studies based on 5 domains covering the randomisation process, deviation from intended interventions, missing outcomes, measurement of data and reported results to give an overall risk of bias of either ‘high risk of bias’, ‘some concerns’ or ‘low risk of bias’. Assessment of the risk of bias was only performed for the 2 primary outcomes for which NMAs were performed. Given that both seizure frequency and seizure freedom would be calculated from the same collected trial data a combined assessment was undertaken for both as it was considered very unlikely that there would be any difference in risk of bias between the two.

Adjusting for placebo response rate

It has been hypothesised that the placebo response rate has changed overtime, so called ‘placebo drift’, which could potentially bias results for or against newer drugs (Guekht 2010).

The baseline response for placebo has most likely changed both through an improvement in the management of epilepsy unrelated to inclusion in the trial and through tougher selection criteria for inclusion in clinical trials.

The aim of this was to estimate any correlation between placebo response rate (measured as a positive outcome on either of the primary outcomes) and response for ASM and identify any statistically significant correlation indicating 'placebo drift'. It also investigated whether the response rate for placebo had, and in which direction, changed overtime by looking for a correlation between study publication date (used as a proxy for trial start date) and placebo response rate. Correlation was estimated by first calculating a pooled response rate in the control arm for all placebo controlled trials identified. A Spearman rank correlation coefficient was then calculated to identify and assess any correlation between placebo response rate and relative effectiveness of interventions using odds ratios. The Spearman rank correlation was then calculated to identify the direction of any placebo drift overtime. Similar investigation was also undertaken using metaregression with placebo response rate and year of publication used as covariates to see if they would be significant coefficients (p-value less than 0.05) in estimating relative effectiveness. For the above analyses active ASMs were all pooled together into one comparator of active treatment. This analysis was performed in Stata 13 statistical software (Statacorp 2013). Metaregression was undertaken using the Stata command Metan (Harris 2008).

The above analyses were also undertaken for baseline seizure frequency over 28 days at baseline as this was also hypothesised to be correlated with the relative effectiveness outcomes. To allow for consistency between the 2 analyses, studies were not included in either if they did not report a median baseline seizure frequency either because they only reported a mean or this was not reported in any form at baseline.

To further investigate and control for any potential 'placebo drift', placebo response was controlled for in further network meta-analyses for the 2 primary outcomes to see if these provided a better model fit for data. Whilst adjusting for any potential differences in placebo response, it may also adjust for multiple known and unknown differences between the studies included in the NMAs (Cameron 2019). Better model fit for the adjusted model would suggest the possibility of placebo drift.

Unadjusted and baseline response adjusted NMAs

Four NMAs were created in total for the primary outcomes and unadjusted and placebo response adjusted NMA for both focal and GTC seizures.

All NMAs for focal seizures were random effects models. It was not considered appropriate to run alternate fixed effects models for these analyses given it was unlikely that the 'true effect' size is exactly the same for all studies given the large number identified, wide time range and preformed hypotheses of placebo drift. Previous NMAs for evidence on focal seizures, which were likely to include a large number of identical studies to those included in this analysis, concluded that random effects models provided a better goodness of fit compared to fixed effects (Bodalia 2013, Charokopou 2019, Hu 2018, Hu 2020, Zhao 2017). It was also anticipated that a large number of RCTs would be identified for this population with focal seizures. It was decided therefore that performing such analyses would not be useful for decision making.

For GTC seizures it was anticipated that the evidence would be much less than that of focal seizures random and fixed effect models were compared to estimate which provided the best fit for the data. The most appropriate model was decided using the same criteria as for the adjusted and unadjusted models as described below.

The NMAs were created to estimate the odds ratio for the two primary outcomes compared to all other ASMs. Predominantly throughout this report the odds ratio for the effectiveness of

any ASM is compared to placebo as this is the most commonly used comparator for such drug trials.

For these NMAs the data for each trial is comprised of a binomial likelihood:

$$r_{jk} \sim \text{Bin}\,(p_{jk}, n_{jk})$$

where p_{jk} is the probability of the relevant primary outcome in trial j under treatment k, r_{jk} is the number of people experiencing the event in trial j under treatment k, and n_{jk} is the total number of people at risk of the event in trial j under treatment k.

Since the parameters of interest, p_{jk}, are probabilities and therefore can only take values between 0 and 1, a transformation (link function) was used that mapped these probabilities into a continuous measure between minus and plus infinity. Since this was a binomial likelihood the logit link function was used. The probabilities of positive outcome p_{jk} were modelled on the logit scale as:

$$\text{logit}(p_{ik}) = \mu_i + d_{12} \text{ x } I_{\{k \neq 1\}}$$

where

$$I_{\{u\}} = \begin{cases} 1 & \text{if u is true} \\ 0 & \text{otherwise} \end{cases}$$

In the fixed effects model the between-trial heterogeneity σ^2 was set to 0 which was equivalent to assuming homogeneity of the underlying true treatment effects.

The analysis was undertaken following Bayesian statistical principles.

For the adjusted models additional code was added to adjust for baseline response, through meta-regression, as outlined by NICE TSU technical report 3 (Dias 2016). To establish if the adjusted models were a better fit for data information including the deviance information criteria, the posterior residual deviance and the size of the 95% credible intervals were compared between the adjusted and unadjusted models in line with TSU technical report 3.

NMAs were undertaken in WinBUGS 14 (Lunn 2000) using code adapted from Dias 2016. All WinBUGS code is reported in additional information A.

For the analyses a 100,000 'burn-in simulations were run to allow convergence in the models. Following that 60,000 simulations were run to estimate the outputs for the analysis. To assess whether the model had good convergence the history and kernel density plots were checked.

Network meta-analyses also have to respect the assumption of consistency that is that the indirect and direct estimates of any treatment effect do not contradict each other. Inconsistency was assessed by comparing the results from the direct estimates to those of indirect estimates. Results were highlighted as inconsistent if the point estimate from the direct estimate did not fit within the 95% credible intervals of the indirect estimates.

Sensitivity analyses

As per the protocol for this review the following sensitivity analyses, which further restrict the inclusion criteria for this review, would be carried out for the two primary outcomes if sufficient networks could be formed (defined as including >75% of the treatments identified in the primary analysis):

- Studies which excluded women of childbearing aged due to teratogenic risk were excluded from the network

In addition to the above the following NMAs for sub-groups were created if sufficient networks could be formed:

- By previous treatment
- Those with treatment resistant epilepsy (defined as “failure of two tolerated, appropriately chosen and used antiepileptic drug schedules”)

Furthermore, if evidence of inconsistency in the network was identified (as discussed above), studies contributing to this were checked for data accuracy and assessment of study inclusion. Baseline characteristics will be checked to identify any differences in effect modifiers across studies. Analyses will be repeated if corrections in the data extraction or study inclusion are made. If an important effect modifier is identified, then this may be explored in subgroup analyses if sufficient evidence is available. However, if evidence of inconsistency is still present following data corrections, revisiting inclusion criteria and exploring effect modification, no further studies will be excluded from the analysis, as their results cannot be considered as less valid than those of other studies solely because of the inconsistency findings. The presence of inconsistency in the NMA will be highlighted and results will be interpreted accordingly.

Presentation of results

For all primary outcomes odds ratio (including 95% credible intervals) were presented between the active treatment and placebo unless otherwise stated. Odds ratios were sorted by the point estimate of the odds-ratio with higher odds ratios (indicating higher effectiveness) being presented first in any tables or forest plots. This ordering needs to be interpreted with caution given the potential for large credible intervals around some estimates indicating great uncertainty. Given the large number of interventions and the opinion of the committee that more than 1 drug was likely to be recommended for treatment of seizures in these populations, probabilities of treatments being optimal (being the most effective treatment) were not presented in this report as they were not considered helpful to decision making.

Registration of systematic review

The above systematic review and network meta-analysis protocol were registered with PROSPERO registration number: CRD42020176581

Results

Results of literature search

From the search of the relevant databases 18,066 potentially eligible studies were identified of which 448 were retrieved for full text review. Systematic reviews were also checked for potentially eligible studies but did not yield any that were not identified by the database search. Five studies were excluded because they reported duplicate trials or the trial population was a sub-set of one already identified. Overall 109 RCTs were identified reported across 106 journal articles. One study reported outcomes disaggregated by focal and GTC seizures and was treated as two separate RCTs for the purposes of the PRISMA flowchart. More detail of which analyses studies are presented in appendix D. For the PRISMA diagram of study selection see appendix C.

Risk of bias

The assessment of risk of bias are presented in additional information B. Across all studies 43 were judged to have a 'low risk of bias', 41 'some concerns' and 26 had a 'high risk of bias'. The reason for downgrading was consistently high across all the domains (ranging from 20 to 41 studies downgraded per domain) apart from domain 5, concerned with selective reporting of outcomes, for which only 5 studies scored less than 'low risk'.

Placebo response rate

A total of 73 trials eligible for inclusion in the focal seizure NMA were also eligible for conducting a meta-analysis of placebo response for the outcome 50% reduction in seizure frequency and 41 trials for seizure freedom involving 25824 and 13579 trial participants, respectively. The same analyses for GTC seizures were not undertaken given the paucity of evidence identified.

Placebo response rates for 50% reduction in seizure frequency varied from 0 (not presented in forest plot) and 41% (Figure 3) and 1-9% for seizure freedom (Figure 4). There was significant heterogeneity for this outcome between studies for 50% reduction in seizure frequency (Cochran's Q test of homogeneity had a p-value <0.001) but this was not the case for seizure freedom (Cochran's Q test of homogeneity had a p-value=0.30). The random effects meta-analysis estimated a pooled placebo response rate of 16% (95%CI 15%-17%). Random effects metaregression did find a positive relationship between a later year of publication and increased placebo response (regression coefficient=0.0049, p=0.005) suggesting a 0.5 percentage point (95%CrI 0.2-0.8) increase in placebo response rate per year if a linear relationship is assumed. No relationship was identified between median baseline seizure frequency and placebo response rate (p=0.053) with a coefficient of -0.00483 or 0.48% reduction in response rate for each seizure at baseline. Spearman rank coefficient however suggested a correlation for baseline median seizure frequency and placebo response rate (Spearman's q =-0.2918, P = 0.0184) but not year of publication (Spearman's q =0.2372, P = 0.06)

For seizure freedom the pooled placebo response rate was 1% (95% CI 1%-2%) a significant result above zero despite only 4 of the 41 eligible trials showing a response rate significantly above zero. Metaregression found no relationship between publication year (p=0.591) or baseline median response (p=0.704) on placebo response. This was supported by Spearman rank coefficients with the hypothesis test of no correlation both having p-values of 0.571 and 0.170 respectively. The forest plots of all trials included the above analyses with their estimated placebo response rate and 95% confidence intervals are presented in Figure 3 and Figure 4.

