National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[J] Effectiveness of antiseizure therapies in the treatment of idiopathic generalised epilepsies, including juvenile myoclonic epilepsy

NICE guideline number tbc

Evidence reviews underpinning recommendations 5.6.1-5.6.5 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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Evidence review for effectiveness of antiseizure therapies in the treatment of idiopathic generalised epilepsy, including juvenile myoclonic epilepsies

Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Introduction

The most common group of epilepsy syndromes diagnosed are those that present in otherwise normal individuals, with generalised seizures and a specific pattern of Electroencephalogram (EEG) of generalised spike wave (SW) activity of ≥ 3 per second. These are idiopathic generalised epilepsies (IGEs), previously called genetic generalised epilepsies (GGEs), it is thought there is an idiopathic basis to these syndromes, but they are not monogenic (single gene) in cause.

These epilepsies are well defined and common, accounting for a significant portion of all forms of epilepsy. The IGEs usually begin in adolescence (age 12-16 years) but can begin from 8 years old to twenties. Seizures will continue into middle age, after which there is some evidence that seizures will remit but is not possible to predict the patients for whom this will occur. Many have a good prognosis for seizure control with initial antiseizure medication, and the goal of treatment is seizure freedom. The aim of this review is to determine which antiseizure therapies are the most effective in improving outcomes for those with IGEs, including juvenile myoclonic epilepsy (JME).

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 confirmed idiopathic generalised epilepsies, including juvenile myoclonic epilepsy
Intervention	• acetazolamide • brivaracetam • carbamazepine • clobazam • clonazepam • eslicarbazepine • ethosuximide • ketogenic diet • lacosamide • lamotrigine • levetiracetam • methosuximide/ mesuximide • oxcarbazepine • perampanel • phenobarbital • phenytoin • primidone • sodium valproate • topiramate • zonisamide Interventions may be monotherapy or add-on therapy
Comparison	• No treatment/placebo • Comparison between the listed interventions (monotherapy or add-on therapy, including their combinations, different doses, and different lengths of treatment)
Outcome	**Critical** • Time to withdrawal of treatment or change of medication (e.g. because of uncontrollable seizures) • Reduction in seizure frequency >50% • Short term seizure freedoms (seizure free for minimum of 4 weeks, within 3 months of starting treatment) • Adverse events, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse events) ○ Treatment cessation due to adverse drug effects (dichotomous outcome only) ○ Mortality **Important** • EEG resolution • Health-related quality of life (measured using validated tools)

EEG: electroencephalogram

When this review was originally conducted, the name of the epilepsy syndrome used in the searches and the review was genetic generalised epilepsies (GGEs), however the name of this epilepsy syndrome changed during guideline development to idiopathic generalised epilepsies (IGEs), and amendments to reflect this change were done as appropriate throughout this report.

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 and the methods document (supplementary document 1).

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

Effectiveness

Included studies

Thirteen randomised controlled trials (RCTs) were identified for inclusion in this review (Berkovic 2007, Biton 2005, French 2015, Levisohn 2007, Machado 2013, Marson 2007a, Marson 2007b, Marson 2021, Nejad 2009, Noachtar 2008, Park 2013, Sundquist 1998, Wu 2018). Marson 2007a and Marson 2007b presented the same data and have been combined.

Three RCTs compared add-on levetiracetam to placebo (Berkovic 2007, Noachtar 2008, Wu 2018), 1 RCT compared add-on topiramate to placebo (Biton 2005), 1 RCT compared add-on perampanel to placebo (French 2015), 3 RCTs compared topiramate to valproate (Levisohn 2007, Marson 2007, Park 2013), 3 RCTs compared lamotrigine to valproate (Machado 2013, Marson 2007, Nejad 2009), 1 RCT compared valproate to levetiracetam (Marson 2021) and 1 RCT compared differed doses of valproate (Sundquist 1998). It was not suitable to conduct a network meta-analysis as the network of comparisons were not adequately connected.

The included studies are summarised in Table 2 to Table 8.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

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

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2 to Table 8.