Figure 3:Forest plot of placebo response rate for reduction of 50% focal seizures

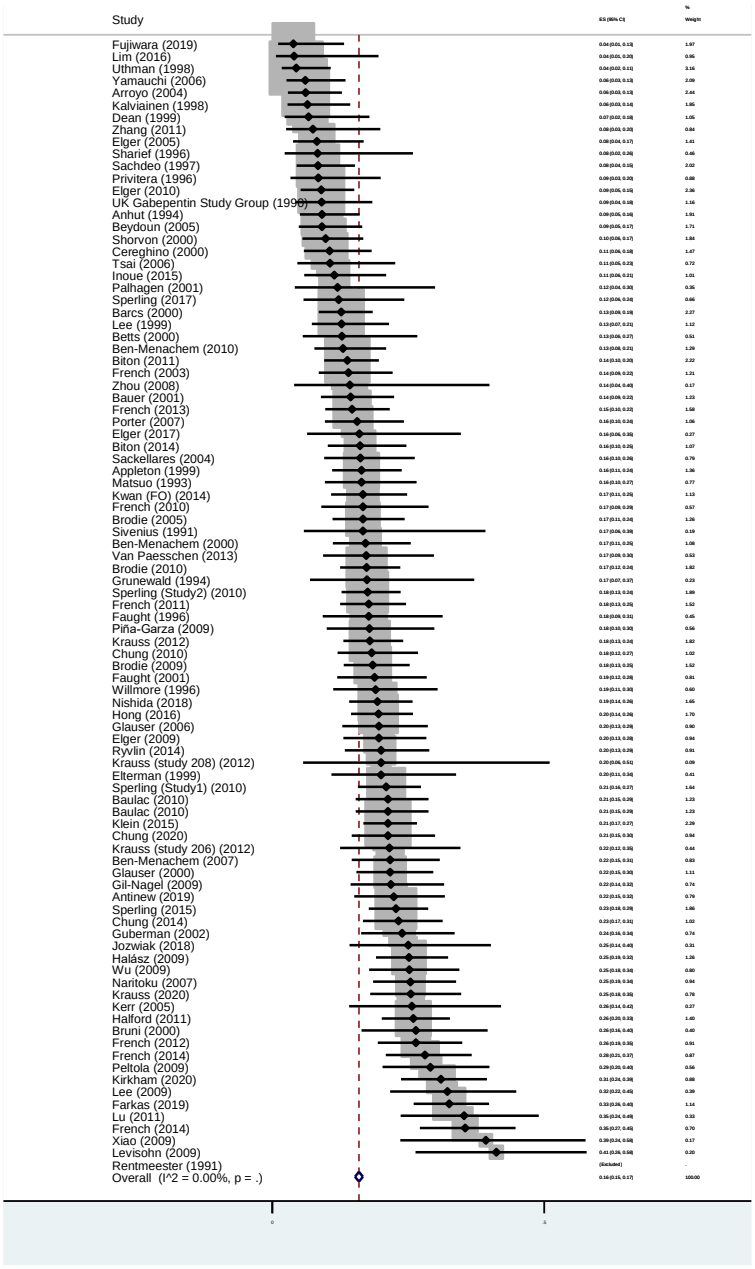
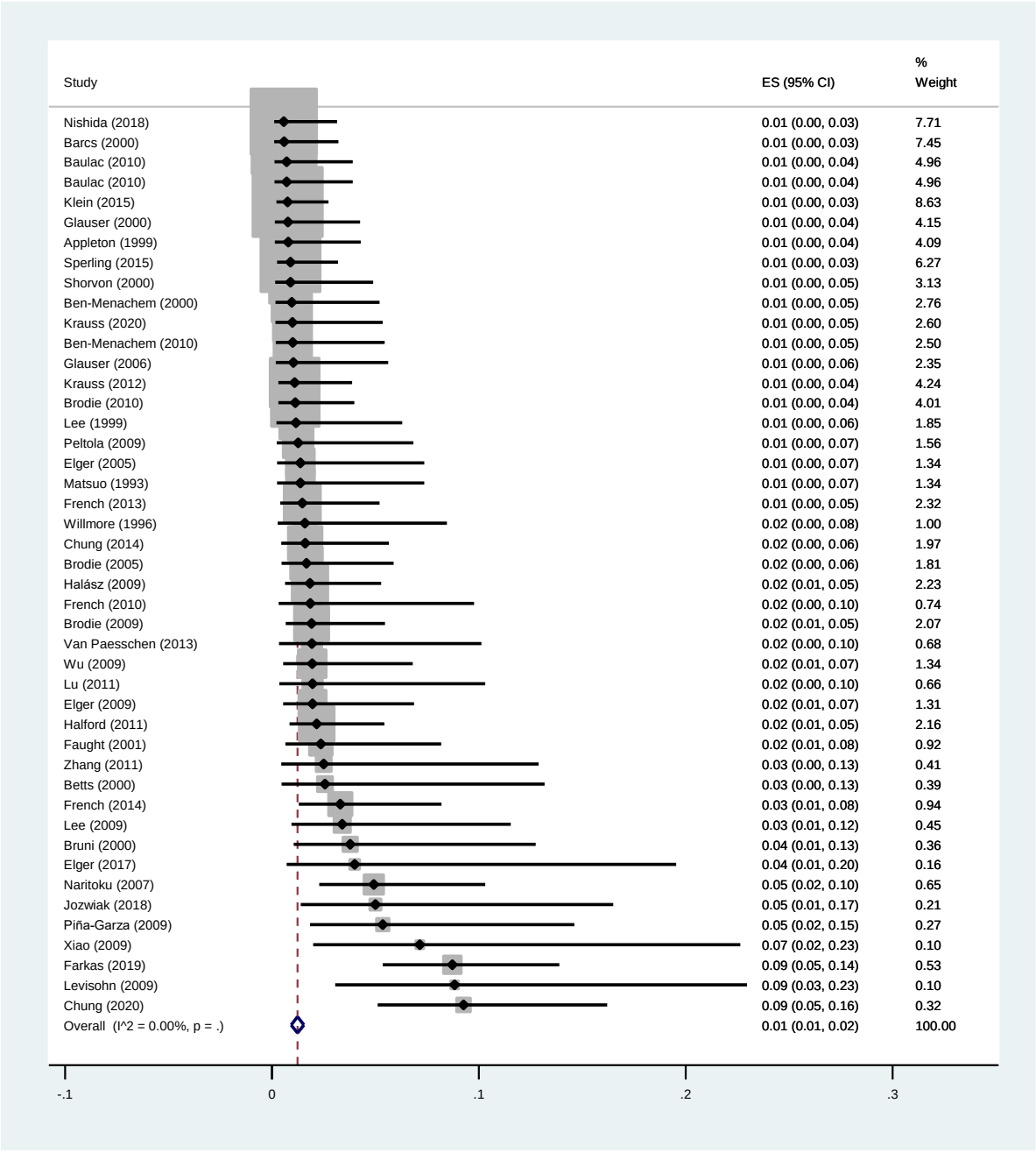


Figure 4:Forest plot of placebo response rate for reduction of seizure freedom in focal seizures



Data and network plot of unadjusted and adjusted network meta-analysis for 50% reduction in seizure frequency for focal seizures

The network plot for 50% reduction in seizure frequency in people with focal seizures is presented in Figure 5. As with all network plots in this report larger nodes indicate more people randomised to those ASMs and wider arms indicate greater number of trials with that direct comparison. Where there are no arms linking specific ASMs then no direct evidence was identified in the literature search. The network plot for the 99 studies reported across 97 articles were identified as reporting the 50% reduction in seizure frequency outcome involving 27,686 individuals. Evidence for a total of 26 treatments were identified (25 active ASMs and placebo) with 8,873 people were randomised to placebo (32.0%) with 25,284

(91.3%) being part of a placebo controlled trial where participants in at least one arm received placebo.