Table 2: Summary of included studies. Comparison 1: add-on levetiracetam versus placebo

Study	Population	Intervention	Comparison	Outcomes
Berkovic 2007 Multi-centre RCT Europe, North America, Mexico, Australia and New Zealand	N=164 adults or children with IGEs and GTC seizures This included 26 people with absence epilepsy and 7 with unknown syndrome Age, years, mean (SD):	Levetiracetam n=80 Target dose Adult: 3,000 mg/day Paediatrics and adolescents (<50 kg): 60 mg/kg/day	Placebo n=84	• Reduction of seizure frequency >50% • Free of all seizures for the treatment period • Treatment cessation due to adverse drug effects • Serious adverse events • Health-related quality of life

Study	Population	Intervention	Comparison	Outcomes
	Levetiracetam: 26.9 (11.2), placebo: 30.6 (12.1)			
Noachtar 2008 Global multicentred RCT 14 countries across Oceania, Europe, North and Central America	N=121 adults and children with IGEs and myoclonic seizures 113 had Juvenile myoclonic epilepsy and 8 had Juvenile absence epilepsy Age, years, mean (SD): levetiracetam 25 (7.4), placebo 26.8 (9.5)	Levetiracetam n=61 Target dose: 3,000 mg/day. 1 concomitant ASM was to be taken with the study treatment at a stable dose.	Placebo n=60 1 concomitant ASM was to be taken with the study treatment at a stable dose.	• Reduction of myoclonic seizure frequency >50% • Short-term seizure freedom • Serious adverse events • Treatment cessation due to adverse drug events • Health-related quality of life
Wu 2018 RCT China and Japan	Whole study: N=251 IGEs population: N = 117 Age, years, mean (SD) Levetiracetam: 31.5 (11.3), placebo: 32.8 (12.5)	Levetiracetam n=59 1000 mg/day for those who had no GTC seizures up to week 8 after randomization. For those who had ≥1 GTC seizure, levetiracetam was increased to 3,000 mg/day in steps of 1,000 mg/day/2 weeks.	Placebo n=58 Same regimen as for Levetiracetam	• Percentage reduction in GTC seizures

ASM: antiseizure medication; GTC: generalised tonic clonic seizures; IGEs: idiopathic generalised epilepsies; RCT: randomised controlled trial

Table 3: Summary of included studies. Comparison 2: add-on topiramate versus placebo

Study	Population	Intervention	Comparison	Outcomes
Biton 2005 RCT US	N=22 people with juvenile myoclonic epilepsy Median age: topiramate 27, placebo 34	Topiramate n=11 Target dose Adults: 400 mg day Children: 6 mg/kg/day	Placebo n=11	• Reduction of generalised seizure frequency >50% • Treatment cessation due to adverse drug effects

RCT: randomised controlled trial

Table 4: Summary of included studies. Comparison 3: add-on perampanel versus placebo

Study	Population	Intervention	Comparison	Outcomes
French 2015 Global multicentre RCT Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania, Poland, Serbia, South Korea, United States	N =164 people with IGEs Age, years, mean (SD): 28.4 (11.4)	Perampanel n=82 3 phases: titration (weeks 1–4), maintenance (weeks 5–17), and follow-up (weeks 18–21).	Placebo n=82 same regimen as intervention	• 50% PGTC seizure responder rate • Seizure freedom (during maintenance phase) • Serious TEAEs • Treatment cessation due to adverse effects

PGTC: primary generalised tonic clonic seizures; IGEs: idiopathic generalised epilepsies; RCT: randomised controlled trial; TEAEs: treatment emergent adverse events

Table 5: Summary of included studies. Comparison 4: topiramate versus valproate

Study	Population	Intervention	Comparison	Outcomes
Levisohn 2007 RCT US	N=28 children and adults with juvenile myoclonic epilepsy Age, years, median (range): topiramate 15 (9-42), valproate 16 (12-34)	Topiramate n=19 Target dose >16 years old: 200 mg/day 12–16 years old: 3–4 mg/kg/day	Valproate n=9 Target dose >16 years: 750 mg/day 12–16 years old: 10 mg/kg/day	• Reduction of seizure frequency >50% (myoclonic seizure frequency, PGTCs) • Treatment cessation due to adverse drug events
Marson 2007 RCT UK	N=716 people with generalised onset seizures IGE, n (%) 450 (63%) Age, years, mean (SD): Topiramate 22.3 (13.3), Valproate 22.5 (14.5)	Topiramate n=239 (151 IGEs) Dose decided by treating physician	Valproate n=238 (154 IGEs) Dose decided by treating physician	*Outcomes taken from the subgroup of people with IGEs* • Time to treatment failure • Time to 12 month remission • Time to 24 month remission • Time to first seizure
Park 2013 RCT Republic of Korea	N=33 adults and children with juvenile myoclonic epilepsy Age, years, median (range) topiramate: 19 (13 to	Topiramate n=16; n=11 finished the 24-week maintenance period Titrated up to 100 mg day for	Valproate n=17; n=16 finished the 24-week maintenance period Titrated up to 1200 mg day for	• Number of participants who were seizure-free