Figure 5: Network plot for 50% reduction in seizure frequency in people with focal seizures

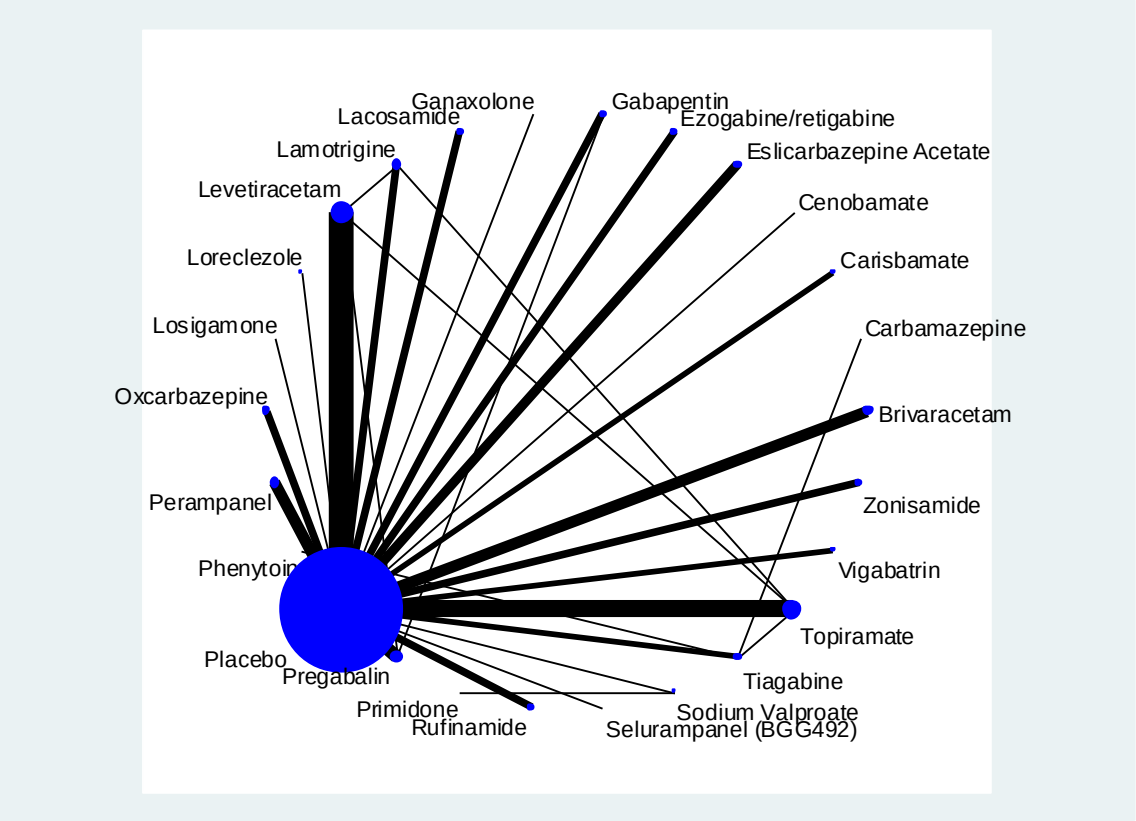
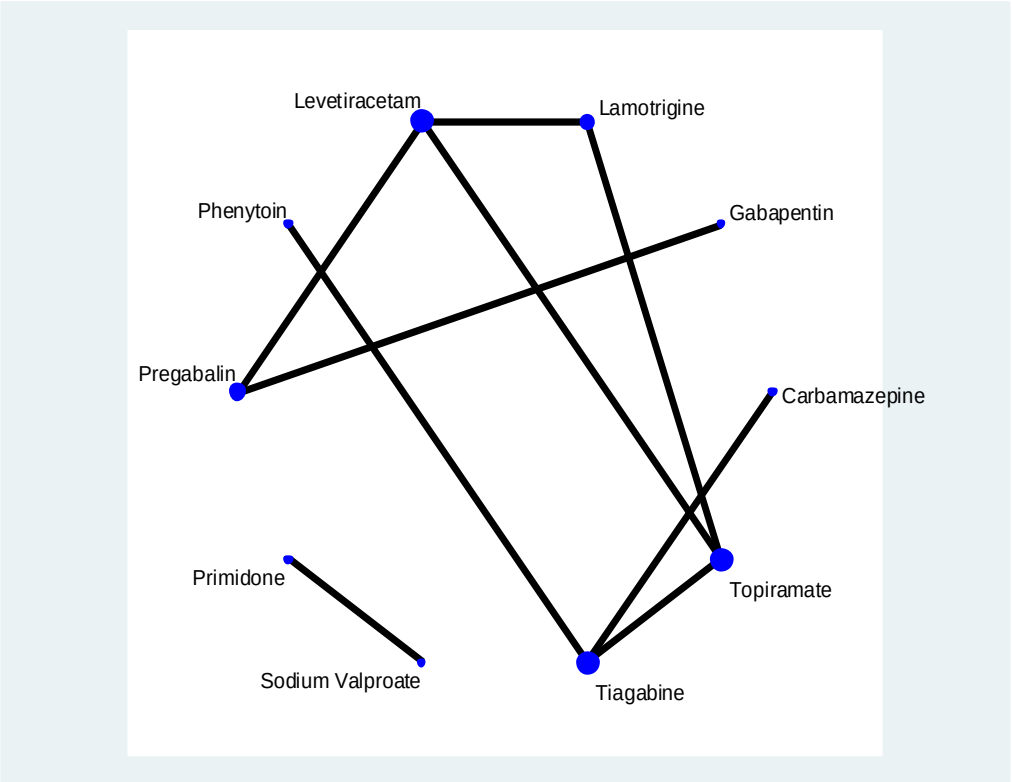


Figure 6 presents the network plot for the same analysis with placebo removed. Where trials with greater than 2 arms have two active treatments compared to placebo, the arm linking the active treatments is included. This diagram is for illustrative purposes only (to show the direct comparisons between active treatments in the analysis and it is not a separate analysis). Direct comparisons between active treatments makes up less than 10% of all the evidence in the NMA.

Figure 6: Network plot 50% reduction in seizure frequency in people with focal seizures placebo removed

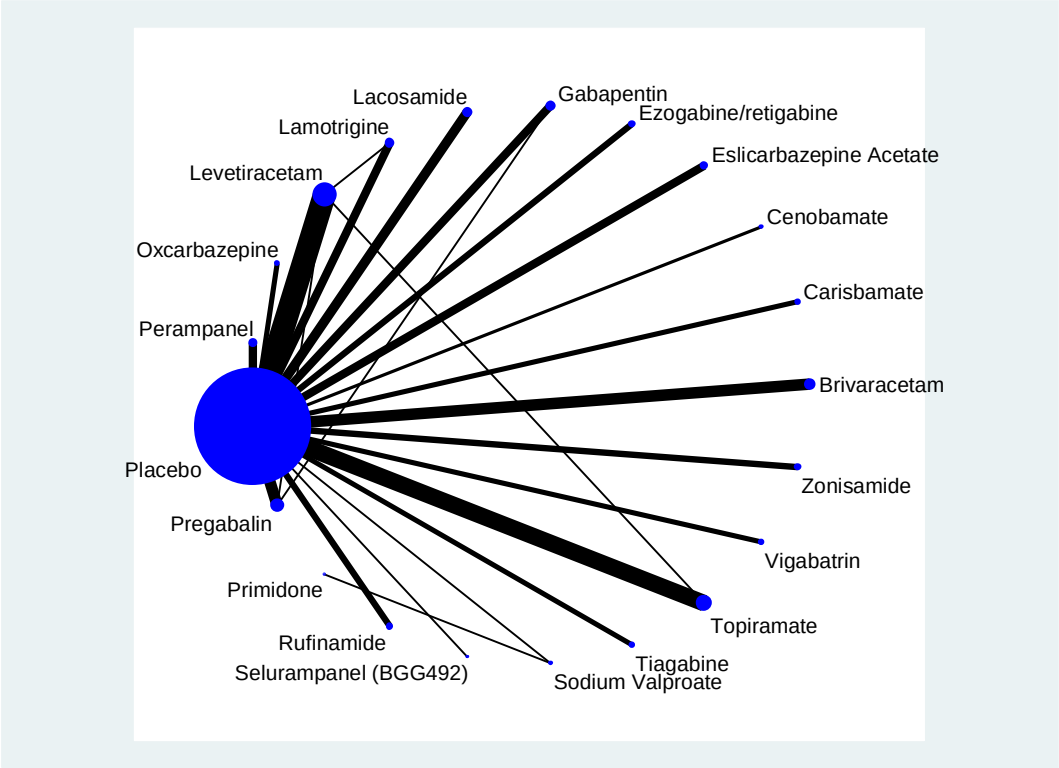


Full list of included studies and the trial data are presented in additional information C

Data and network plot of unadjusted and adjusted network meta-analysis for seizure freedom in focal seizures

The network plot for the 72 studies involving 20,826 people were identified as reporting the seizure freedom outcome. Evidence for a total of 21 active ASMs and placebo was identified. All studies which compared an active ASM to another active ASM were included in both NMAs and therefore the illustrative network plot of direct evidence between active ASMs is identical to that for 50% reduction in seizure frequency (Figure 6). Overall 70 of the 72 trials identified were also included in the 50% seizure reduction in focal seizures NMA discussed above with only 2 studies unique to this NMA. 6600 (31.7%) people were randomised to placebo with 19,605 (94.1%) being part of a placebo controlled trial.

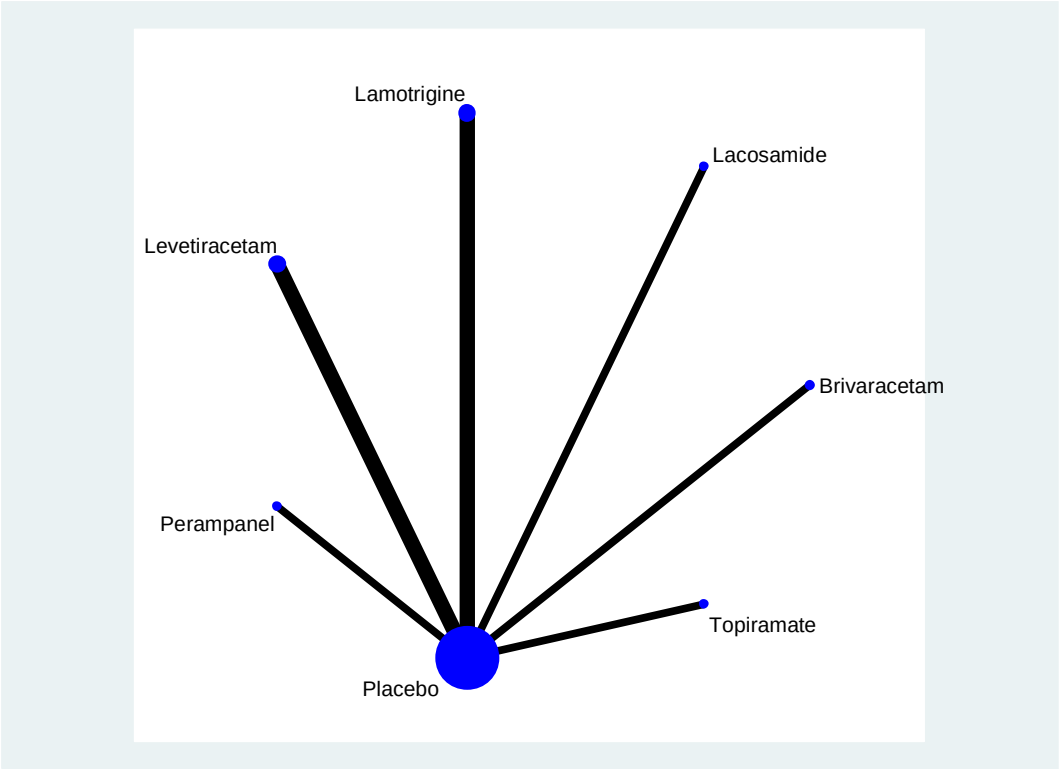
Figure 7: Network diagram seizure freedom in people with focal seizures



Data and network plot of network meta-analysis for 50% reduction in seizure frequency and seizure freedom in generalised tonic-clonic seizures

Eight studies were identified for both 50% reduction in seizure frequency and seizure freedom. The studies in both NMAs are identical and involve the same people resulting in an identical network plot for both (Figure 8). Evidence for 6 active ASMs and placebo was identified. All evidence was for active drugs compared to placebo and no direct evidence was identified between two active treatments. The network has 1218 people, 599 of which were randomised to placebo (49.2%).

Figure 8: Network diagram for 50% reduction in seizure frequency and seizure freedom in people with focal seizures



Outcomes for unadjusted and adjusted network meta-analysis for 50% reduction in seizure frequency for focal seizures

The median estimate of the comparative effectiveness and the 95% credible intervals for all ASMs in the unadjusted and adjusted NMA are presented in Table 5. All effectiveness estimates are presented as odds ratios compared to placebo. The table is sorted by median estimate of comparative effectiveness for the placebo response adjusted NMA. Loreclezole has the highest median estimate of comparative effectiveness (although with an extremely large range between the 95% credible intervals) in both NMAs. Carbamazepine has the second highest estimate odds ratio although again with large 95% credible intervals, although neither cross the value 1 where the drug has no effect compared to placebo. Carbamazepine, cenobamate, vigabatrin, topiramate, levetiracetam, lacosamide, oxcarbazepine, retigabine, zonisamide, pregablin, lamotrigine, eslicarbazepine acetate, brivaracetam and perampanel had 95% credible intervals which did not pass the line of no effect in both NMAs. For all drugs where the 95% credible intervals did not cross 1 in the adjusted NMA the same was true for the unadjusted NMA. For loreclezole, tiagabine, rufinamide, losigamone and gabapentin for which 95% credible intervals did not cross 1 in the unadjusted NMA the same was not true for the adjusted NMA. Forest plots for the adjusted NMA are presented in Appendix E. Median estimates of comparative effectiveness are lower for all drugs in the adjusted NMA compared to the unadjusted NMA other than cenobamate.

The 95% credible intervals for all ASMs in the adjusted NMA were narrower than for the unadjusted with the exception of cenobamate. The unadjusted model reported a deviance information criterion (DIC) statistic of 1301.93 compared to 1273.75 for the adjusted model. The posterior mean of the residual deviance is also lower for the adjusted NMA compared to the unadjusted NMA (199.7 compared to 196.3).

A matrix of comparative effectiveness estimates of all possible pairings of ASMs in the adjusted model for 50% reduction in seizure frequency are presented in additional information C. When comparing active treatments to other active treatments cenobamate shows relative effectiveness compared to a large number of other drugs in the network including lamotrigine, levetiracetam and perampanel. Levetiracetam also has an estimated greater relative effectiveness than perampanel. Gabapentin which was recommended for the pharmacological treatment of focal seizures in the previous NICE guidance has an estimated relative effectiveness compared to placebo where the 95% credible intervals pass the line of no effect. It is also estimated that levetiracetam, cenobamate, oxcarbazepine, vigabatrin and topiramate were more effective than gabapentin.

Table 5: Estimated odds ratios of comparative effectiveness for the unadjusted and adjusted network meta-analyses for 50% reduction in seizure frequency for focal seizures

Antiseizure medication	Unadjusted NMA OR (95% CrI)	Adjusted NMA OR (95% CrI)
Loreclezole	30.08(1.71-13360)	8.36(0.57-1001)
Carbamazepine	9.76(2.91-32.94)	4.19(1.62-11.34)
Cenobamate	2.30(1.23-4.29)	3.77(2.43-6.00)
Vigabatrin	4.38(2.14-9.22)	2.92(1.58-5.45)
Topiramate	3.54(2.54-5.03)	2.27(1.73-3.01)
Levetiracetam	3.10(2.37-4.09)	2.23(1.80-2.77)
Lacosamide	2.42(1.64-3.55)	2.07(1.61-2.68)
Oxcarbazepine	2.91(1.81-4.74)	2.03(1.45-2.83)
Phenytoin	4.47(1.42-14.11)	1.97(0.78-4.83)
Ezogabine/retigabine	3.13(1.93-5.18)	1.91(1.33-2.75)
Zonisamide	2.43(1.47-4.02)	1.89(1.29-2.75)
Sodium valproate	2.64(0.92-7.86)	1.86(0.82-4.65)
Pregabalin	2.41(1.8-3.26)	1.72(1.39-2.14)
Lamotrigine	1.74(1.04-2.92)	1.58(1.09-2.28)
Eslicarbazepine Acetate	1.96(1.35-2.87)	1.55(1.2-2.02)
Brivaracetam	2.26(1.55-3.33)	1.54(1.16-2.03)
Ganaxolone	2.71(0.83-9.74)	1.47(0.52-4.28)
Perampanel	2.03(1.38-2.99)	1.46(1.11-1.94)
Tiagabine	3.26(1.76-6.17)	1.42(0.81-2.49)
Gabapentin	2.28(1.46-3.58)	1.4(0.96-1.96)
Selurampanel (BGG492)	2.17(0.56-10.31)	1.31(0.41-5.26)
Rufinamide	2.04(1.24-3.42)	1.16(0.77-1.71)
Carisbamate	1.44(0.89-2.33)	1.12(0.83-1.53)
Losigamone	1.72(0.62-4.85)	0.98(0.44-2.19)
Primidone	1.26(0.29-5.59)	0.89(0.30-2.91)

Outcomes for unadjusted and adjusted network meta-analysis for seizure freedom for focal seizures

Table 6 presents the unadjusted and adjusted NMAs for seizure freedom. The 95% credible intervals for the estimates of relative effectiveness are, in general. wider for this analysis than for the 50% reduction in seizure frequency outcome. Cenobamate had the highest estimated comparative effectiveness in the adjusted NMA and levetiracetam had the highest

in the unadjusted and second highest in the adjusted. However 95% credible intervals were wide for both drugs. The 2 ASMs with the narrowest 95% credible intervals lamotrigine and pregabalin did not demonstrate effectiveness for this outcome (the 95% credible intervals passed the line of no effect) in either NMA although the intervals were still relatively wide. All median estimates of comparative effectiveness were lower in the adjusted NMA compared to the unadjusted apart from for cenobamate and lamotrigine. Levetiracetam, brivaracetam, retigabine, oxcarbazepine, topiramate, perampanel, lacosamide and eslicarbazepine all had credible intervals for seizure freedom which did not cross the line of no effect in both NMAs with cenobamate doing the same in only the unadjusted NMA.

95% credible intervals are narrower in the adjusted NMA for all ASMs, apart from cenobamate, compared to the unadjusted NMA. The DIC statistic (651.73 versus 656.40) and posterior mean of the residual deviance (139.8 versus 150.3 on 71 data points) is higher for the adjusted NMA compared to the unadjusted NMA.

Table 6: Estimated odds ratios of comparative effectiveness for the unadjusted and adjusted network meta-analyses for seizure freedom for focal seizures

Antiseizure medication	Unadjusted NMA OR (95% CrI)	Adjusted NMA OR (95% CrI)
Cenobamate	4.06(0.92-20.96)	12.62(1.01-453.1)
Levetiracetam	10.19(5.01-22.59)	8.84(4.65-17.14)
Brivaracetam	9.85(2.63-50.63)	6.75(1.89-31.17)
Ezogabine/retigabine	9.53(1.45-111.5)	6.15(1.02-61.76)
Sodium valproate	7.98(0.47-373)	5.76(0.37-236.2)
Oxcarbazepine	7.07(1.72-33.54)	5.29(1.36-21.82)
Vigabatrin	6.42(0.84-78.36)	5.03(0.71-54.1)
Topiramate	5.63(2.07-17.72)	4.88(1.95-13.36)
Perampanel	5.49(1.46-25.25)	4.45(1.57-13.78)
Lacosamide	4.76(1.54-19.37)	3.85(1.34-13.81)
Primidone	4.34(0.12-324.4)	3.14(0.11-185.6)
Eslicarbazepine Acetate	4.05(1.31-13.7)	3.12(1.03-10.04)
Gabapentin	4.5(0.22-202.6)	2.92(0.18-114.9)
Carisbamate	2.73(0.31-26.7)	2.07(0.28-16.08)
Pregabalin	2.46(0.82-7.65)	2.02(0.70-5.62)
Lamotrigine	1.73(0.61-5.00)	1.88(0.88-4.04)
Selurampanel (BGG492)	2.08(0.11-93.76)	1.85(0.12-79.15)
Zonisamide	2.41(0.52-12.27)	1.8(0.42-8.12)
Tiagabine	2.05(0.04-69.26)	1.75(0.03-48.42)
Rufinamide	2.21(0.21-26.15)	1.68(0.19-16.07)

Outcomes for network meta-analysis for 50% reduction in seizure frequency and seizure freedom for generalised tonic-clonic seizures

Table 7 presents the results of the fixed effects NMA for 50% reduction in seizure frequency and seizure freedom in people with GTC seizures. The random effects meta-analysis estimated very wide 95% credible intervals and provided a very poor fit for the data points as predicted given the paucity of evidence identified.