Study	Population	Intervention	Comparison	Outcomes
	42), valproate: 17 (14 to 36)	24 week maintenance period	24 week maintenance period	

PGTCs: primary generalised tonic clonic seizures; IGEs: idiopathic generalised epilepsies; RCT: randomised controlled trial

Table 6: Summary of included studies. Comparison 5: lamotrigine versus valproate

Study	Population	Intervention	Comparison	Outcomes
Machado 2013 RCT Cuba	N=82 people with juvenile myoclonic epilepsy Age, years, mean (SD): Lamotrigine 26 (11), valproate 27 (13)	Lamotrigine n=43 Dose prescribed by treating physician.	Valproate n=39 Dose prescribed by treating physician.	• Time to withdrawal for any reason • Percentage of patients with reported side effects • Health-related quality of life
Marson 2007 RCT UK	N=716 people with generalised onset seizures IGE, n (%) 450 (63%) Age, years, mean (SD): Lamotrigine: 22.8 (14.3) Topiramate: 22.3 (13.3) Valproate: 22.5 (14.5)	Lamotrigine n=239 (145 IGEs) Dose decided by treating physician	Valproate n=238 (154 IGEs) Dose decided by treating physician	*Outcomes in subgroup of people with IGEs* • Time to treatment failure • Time to 12-month remission • Time to 24-month remission • Time to first seizure
Nejad 2009 RCT Iran	N=46 women with juvenile myoclonic epilepsy Age range: 8-30 years old	Lamotrigine n=23 Mean target dose was 1500-2000 mg per day	Valproate n=23 Mean target dose was 800 mg per day	• Mean juvenile myoclonic seizure reduction from baseline • Mean tonic-clonic seizure reduction from baseline

IGEs: idiopathic generalised epilepsies; RCT: randomised controlled trial

Table 7: Summary of included studies. Comparison 6: valproate versus levetiracetam

Study	Population	Intervention	Comparison	Outcomes
Marson 2021 RCT UK	N=520 people with generalised or unclassified epilepsy	Valproate n=260 (201 generalised epilepsy)	Levetiracetam n=260 (196 generalised epilepsy)	*Outcomes in subgroups of people with absence epilepsy and people with other generalised epilepsy*

Study	Population	Intervention	Comparison	Outcomes
	397 had generalised epilepsy, including people with absence epilepsy (childhood absence epilepsy, juvenile absence epilepsy) and people with other generalised epilepsy (juvenile myoclonic epilepsy, epilepsy with tonic-clonic seizures on awakening, other IGE not specified, and other epilepsy syndrome). Age, years, median (IQR): Valproate: 13·6 (8·8–19·7) Levetiracetam: 14·1 (9·1–19·8)	Initial recommended treatment dosages: Participants aged ≥12 years: 500mg twice per day Participants aged 5-12 years: 25mg/kg daily maintenance dose Treatment and dosage adjustments made by clinician	Initial recommended treatment dosages: Participants aged ≥12 years: 500mg twice per day Participants aged 5-12 years: 40mg/kg daily maintenance dose Treatment and dosage adjustments made by clinician	• Time to 12 month remission

IGEs: idiopathic generalised epilepsies; RCT: randomised controlled trial

Table 8: Summary of included studies. Comparison 7: low-dose valproate versus high-dose valproate

Study	Population	Intervention	Comparison	Outcomes
Sundqvist 1998 Single centre crossover RCT Sweden	N=18 adults and children with juvenile myoclonic epilepsy Age, years, median (range): 25 (15-46)	Valproate low dose: 500 mg	Valproate high dose: 1000 mg	• Seizure frequency increase of 50% or more • Treatment cessation due to adverse drug events

RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Overall sodium valproate appeared to have an important benefit over topiramate, lamotrigine and levetiracetam in terms of seizure control. However, lamotrigine also showed an important benefit in terms of time to 12- and 24-month remission when compared to valproate. When compared to placebo, levetiracetam showed an important benefit in terms of reduction of seizure frequency >50%, short-term seizure freedom and quality of life. Perampanel had an important benefit in terms of reduction of primarily generalised tonic-clonic seizures and seizure freedom (all seizures) when compared to placebo. The majority of the evidence from these studies was low to moderate quality; therefore the true effect may be different from the estimated effect.

Some of the comparisons evaluated did not show any important difference across the outcomes assessed, such as topiramate versus placebo or low-dose versus high-dose valproate.

Typically, the comparisons where no difference between interventions was found included less participants and had serious imprecision in the findings, therefore they should not be taken as definitive evidence of no difference between the interventions. No data were identified for outcomes related to EEG resolution.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

Two papers relevant to the review question were identified in the literature review of published economic evidence (Marson 2007a; Marson 2007b). Both papers reported the same economic evaluation and therefore have been summarised together.

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

Excluded studies

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

Summary of studies included in the economic evidence review

The review of the economic evidence identified 2 papers (Marson 2007a, Marson 2007b) reporting the same economic evaluation conducted alongside a UK RCT. The study considered the cost effectiveness of topiramate and lamotrigine compared to sodium valproate in patients for whom sodium valproate was the better standard treatment option than carbamazepine. The patient group consisted of 63% of patients with idiopathic generalised epilepsy. Unlike the clinical evidence, cost effectiveness results were not presented separately for this group.

The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs) scored using patient reported EQ-5D responses and UK population tariff values. The analysis adopted the perspective of the NHS & PSS.

The studies estimated a base-case incremental cost effectiveness ratio was £1,106 per additional QALY when comparing topiramate to sodium valproate; below the £20,000 per QALY threshold at which NICE usually approve new interventions. Lamotrigine was dominated by topiramate (lamotrigine was both more expensive and less effective).

Uncertainty was estimated using both deterministic and probabilistic sensitivity analysis. Varying drug costs between high and low estimates and different assumptions around quality of life estimates did not change the conclusions of the analysis. Probabilistic sensitivity analysis estimated that TPM and LTG have a 95% and 63% respectively of being cost effective when compared individually to sodium valproate at a threshold of £20,000 per QALY.

Despite taking a UK NHS perspective the study was downgraded to partially applicable to the decision problem. This is because only 63% of the trial cohort meet the population inclusion criteria specified by the review protocol. The study is also relatively old with significant changes in the price of topiramate and lamotrigine given they now come off patent. The

study was deemed to only have minor methodological limitations. The study did not present a probabilistic sensitivity analysis that compared all interventions simultaneously.

See appendix H and appendix I for the economic evidence tables and economic evidence profiles.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

There was evidence from 1 UK cost utility analysis alongside an RCT showing that that topiramate and lamotrogine have a 95% and 63% probability respectively of being cost effective when compared individually to sodium valproate at a threshold of £20,000 per QALY. Despite taking a UK NHS perspective the study was downgraded to partially applicable to the decision problem because only 63% of the trial cohort meet the population inclusion criteria specified by the review protocol. The study only had minor methodological limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that as the main goal of treatment for people with IGEs, including juvenile myoclonic epilepsy, is seizure freedom, this should be included as a critical outcome in this review. However, the committee acknowledged that seizure freedom can be difficult to achieve and agreed that it was therefore also appropriate to specify reduction in seizure frequency as a critical outcome for the review. Given the difficulties in achieving seizure freedom and the importance of balancing the need to reduce the occurrence of seizures with the side effects associated with certain medications, the committee agreed that time to withdrawal and adverse events should also be included as critical outcomes.

As IGEs are characterised by a specific EEG pattern; the committee agreed that EEG resolution should be included as an important outcome. In addition, health related quality of life was included as an important outcome, as this reflects the impact that seizures can have on the daily lives of individuals who have epilepsy and it is expected that a reduction in seizues will lead to improvements in this outcome.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The outcomes ranged from very low to moderate quality, indicating uncertainty in some of the outcomes. Those outcomes which were downgraded were generally downgraded due to risk

of bias arising from potential bias in measurement of outcomes, and bias in the selection of reporting results. Some outcomes were further downgraded due to imprecision in the data.