For all ASMs in the fixed effects NMA the 95% credible intervals did not cross 1 suggesting they are more effective than placebo for 50% reduction in seizure frequency. For seizure

freedom the same was true of levetiracetam, perampanel and lacosamide although 95% credible intervals were often wide with the exception of lacosamide. The fixed effects model had a posterior mean of residual deviance of 21.22 from 8 data points and a DIC statistic of 107.5 for 50% reduction in seizure freedom and 16.04 and 87.14 respectively for seizure freedom.

Table 7: Estimated odds ratios of comparative effectiveness for meta-analyses for 50% reduction in seizure frequency and seizure freedom for generalised tonic-clonic seizures- fixed effects network meta-analysis

Antiseizure medication	50% reduction in seizure frequency OR (95% CrI)	Seizure free OR (95% CrI)
Brivaracetam	5.10(1.08-41.1)	2.62(0.11-1327)
Levetiracetam	5.08(3.36-7.77)	12.24(5.1-37.1)
Topiramate	3.71(1.36-11.15)	7.14(0.31-3455)
Lamotrigine	3.53(2.14-5.91)	1.79(0.92-3.54)
Perampanel	2.93(1.55-5.62)	3.44(1.56-8.11)
Lacosamide	1.94(1.16-3.31)	2.03(1.15-3.63)

Forest plots of the estimates for 50% reduction in seizure frequency are shown in appendix E. The matrix showing odds ratios for all possible comparisons of ASMs are presented in additional information C. The only identified ASM with effectiveness when compared to another active treatment was levetiracetam which was more effective than lacosamide.

Sensitivity analyses

No sufficient networks (defined as including >75% of the treatments identified in the primary analysis) for any of the planned analyses were identified. Therefore, none of the planned sensitivity analyses were carried out.

Summary analysis of adverse events

A summary of adverse events are presented in additional information D.

Discussion

For focal seizures this analysis estimated that loreclezole and carbamazepine had the highest point estimate of relative effectiveness compared to placebo for 50% reduction in seizure frequency however both these estimates had wide 95% credible intervals. All the evidence for loreclezole came from one older study (published in 1991) which was rated as having a 'some concern' with risk of bias when using the Cochrane ROB v2 tool. Loreclezole was also the only study in the focal seizure NMA to report zero events in an arm for 50% reduction in seizure frequency outcome. Similarly, for carbamazepine all evidence was from one older study with a high risk of bias as rated for all domains. It is difficult therefore to have great confidence in these estimates. Neither study provided indirect evidence for other ASMs in the network and therefore the inclusion or exclusion of these two studies would not have a significant impact on results or conclusions of the NMAs. Cenobamate was third highest point estimate of relative effectiveness compared to placebo and had relatively narrow credible intervals. All evidence was based on two studies published in 2020 rated as having a low risk of bias. The estimated effectiveness for cenobamate was also greater than that for lamotrigine, levetiracetam and gabapentin all drugs recommended in the previous NICE guideline for add-on treatment for focal seizures. Brivaracetam, carbamazepine, cenobamate, , eslicarbazepine acetate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregablin, retigabine,vigabatrin and zonisamide were all effective compared to placebo for a 50% reduction in seizure frequency.

For GTC seizures all ASMs identified for the network had estimated relative effectiveness when compared to placebo with the only estimated relative effect between 2 active treatments being levetiracetam showing higher relative effectiveness than lacosamide.

For all analyses the NMAs for estimating seizure freedom did not provide a great fit for the data and it was difficult to lend weight to any of the conclusions. Even those estimates with 95% credible intervals that did not pass the line of no effect were very wide. Even though seizure freedom is often seen as a strong predictor of higher quality of life it was reasonably rare in people receiving add-on treatment. Studies often explicitly stated, even when this outcome was considered, that the numbers did not give it sufficient statistical power to consider this outcome given it is particularly rare especially in the placebo group (pooled seizure freedom rate of 1%) with 21 studies having zero events in the placebo arm and 2 studies reporting zero events in either arm of the trial.

This is the first meta-analysis to identify a 'placebo drift' where the response rate for placebo has changed overtime for 50% reduction in seizure frequency. This was supported by the Spearman rank coefficient test, meta-regression and the improved fit of the adjusted model in the NMA. Guekht 2010 had previously investigated this in people with focal seizures but found no statistically significant correlation although from a smaller sample of 27 studies involving 5,662 randomised individuals. The median effectiveness of ASMs also differed between the unadjusted and adjusted NMAs with adjusting for placebo response generally favouring newer drugs such as cenobamate. This was particularly true when comparing active treatments to each other as is an often listed benefits of network meta-analysis. Future meta-analyses and network meta-analyses in treatment and management of focal seizures should ensure that potential 'placebo drift' is explored and adjusted for.

Previous published NMAs have been identified for this patient group although they were exclusively in patients with focal seizures. No previously published network meta-analysis for GTC seizures was identified. All NMAs had tighter inclusion criteria than this analysis mostly in terms of drugs included and patient group and none adjusted for placebo response (Badolta 2013, Charokopou 2019, Hu 2018, Hu 2020, Zhao 2017). All studies showed effectiveness for some ASMs compared to placebo which were largely in line with estimates from this analysis. All studies found little evidence of effectiveness between active

treatments. This analysis did identify some difference in relative effectiveness between active treatments, although a large number of these were in comparisons to cenobamate which was not included in any of the identified published NMAs. For the analysis in this report and those previously published NMAs the majority of the evidence came from indirect comparators through placebo with the authors the previously published studies analyses recommending that head-to-head trials between active treatments would be beneficial in estimating relative effectiveness.

The impact of publication bias on the results was not investigated for either focal or GTC seizures. The results of these analyses may have been impacted by publication bias, for example where results had not been published because they were unfavourable to the active treatment. None of the trials in the analyses were funded from public sources. Charokopou 2019 in their NMA attempted to investigate publication bias in active ASMs with greater than 10 published trials using Egger's test and funnel plot in line with the Cochrane handbook. However, they found no evidence of publication bias for 50% reduction in seizure frequency or seizure freedom outcomes identical to the primary outcomes used in this analysis. This analysis also only attempted to find published evidence with records in publicly available databases. No attempt was made to identify unpublished data for example through looking through clinical trial databases. Clinical trials with independent funders may be beneficial in investigating the effectiveness of ASMs. It was unlikely given the paucity of evidence that publication bias could have been adequately explored for GTC seizures and no previous evidence was identified on the topic.

These NMAs pooled all arms of drugs regardless of dosage. It was decided to do this as dosage was often fluid being titrated upwards or downwards based upon tolerability and adverse events. Most RCTs also allowed for the physician in charge of treatment for the person to use their own clinical judgement in deciding dosage even if this was against protocol. Given the large potential for cross-over between dosage arms, and to better reflect clinical practice, dosages were not disaggregated in the analysis. Previous studies have excluded RCTs or arms of RCTs if dosages were outside the approved range for prescribing. For identical reasons for pooling dosages such trials or arms were not excluded.

All ASMs were included in the NMAs to maximise the evidence around placebo and potential indirect evidence of relative effectiveness regardless of whether they were licensed for use in this patient group in England. The entirety of the results have been presented here but consideration needs to be given to licensing considerations when recommending ASMs alongside the effectiveness and safety data, the accompanying cost effectiveness model and other available evidence not covered by the scope of this review.

The model suggests that comparative synthesis of evidence on ASMs should consider a potential 'placebo drift' when analysing data and interpreting results. This analysis found good evidence for the effectiveness of cenobamate compared to placebo and a number of prescribed ASMs in terms of achieving a 50% reduction in seizure frequency. There was limited evidence for the GTC group but it appeared a number of ASMs could be effective in achieving a 50% reduction in seizure frequency. There was very limited evidence on seizure freedom and it was difficult to make any strong conclusions from any of the NMAs. Large trials are needed to better investigate this outcome, although recruiting such numbers may prove difficult. Direct comparative trials between active treatments with independent funders would be useful in confirming the most effective treatments for managing seizure frequency. Evidence on adverse events, tolerability, deaths and health related quality of life were reported inconsistently or not at all between different trials and therefore comparing between different ASMs for these outcomes was difficult. These outcomes are important to people with epilepsy and better evidence on these outcomes would aid in decision making around the 'best' ASM for focal and GTC seizures.

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Additional Information A: WinBUGS code

Unadjusted model (focal seizures- both primary outcomes, random effects model GTC seizures- both primary outcomes)

```
# Binomial likelihood, logit link
# Random effect model, multi-arm trials
model{                                          # *** PROGRAM STARTS
for(i in 1:ns){                                  # LOOP THROUGH STUDIES
  w[i,1] <- 0                                   # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0                                # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)                          # vague priors for all trial baselines
  for (k in 1:na[i]) {                           # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])                 # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]           # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k]                 # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))      #Deviance contribution
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])              # summed residual deviance contribution for this trial
  for (k in 2:na[i]) {                          # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])        # trial-specific LOR distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]   # mean of LOR distributions (with multi-arm correction)
    taud[i,k] <- tau *2*(k-1)/k                  # precision of LOR distributions (with multi-arm correction)
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])  # adjustment for multi-arm RCTs
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)             # cumulative adjustment for multi-arm trials
   }
}
totresdev <- sum(resdev[])                       #Total Residual Deviance
d[1]<- 0                                        # treatment effect is zero for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001)}         # vague priors for treatment effects
sd ~ dunif(0,2)
```

```
tau <- pow(sd,-2)

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
      or[c,k] <- exp(d[k] - d[c])
      lor[c,k] <- (d[k]-d[c])
     }
}

# ranking
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[],k)          # assumes events are “good”
  # rk[k] <- rank(d[],k)             # assumes events are “bad”
  best[k] <- equals(rk[k],1)         #calculate probability that treat k is best
}                                    # *** PROGRAM ENDS
```

Adjusted model (focal seizures- both primary outcomes)

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                               # *** PROGRAM STARTS
for(i in 1:ns){                      # LOOP THROUGH STUDIES
   w[i,1] <- 0                       # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0                   # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
   for (k in 1:na[i]) {              # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])   # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + delta[i,k]
            + (beta[t[i,k]]-beta[t[i,1]]) * (x[i]-mx)
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
```

```
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                    # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
# covariate effect relative to treat in arm 1
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])              # Total Residual Deviance
d[1]<-0                                 # treatment effect is zero for reference treatment
beta[1] <- 0                            # covariate effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){
    d[k] ~ dnorm(0,.0001)
    beta[k] <- B # common covariate effect
  }
B ~ dnorm(0,.0001)                      # vague prior for covariate effect
sd ~ dunif(0,5)                         # vague prior for between-trial SD
tau <- pow(sd,-2)                       # between-trial precision = (1/between-trial variance)
# treatment effect when covariate = z[j] (un-centring treatment effects)
for (k in 1:nt){
    for (j in 1:nz) { dz[j,k] <- d[k] - (beta[k]-beta[1])*(mx-z[j]) }
  }
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
# at mean value of covariate
```

```
        or[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
# at covariate=z[j]
        for (j in 1:nz) {
          orz[j,c,k] <- exp(dz[j,k] - dz[j,c])
          lorz[j,c,k] <- (dz[j,k]-dz[j,c])
        }
      }
 }
  }
}                                          # *** PROGRAM ENDS
```

Fixed effects model GTC seizures- both primary outcomes

```
# Binomial likelihood, logit link, MTC
# Fixed effect model
model{                                                  # *** PROGRAM STARTS
for(i in 1:ns){                                         # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)                                 # vague priors for all trial baselines
  for (k in 1:na[i]) {                                  # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])                        # binomial likelihood
    logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]        # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k]                        # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))      #Deviance contribution
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])              # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[])                      #Total Residual Deviance
d[1]<- 0                                        # treatment effect is zero for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001) }      # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
```

```
        or[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
       }
}

# ranking
for (k in 1:nt) {
   rk[k] <- nt+1-rank(d[],k)              # assumes events are “good”
   # rk[k] <- rank(d[],k)                 # assumes events are “bad”
   best[k] <- equals(rk[k],1)             #calculate probability that treat k is best
}