Benefits and harms

The committee used the evidence presented and their clinical knowledge and expertise to make the recommendations.

The committee agreed that, prior to starting antiseizure medication there should be a discussion with the person, their family and carers, if appropriate, about an individualised antiseizure therapy 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 evidence included demonstrated that sodium valproate was the most effective medication for treating IGEs. The committee agreed that this was also generally accepted across clinical practice and dicussed some specific groups in which sodium valproate should be offered as a first-line treatment.

The committee discussed at length that sodium valproate has risks to women and girls who are able to have children as it is associated with a risk of birth defects and developmental disorders. There was evidence for the use of lamotrigine and levetiracetam, therefore the committee agreed to recommend either of these medications as first-line treatment for women, and girls with IGEs who are likely to need treatment when they are old enough to have children.

If first line treatment is unsuccessful, the committee prioritised some ASMs which could be used as alternative or add-on treatment. 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.

The evidence supported the use of levetiracetam and lamotrigine as second-line alternative or add-on treatment for those with IGEs in whom sodium valproate had been unsuccessful. Based on this evidence, the committee agreed that these drugs should be recommended as second-line alternative or add-on treatment.

There was not enough evidence to support the use of topiramate, however the committee agreed that this drug is useful in clinical practice. Add-on perampanel appeared to be effective for seizure reduction, therefore, based on their clinical expertise and on the evidence reviewed, repectively, the committee agreed that these drugs should be recommended as a third-line add-on treatment for people with IGEs.

The committee agreed that, in cases where women and girls in which first-line treatment has been unsuccessful, valproate should be available as an option after a full and clear discussion with the girl or woman, ensuring she understands all the important safety issues associated with this medicine. The committee noted that, if prescribed, the relevant MHRA safety advice on valproate use in women and girls has to be followed. This includes ensuring the

continuous use of highly effective contraception and the enrollment of the girl or woman in a pregnancy prevention programme, if appropriate.

Cost effectiveness and resource use

One economic evaluation was identified and considered by the committee in making recommendations for this question. The study was a cost utility analysis conducted alongside an RCT comparing three drugs- sodium valproate, topiramate and lamotrigine in a mixed population of which two thirds of participants had a diagnosis of IGEs. Whilst the study took a UK NHS and PSS perspective and was deemed to only have minor methodological limitations it was deemed only partially applicable to the decision problem given the study was conducted over 10 years ago.

In the analysis outcomes in terms of cost per QALY, strongly suggested that topiramate was the preferred intervention (£1,106 per additional QALY compared to sodium valproate), and this was robust to alternative assumptions. However, this conflicted with the cost per seizure avoided outcomes which showed sodium valproate as both cost saving and seizure reducing under all assumptions in the economic evaluation. Despite the cost per QALY outcomes favouring topiramate the committee agreed with the conclusions of the study authors that this result was most likely caused by an unrepresentative response to the quality of life questionnaire. The committee therefore recommended sodium valproate, based on reduced number of seizures and lower costs, as the first line treatment for people with IGEs in line with the authors' conclusions.

No economic evidence was identified for levetiracetam, although the committee highlighted that costs were similar to other antiseizure medications and that there was unlikely to be a large resource impact from recommending its use as first line treatment for women of childbearing potential and girls with idiopathic generalised epilepsy whose epilepsy is likely to continue into adulthood.

All recommendations reinforce current practice and will not lead to any significant impact upon resource use.

Other factors the committee took into account

In line with the MHRA, the committee emphasised that long-term treatment with 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.