}                                                  # *** PROGRAM ENDS
```

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Additional Information B: Assessment of risk of bias for included studies

Table 8:Risk of bias assessment for studies included in the network meta-analyses

	Domain 1 Risk of bias arising from the randomisation process	Domain 2 Risk of bias due to deviations from the intended interventions	Domain 3 Missing outcome data	Domain 4 Risk of bias in measurement of the outcome	Domain 5 Risk of bias in selection of the reported result	Overall risk of bias
Anhut 1994	Low	Low	High	Low	Low	High
Antinew 2019	Some	Some	Low	Some	Low	Some
Appleton 1999	Some	Some	Low	Some	Low	High
Arroyo 2004	Low	Low	Low	low	Low	Low
Barcs 2000	Some	Some	High	Some	Low	High
Bauer 2001	Some	Low	Low	High	Low	High
Baulac 2010	Some	Some	Low	Some	Low	High
Ben-Menachem 2000	Low	Low	Low	low	Low	Low
Ben-Menachem 2007	Some	Low	High	Low	Low	High
Ben-Menachem 2010	Low	Low	High	Low	Low	High
Berkovic 2007	Low	Low	Low	Some	Low	Some
Betts 2000	Low	Low	High	low	Low	High
Beydoun 2005	Low	Low	Low	low	Low	Low
Biton 1999	Low	Low	Low	Low	Low	Low
Biton 2005	Some	Some	Some	Some	Low	High
Biton 2010	Some	Some	Some	Some	Low	High
Biton 2011	low	Low	Low	low	Low	low
Biton 2014	Low	Low	Low	Low	Low	Low
Blum 2006	Low	Some	Low	Some	Low	Some
Brodie 2005	Some	Low	Low	Some	low	Some
Brodie 2009	low	Low	Low	low	Low	low
Brodie 2010	Low	Low	Low	Low	Low	Low
Bruni 2000	Low	Some	Low	Some	Low	Some
Cereghino 2000	Low	Low	Low	low	Low	Low
Chung 2010	Low	Low	Some	Low	Low	Some
Chung 2014	Low	Low	Low	Low	Low	Low
Chung 2020	Low	Low	Low	Low	Low	Low
CramerA 2001	Some	Some	Some	Some	Some	High
CramerB 2001	Some	Some	Some	Some	Some	High
Dean 1999	Low	Low	Low	Low	Low	Low
Elger 2005	Low	Low	Low	low	Low	Low
Elger 2009	Low	Low	High	Low	Low	High

	Domain 1 Risk of bias arising from the randomisation process	Domain 2 Risk of bias due to deviations from the intended interventions	Domain 3 Missing outcome data	Domain 4 Risk of bias in measurement of the outcome	Domain 5 Risk of bias in selection of the reported result	Overall risk of bias
Elger 2010	Low	Some	Low	Some	Low	Some
Elger 2017	Some	Low	Low	Some	Low	Some
Elterman 1999	low	Low	Low	Some	Low	low
Farkas 2019	Some	Some	Low	Some	Low	Some
Faught 1996	low	Low	Low	Some	Low	Some
Faught 2001	Low	Some	Some	Some	low	Some
French 2003	Low	Low	Low	low	Low	Low
French 2010	Low	Low	Low	Low	Low	Low
French 2011	Low	Low	Low	Low	Low	Low
French 2012	Low	Low	Low	Low	Low	Low
French 2013	Low	Low	Some	Low	Low	Some
French 2014	Low	Low	High	low	Low	High
French 2014	Some	Some	Low	Some	Low	Some
French 2015	Low	Low	Low	Low	Low	Low
French 2016	Low	Low	Low	Some	Low	Some
Fritz 2005	High	High	Low	High	Some	High
Fujiwara 2019	Some	Low	Low	Some	Low	Some
Gil-Nagel 2009	Low	Low	High	Low	Low	High
Glauser 2000	Low	Low	Some	low	Low	Low
Glauser 2006	Low	Low	Low	low	Low	Low
Grunewald 1994	Low	Some	Some	Low	Low	Some
Guberman 2002	Some	Low	Low	Some	Low	Some
Halász 2009	Low	Low	Some	Low	Low	Some
Halford 2011	Low	Some	High	Some	Low	High
Hong 2016	Low	Low	Low	Low	Low	Low
Inoue 2015	Some	Low	Low	Some	Low	Some
Jozwiak 2018	Some	Some	High	Low	Low	High
Kalviainen 1998	low	Low	Low	low	Low	low
Kerr 2005	Some	Low	High	Some	Low	Low
Kirkham 2020	Some	Some	Low	Low	Low	Some
Klein 2015	Low	Low	Low	Low	Low	Low
Krauss (study 206) 2012	Low	Low	Low	Low	Low	Low
Krauss (study 208) 2012	Low	Low	Low	Low	Low	Low
Krauss 2012	Low	Low	Low	Low	Low	Low
Krauss 2020	Low	Low	Low	Low	Low	Low
Kwan 2014	Some	Low	Low	Low	Low	Some
Labiner 2009	Some	Some	Low	Some	Low	Some

	Domain 1 Risk of bias arising from the randomisation process	Domain 2 Risk of bias due to deviations from the intended interventions	Domain 3 Missing outcome data	Domain 4 Risk of bias in measurement of the outcome	Domain 5 Risk of bias in selection of the reported result	Overall risk of bias
Lee 1999	low	Low	Low	Some	Low	low
Lee 2009	Some	Some	Low	Some	Low	Some
Lee 2019	Low	High	Some	Some	Low	High
Levisohn 2009	Some	Some	Low	Some	Low	High
Lim 2016	Some	Some	Low	Some	Low	Some
Lu 2011	Some	Low	Some	Some	low	Some
Matsuo 1993	Low	Low	Low	Some	Low	Some
Naritoku 2007	Some	Some	Low	Some	Low	High
Nishida 2018	Low	Low	Low	Low	Low	Low
Palhagen 2001	Some	Low	Low	Low	Low	Some
Peltola 2009	Low	Low	Low	low	Low	Low
Piña-Garza 2009	Low	Low	Low	Low	Low	Low
Porter 2007	Some	Low	Low	Some	Low	Some
Privitera 1996	low	Low	Low	Some	Low	Some
Rentmeester 1991	Low	Low	Low	Low	Some	Some
Ryvlin 2014	Some	Low	Low	Low	Low	Some
Sachdeo 1997	Low	Low	Low	Low	Low	Low
Sackellares 2004	low	Low	Some	low	low	low
Sharief 1996	low	Low	Low	low	Low	low
Shorvon 2000	Low	Low	Low	low	Low	Low
Sivenius 1991	Some	Some	Low	Some	Low	Some
Sperling (Study1) 2010	Low	Low	Some	Some	Low	Some
Sperling (Study2) 2010	Low	Low	Some	Some	Low	Some
Sperling 2015	Low	Low	High	Low	Low	High
Sperling 2017	Some	Some	Low	Some	Low	Some
Sun 2009	Some	High	Low	Some	Low	High
Tsai 2006	Low	Low	Low	low	Low	Low
UK Gabepentin Study Group 1990	Low	Low	High	Low	Low	High
Uthman 1998	Some	Low	Low	low	Low	low
Van Paesschen 2013	Low	Low	Low	Low	Some	Some
Vossler 2020	Low	Low	Low	Low	Low	Low
Willmore 1996	Some	Low	Some	Low	Low	Some
Wu 2009	Low	Low	Low	Some	Low	Some
Wu 2018	Low	Low	Low	Low	Low	Low
Xiao 2009	Low	Low	Low	low	Low	Low
Yamauchi 2006	Some	Low	High	Low	Low	High

	Domain 1 Risk of bias arising from the randomisation process	Domain 2 Risk of bias due to deviations from the intended interventions	Domain 3 Missing outcome data	Domain 4 Risk of bias in measurement of the outcome	Domain 5 Risk of bias in selection of the reported result	Overall risk of bias
Zaccara 2014	Low	Low	Low	Low	Low	Low
Zhang 2011	Some	Some	Low	Some	Low	High
Zhou 2008	Low	Some	Low	Some	Low	Some

Additional Information C: Relative effect matrices

Table 9:Relative effect matrix for 50% reduction in seizure frequency in focal seizures adjusted network meta-analysis

	Placebo	Eslicarbazepine Acetate	Retigabine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Oxcarbazepine	Perampanel	Brivaracetam	Pregabalin	Rufinamide	Seluram panel (BGG492)	Sodium valproate	Tiagabine	Topiramate	Zonisamide	Primidone	Carisbamate	Cenobamate
Eslicarbazepine Acetate	**1.55(1.2, 2.02)**																			
Retigabine	**1.91(1.33 ,2.75)**	1.23(0.8, 1.88)																		
Gabapentin	1.4(0.96, 1.F96)	0.9(0.58, 1.35)	0.73(0.44 ,1.15)																	
Lacosamide	**2.07(1.61 ,2.68)**	1.34(0.94 ,1.92)	1.09(0.71 ,1.68)	1.49(0.99 ,2.33)																
Lamotrigine	**1.58(1.09 ,2.28)**	1.02(0.64 ,1.58)	0.83(0.49 ,1.38)	1.13(0.7, 1.86)	0.76(0.48 ,1.17)															
Levetiracetam	**2.23(1.8, 2.77)**	**1.44(1.03 ,1.98)**	1.17(0.78 ,1.74)	**1.6(1.1,2. 41)**	1.08(0.78 ,1.48)	1.42(0.94 ,2.16)														
Oxcarbazepine	**2.03(1.45 ,2.83)**	1.31(0.86 ,1.97)	1.06(0.66 ,1.7)	1.46(0.91 ,2.36)	0.98(0.65 ,1.48)	1.29(0.79 ,2.11)	0.91(0.62 ,1.34)													
Perampanel	**1.46(1.11 ,1.94)**	0.95(0.65 ,1.37)	0.77(0.5, 1.19)	1.05(0.7, 1.64)	0.71(0.49 ,1.02)	0.93(0.59 ,1.47)	**0.66(0.47 ,0.91)**	0.72(0.48 ,1.1)												
Brivaracetam	**1.54(1.16 ,2.03)**	0.99(0.69 ,1.43)	0.8(0.53, 1.25)	1.1(0.73, 1.72)	0.74(0.51 ,1.07)	0.97(0.62 ,1.55)	**0.69(0.49 ,0.96)**	0.76(0.5, 1.15)	1.05(0.72 ,1.53)											
Pregabalin	**1.72(1.39 ,2.14)**	1.11(0.8, 1.54)	0.9(0.61, 1.36)	1.23(0.9, 1.79)	0.83(0.6, 1.15)	1.09(0.74 ,1.64)	0.77(0.6, 1.01)	0.85(0.58 ,1.26)	1.17(0.84 ,1.64)	1.12(0.81 ,1.57)										
Rufinamide	1.16(0.77 ,1.71)	0.75(0.47 ,1.18)	0.6(0.36, 1)	0.83(0.51 ,1.38)	0.56(0.35 ,0.88)	0.73(0.43 ,1.25)	**0.52(0.34 ,0.78)**	**0.57(0.35 ,0.92)**	0.79(0.5, 1.24)	0.75(0.48 ,1.17)	0.67(0.44 ,1.02)									
Seluram panel (BGG492)	1.31(0.41 ,5.26)	0.85(0.26 ,3.44)	0.68(0.21 ,2.93)	0.95(0.28 ,3.98)	0.63(0.2, 2.6)	0.82(0.25 ,3.49)	0.58(0.18 ,2.4)	0.65(0.19 ,2.68)	0.89(0.27 ,3.71)	0.85(0.26 ,3.5)	0.76(0.23 ,3.1)	1.13(0.34 ,4.74)								
Sodium valproate	1.86(0.82 ,4.65)	1.2(0.51, 3.07)	0.97(0.4, 2.57)	1.33(0.56 ,3.54)	0.9(0.38, 2.33)	1.18(0.49 ,3.15)	0.83(0.36 ,2.14)	0.92(0.38 ,2.39)	1.27(0.54 ,3.25)	1.21(0.52 ,3.09)	1.08(0.46 ,2.71)	1.62(0.66 ,4.28)	1.42(0.28 ,6.24)							
Tiagabine	1.42(0.81 ,2.49)	0.93(0.5, 1.68)	0.75(0.4, 1.42)	1.03(0.53 ,1.93)	0.69(0.36 ,1.26)	0.91(0.47 ,1.75)	0.64(0.34 ,1.16)	0.71(0.37 ,1.33)	0.98(0.52 ,1.77)	0.93(0.53 ,1.67)	0.83(0.47 ,1.45)	1.24(0.64 ,2.38)	1.08(0.25 ,3.97)	0.77(0.27 ,2.05)						
Topiramate	**2.27(1.73 ,3.01)**	**1.47(1.02 ,2.12)**	1.19(0.78 ,1.84)	**1.63(1.09 ,2.53)**	1.1(0.77, 1.6)	1.43(0.94 ,2.3)	1.02(0.75 ,1.39)	1.12(0.74 ,1.7)	**1.55(1.07 ,2.28)**	**1.48(1.03 ,2.15)**	1.32(0.96 ,1.84)	**1.96(1.28 ,3.12)**	1.75(0.42 ,5.66)	1.23(0.47 ,2.88)	1.59(0.9, 2.95)					
Zonisamide	**1.89(1.29 ,2.75)**	1.22(0.78 ,1.91)	1(0.59,1. 62)	1.36(0.83 ,2.26)	0.91(0.58 ,1.43)	1.2(0.71, 2.03)	0.85(0.55 ,1.28)	0.93(0.57 ,1.54)	1.28(0.82 ,2.02)	1.24(0.78 ,1.95)	1.1(0.71, 1.66)	1.63(0.97 ,2.79)	1.44(0.35 ,4.88)	1.02(0.38 ,2.48)	1.31(0.69 ,2.58)	0.83(0.52 ,1.28)				