Recommendations supported by this evidence review

This evidence review supports recommendations 5.6.1-5.6.5.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 9: Review protocol

Field	Content
PROSPERO registration number	Not registered
Review title	Effectiveness of antiseizure therapies in the treatment of idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy Note: Idiopathic generalised epilepsies (IGEs) was formerly termed genetic generalised epilepsies (GGEs)
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?
Objective	The objective of this review is to determine which antiseizure therapies are the most effective at improving outcomes for those with idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy. This review will determine the effectiveness of therapies given alone or in combination (add-on therapy)
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations

Field	Content
	• Embase • EMCare • Searches will be restricted by: • Date: no date limit • English language studies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy
Population	Inclusion: • people with confirmed idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy Exclusion: • newborn babies (under 28 days) with acute symptomatic seizures • studies including syndromes not covered in the list of IGEs recognised by the International League Against Epilepsy (ILAE)
Intervention	The following antiseizure therapies and their combinations will be considered: • acetazolamide • brivaracetam • carbamazepine • clobazam • clonazepam • eslicarbazepine • ethosuximide • ketogenic diet • lacosamide • lamotrigine • levetiracetam

Field	Content
	• methosuximide/ mesuximide • oxcarbazepine • perampanel • phenobarbital • phenytoin • primidone • sodium valproate • topiramate • zonisamide
Comparator	• any of the above (including their combinations, different doses, and different lengths of treatment) • placebo/no treatment
Types of study to be included	• Systematic review of RCTs • RCTs 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. • Studies with a mixed population (i.e. including people with idiopathic generalised epilepsies [IGEs] and other syndromes) will be excluded, unless subgroup analysis for idiopathic generalised epilepsies [IGEs] has been reported. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Studies including surgery as part of the interventions

Field	Content
Context	Recommendations will apply to those receiving care in any healthcare settings (e.g. community, primary, secondary care)
Primary outcomes (critical outcomes)	• Time to withdrawal of treatment or change in medication • Reduction of seizure frequency >50% • Short term seizure freedom (seizure free for minimum of 4 weeks within 3 months of starting treatment) Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as "time to 3 months seizure freedom", (i.e. time to event: HR or mean time) followed by "achievement of 3 months seizure freedom" (RR). • Adverse events, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse drug effects [dichotomous outcome only] Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/searchresults
Secondary outcomes (important outcomes)	• EEG resolution • Health-related quality of life (only validated scales will be included)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.

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	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data synthesis</u> Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm. Mean differences or standardised mean differences will be presented for continuous outcomes. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • by age (older people/adults/children) • study location Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. <u>Minimal important differences (MIDs):</u> Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes

Field	Content	
	For risk ratios: 0.8 and 1.25. For continuous outcomes: • For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm. • For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. • For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. • For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. <u>Validity</u> The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
Analysis of sub-groups	Stratification If data is available, separate analysis will be conducted on: • Women of child bearing age Recommendations will apply to all those with GGE unless there is evidence of a difference in these strata	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)

Field	Content		
Language	English		
Country	England		
Anticipated or actual start date	19th August 2019		
Anticipated completion date	7th April 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	x	x
	Piloting of the study selection process	x	x
	Formal screening of search results against eligibility criteria	x	x
	Data extraction	x	x
	Risk of bias (quality) assessment	x	x
	Data analysis	x	x
Named contact	5a. Named contact National Guideline Alliance 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		

Field	Content
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	Not registered in PROSPERO
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.

Field	Content	
Keywords	Epilepsies, genetic generalised epilepsy, idiopathic generalised epilepsy	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	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	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; EEG: Electroencephalogram; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; IGEs: idiopathic generalised epilepsies; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SD: Standard Deviation

Appendix B – Literature search strategies

Literature search strategies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Clinical

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

EMCare 1995 to April 21, 2021; Embase Classic+Embase 1947 to 2021 April 21; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 April 21, 2021

Date of last search: 21 April 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 generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
2	(((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.
3	or/1-2
4	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.
5	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.
6	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.
7	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.
8	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
9	8 use emczd, emcr
10	diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycerides/
11	10 use ppez
12	((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.
13	or/9,11-12
14	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
15	lamotrigine/ use emczd, emcr or lamotrigine/ use ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine 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 trileptin).ti,ab.
18	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.