Primidone	0.89(0.3, 2.91)	0.57(0.19 ,1.91)	0.46(0.15 ,1.58)	0.64(0.21 ,2.22)	0.43(0.14 ,1.43)	0.57(0.18 ,1.96)	0.4(0.13, 1.32)	0.44(0.14 ,1.48)	0.61(0.2, 2.03)	0.58(0.19 ,1.92)	0.52(0.17 ,1.7)	0.77(0.25 ,2.68)	0.67(0.12 ,3.61)	0.48(0.22 ,1.02)	0.62(0.18 ,2.25)	0.39(0.13 ,1.31)	0.47(0.15 ,1.61)			
Carisbamate	1.12(0.83 ,1.53)	0.73(0.49 ,1.07)	**0.59(0.37 ,0.93)**	0.81(0.52 ,1.3)	**0.54(0.36 ,0.81)**	0.71(0.45 ,1.15)	**0.5(0.35, 0.72)**	**0.55(0.35 ,0.86)**	0.77(0.51 ,1.15)	0.73(0.49 ,1.1)	**0.65(0.45 ,0.94)**	0.97(0.6, 1.58)	0.85(0.21 ,2.83)	0.6(0.23, 1.44)	0.79(0.42 ,1.44)	**0.49(0.33 ,0.73)**	**0.59(0.37 ,0.96)**	1.26(0.37 ,3.89)		
Cenobamate	**3.77(2.43 ,6)**	**2.44(1.44 ,4.17)**	**1.97(1.09 ,3.62)**	**2.71(1.53 ,5)**	**1.81(1.09 ,3.08)**	**2.39(1.35 ,4.37)**	**1.7(1.01, 2.83)**	**1.87(1.06 ,3.29)**	**2.58(1.49 ,4.48)**	**2.45(1.43 ,4.33)**	**2.19(1.32 ,3.68)**	**3.27(1.74 ,6.13)**	2.9(0.65, 10.21)	2.03(0.73 ,5.21)	**2.65(1.21 ,5.6)**	1.66(0.95 ,2.89)	**2(1.1,3.6 6)**	**4.29(1.19 ,13.83)**	**3.36(1.94 ,5.91)**	

Vigabatrin	**2.92(1.58,5.45)**	1.88(0.98,3.67)	1.54(0.75,3.11)	**2.1(1.05,4.35)**	1.41(0.73,2.76)	1.85(0.91,3.86)	1.31(0.69,2.54)	1.43(0.73,2.93)	**1.98(1.04,3.95)**	1.91(0.99,3.74)	1.7(0.89,3.24)	**2.52(1.25,5.24)**	2.25(0.48,8.16)	1.57(0.54,4.41)	2.03(0.91,4.77)	1.28(0.66,2.51)	1.53(0.78,3.23)	3.27(0.91,11.66)	**2.6(1.33,5.17)**	0.78(0.35,1.69)	**Vigabatrin**			
Loreclezole	8.36(0.57,1001)	5.4(0.37,631.2)	4.37(0.29,519.9)	6.12(0.4,738.9)	4.04(0.26,485.1)	5.39(0.35,620.8)	3.73(0.26,444.8)	4.12(0.27,485.1)	5.69(0.39,672.4)	5.43(0.38,641.7)	4.88(0.33,570.9)	7.21(0.48,827.3)	6.3(0.34,705.6)	4.46(0.27,551.2)	5.73(0.37,701.7)	3.62(0.25,445.6)	4.43(0.3,525.5)	9.5(0.49,1116)	7.46(0.52,859.3)	2.22(0.14,264.6)	2.86(0.18,350.4)	**Loreclezole**		
Losigamone	0.98(0.44,2.19)	0.64(0.28,1.48)	0.52(0.22,1.21)	0.71(0.31,1.69)	0.47(0.21,1.11)	0.62(0.27,1.5)	**0.44(0.19,0.99)**	0.48(0.21,1.14)	0.67(0.29,1.54)	0.64(0.28,1.46)	0.57(0.25,1.29)	0.85(0.36,1.99)	0.75(0.15,3.01)	0.53(0.16,1.65)	0.68(0.27,1.77)	0.43(0.19,1)	0.52(0.22,1.25)	1.1(0.27,4.25)	0.87(0.38,2.09)	**0.26(0.1,0.66)**	**0.34(0.12,0.9)**	0.11(0,1.97)	**Losigamone**	
Phenytoin	1.97(0.78,4.83)	1.27(0.48,3.18)	1.04(0.39,2.66)	1.42(0.52,3.66)	0.95(0.35,2.36)	1.26(0.46,3.24)	0.89(0.33,2.17)	0.97(0.36,2.49)	1.34(0.5,3.4)	1.29(0.51,3.18)	1.14(0.45,2.81)	1.71(0.63,4.42)	1.48(0.3,6.51)	1.05(0.28,3.51)	1.38(0.67,2.74)	0.87(0.33,2.1)	1.04(0.38,2.67)	2.23(0.49,8.92)	1.75(0.68,4.44)	0.52(0.18,1.46)	0.68(0.22,1.94)	0.23(0,3.97)	2.03(0.57,6.47)	**Phenytoin**	
Carbamazepine	**4.19(1.62,11.34)**	**2.7(1.01,7.52)**	2.19(0.81,6.35)	**3.03(1.09,8.59)**	2.02(0.74,5.59)	2.67(0.98,7.71)	1.89(0.71,5.15)	2.07(0.75,5.87)	**2.86(1.03,7.98)**	**2.72(1.05,7.49)**	2.43(0.93,6.66)	**3.63(1.27,10.28)**	3.14(0.62,14.91)	2.22(0.62,8.24)	**2.92(1.34,6.65)**	1.85(0.68,5)	2.22(0.79,6.5)	**4.71(1.09,21.06)**	**3.71(1.38,10.47)**	1.11(0.37,3.42)	1.43(0.46,4.64)	0.51(0,9.04)	**4.26(1.24,14.8)**	2.13(0.78,6.35)	**Carbamazepine**	
Ganaxolone	1.47(0.52,4.28)	0.95(0.33,2.8)	0.77(0.27,2.34)	1.06(0.36,3.16)	0.71(0.25,2.13)	0.93(0.32,2.89)	0.66(0.24,1.98)	0.73(0.25,2.19)	1.01(0.35,2.99)	0.96(0.33,2.87)	0.85(0.3,2.52)	1.27(0.43,3.9)	1.12(0.21,5.23)	0.78(0.2,3.03)	1.02(0.32,3.44)	0.65(0.23,1.91)	0.77(0.26,2.36)	1.66(0.34,7.59)	1.31(0.45,3.95)	0.39(0.12,1.27)	0.5(0.15,1.72)	0.17(0,3.18)	1.51(0.4,5.41)	0.75(0.19,3.14)	0.35(0.08,1.47)	

The matrix shows the estimated relative effect size for all possible pairings of anti-seizure drugs reported as an odds ratio with their 95% credible interval in brackets. The vertical column should be considered as the intervention with odds ratios greater than one favouring that treatment. Text in bold highlight a comparison where the credible intervals do not cross one.

Table 10: Relative effect matrix for 50% reduction in seizure frequency in generalised tonic-clonic seizures fixed effects network meta-analysis

	Placebo					
Brivaracetam	**5.1(1.08,41.1)**	**Brivaracetam**				
Lamotrigine	**3.53(2.14,5.91)**	0.69(0.08,3.56)	**Lamotrigine**			
Levetiracetam	**5.08(3.36,7.77)**	0.99(0.12,4.99)	1.44(0.74,2.78)	**Levetiracetam**		
Perampanel	**2.93(1.55,5.62)**	0.57(0.06,3.09)	0.83(0.37,1.89)	0.58(0.27,1.26)	**Perampanel**	
Topiramate	**3.71(1.36,11.15)**	0.72(0.07,4.92)	1.05(0.34,3.52)	0.73(0.25,2.36)	1.27(0.38,4.48)	**Topiramate**
Lacosamide	**1.94(1.16,3.31)**	0.38(0.04,1.96)	0.55(0.27,1.15)	**0.38(0.2,0.75)**	0.66(0.29,1.52)	0.52(0.16,1.63)

The matrix shows the estimated relative effect size for all possible pairings of anti-seizure drugs reported as an odds ratio with their 95% credible interval in brackets. The vertical column should be considered as the intervention with odds ratios greater than one favouring that treatment. Text in bold highlight a comparison where the credible intervals do not cross one.

1

2 **Table 11: Summary of adverse events identified in studies included in the network meta-analyses**

	Total Number	Number experiencing adverse events during study period	%	Number withdrew during study period due to adverse events	%	Number of deaths	%
Brivaracetam	633	274	43.3%	85	13.4%	2	0.32%
Carbamazepine	1094	413	37.7%	164	15.0%	0	0.00%
Carisbamate	68	0	0.0%	7	10.3%	0	0.00%
Cenobamate	863	547	63.4%	204	23.6%	3	0.35%
Eslicarbazepine Acetate	1686	888	52.7%	102	6.0%	4	0.24%
Gabapentin	1114	279	25.0%	49	4.4%	0	0.00%
Ganaxolone	209	114	54.7%	24	11.5%	0	0.00%
Lacosamide	442	340	76.9%	53	12.0%	0	0.00%
Lamotrigine	1404	941	67.0%	197	14.0%	3	0.21%
Levetiracetam	739	399	54.0%	48	6.5%	1	0.14%
Loreclezole	68	46	67.6%	8	11.8%	0	0.00%
Losigamone	142	0	0.0%	1	0.7%	0	0.00%
Oxcarbazepine	98	82	83.7%	7	7.1%	0	0.00%
Perampanel	1478	648	43.8%	142	9.6%	0	0.00%
Phenytoin	687	73	10.6%	67	9.8%	0	0.00%
Placebo	480	215	44.8%	62	12.9%	0	0.00%
Pregabalin	2017	1472	73.0%	138	6.8%	0	0.00%
Primidone	2212	1313	59.3%	245	11.1%	2	0.09%
Retigabine	76	0	0.0%	0	0.0%	0	0.00%
Rufinamide	32	0	0.0%	0	0.0%	0	0.00%
Selurampanel (BGG492)	99	59	59.6%	11	11.1%	0	0.00%
Sodium valproate	952	784	82.4%	161	16.9%	5	0.53%

	Total Number	Number experiencing adverse events during study period	%	Number withdrew during study period due to adverse events	%	Number of deaths	%
Tiagabine	1708	1304	76.4%	159	9.3%	2	0.12%
Topiramate	101	0	0.0%	0	0.0%	0	0.00%
Vigabatrin	871	697	80.0%	103	11.8%	2	0.23%
Zonisamide	8873	4293	48.4%	467	5.3%	16	0.18%

Additional Information D: Adverse event outcomes

Table 12: Number of adverse events during study period for focal seizures

	Total Number	Number experiencing adverse events	%	Number withdrew due to adverse events	%	deaths†	%
Brivaracetam	1404	941	67.0%	197	14.0%	3	0.21%
Carbamazepine	101	NR	NR	NR	NR	0	0.00%
Carisbamate	2212	1313	59.3%	245	11.1%	2	0.09%
Cenobamate	76	NR	NR	NR	NR	0	0.00%
Eslicarbazepine Acetate	633	274	43.3%	85	13.4%	2	0.32%
Gabapentin	68	NR	NR	7	10.3%	0	0.00%
Ganaxolone	871	697	80.0%	103	11.8%	2	0.23%
Lacosamide	863	547	63.4%	204	23.6%	3	0.35%
Lamotrigine	1686	888	52.7%	102	6.0%	4	0.24%
Levetiracetam	1114	279	25.0%	49	4.4%	0	0.00%
Loreclezole	99	59	59.6%	11	11.1%	0	0.00%
Losigamone	952	784	82.4%	161	16.9%	5	0.53%
Oxcarbazepine	209	114	54.7%	24	11.5%	0	0.00%
Perampanel	442	340	76.9%	53	12.0%	0	0.00%
Phenytoin	1708	1304	76.4%	159	9.3%	2	0.12%

	Total Number	Number experiencing adverse events	%	Number withdrew due to adverse events	%	deaths†	%
Placebo	8873	4293	48.4%	467	5.3%	16	0.18%
Pregabalin	739	399	54.0%	48	6.5%	1	0.14%
Primidone	2017	1472	73.0%	138	6.8%	0	0.00%
Retigabine	1094	413	37.7%	164	15.0%	0	0.00%
Rufinamide	68	46	67.6%	8	11.8%	0	0.00%
Selurampanel (BGG492)	142	NR	0.0%	1	0.7%	0	0.00%
Sodium valproate	98	82	83.7%	7	7.1%	0	0.00%
Tiagabine	1478	648	43.8%	142	9.6%	0	0.00%
Topiramate	687	73	10.6%	67	9.8%	0	0.00%
Vigabatrin	32	NR	NR	NR	NR	0	0.00%
Zonisamide	480	215	44.8%	62	12.9%	0	0.00%

NR: Not reported for any trial
† These are total deaths reported. It was often unclear in studies whether deaths had not occurred or if they had not been reported especially where this outcome was in the study protocol. Therefore, 'not reported' was treated as zero deaths.

Table 13: Number of adverse events during study period for GTC seizures

	Total Number	Number experiencing adverse events	%	Number withdrew due to adverse events	%	deaths†	%
Brivaracetam	36	24	66.0%	5	13.9%	1	2.78%
Lacosamide	121	96	79.3%	5	4.1%	0	0.00%
Lamotrigine	134	54	40.1%	20	14.9%	0	0.00%
Levetiracetam	206	130	63.0%	15	7.3%	0	0.00%
Perampanel	81	67	82.7%	48	59.3%	0	0.00%
Placebo	599	261	43.5%	41	6.8%	3	0.50%
Topiramate	41	NR	NR	5	12.2%	0	0.00%

NR: Not reported for any trial
† These are total deaths reported. It was often unclear in studies whether deaths had not occurred or if they had not been reported especially where this outcome was in the study protocol. Therefore, 'not reported' was treated as zero deat