#	searches
19	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.
20	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
21	acetazolamide/ use emczd, emcr or acetazolamide/ use ppez
22	(acetadiazol or acetamox or acetazol amide or acetazolam or acetazolamid* or acetazolamine or acetazoleamid* or acetozolamine or ak zol or akzol or albox or apoacetazolamide or azetazolamide or carbinib or carbonic anhydrase inhibitor or cidamex or dazamide or defiltran or dehydratin or diacarb or diamox or diluran or diomax or diuramid* or diutazol or edemox or eumicton or fonurit or genephamide or glaucomed* or glauconox or glaupax or huma zolamide or humazolamide or ledamox or lediamox or ledimox or natrionex or nephramid or novozolamide or storzolamide or ulcosilvanil or ulcosylvanil).ti,ab.
23	mesuximide/ use emczd, emcr
24	(alpha methylphensuximide or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin).ti,ab.
25	phenobarbital/ use emczd, emcr or exp phenobarbital/ use ppez
26	(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.
27	primidone/ use ppez or primidone/ use emczd, emcr
28	(apo-primidone or cyral or desoxyphenobarbital or desoxyphenobarbitone or hexadiona or lepsiral or liskantin or liskantin or majsolin or midone or misodine or mizodin or mutigan or mylepsin or mylepsinum or mysolin or mysoline or neurosyn or primaclone or primaclone or primadone or primidon* or prysoline or pyrimidone or resimatil or sertan).ti,ab.
29	phenytoin/ use emczd, emcr or phenytoin/ use ppez
30	(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 di-hydan 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.
31	perampanel/ use emczd, emcr
32	(fycompa or perampanel).ti,ab.

#	searches
33	brivaracetam/ use emczd, emcr
34	(brivaracetam or brivlera or nubriveo or rikelta).ti,ab.
35	exp eslicarbazepine/ use emczd, emcr
36	(eslicarbazepin* or aptiom or zebinix).ti,ab.
37	or/4-7,13-36
38	3 and 37
39	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.
40	39 use ppez
41	(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.
42	41 use ppez
44	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.
45	44 use emczd, emcr
46	or/40,42,45
47	meta-analysis/
48	meta-analysis as topic/ or systematic reviews as topic/
49	"systematic review"/
50	meta-analysis/
51	(meta analy* or metanaly* or metaanaly*).ti,ab.
52	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
53	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
54	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56	(search* adj4 literature).ab.
57	(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.
58	cochrane.jw.
59	((pool* or combined) adj2 (data or trials or studies or results)).ab.
60	(or/47-48,51,53-59) use ppez
61	(or49-52,54-59) use emczd, emcr
62	or/60-61
63	or/46,62
64	38 and 63
65	limit 64 to english language
66	((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.)
67	66 use emez
68	((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.)
69	68 use mesz
70	67 or 69
71	65 not 70

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2021; Cochrane Central Register of Controlled Trials, Issue 4 of 12, April 2021

Date of last search: 21 April 2021

#	search
1	mesh descriptor: [epilepsy, generalized] explode all trees
2	((((akinetic or atonic or central or diffuse or general or generalised or generalized or idiopathic or tonic) near/3 (epilep* or seizure*)) or ((“childhood absence” or “juvenile absence” or myoclonic or myoclonia or “myoclonic astatic” or myoclonus or gtcs) near/2 epilep*) or (epilepsy near/2 “eyelid myoclonia”) or (ige near/2 “phantom absenc*”) or “impulsive petit mal” or (janz near/3 (epilep* or “petit mal”)) or “jeavons syndrome*” or ((janz or lafora or “lafora body” or lundborg or unverricht) near/2 (disease or syndrome)) or ((jme or jmes) and epilep*) or “perioral myoclon*”)):ti,ab,kw

#	search
3	#1 or #2
4	mesh descriptor: [clobazam] explode all trees
5	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab,kw
6	mesh descriptor: [valproic acid] explode all trees
7	((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 "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 "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or "sodium di n propylacetate" or "sodium dipropy 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
8	mesh descriptor: [topiramate] explode all trees
9	((epitomax or topamax or topiramat* 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
10	mesh descriptor: [zonisamide] this term only
11	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
12	mesh descriptor: [levetiracetam] this term only
13	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
14	mesh descriptor: [diet, carbohydrate-restricted] this term only
15	mesh descriptor: [dietary fats] explode all trees
16	mesh descriptor: [glycemic index] this term only
17	mesh descriptor: [diet, ketogenic] this term only
18	mesh descriptor: [triglycerides] explode all trees
19	(((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/1 (tryglyceride* or triglyceride*)) or mct*)):ti,ab,kw
20	mesh descriptor: [carbamazepine] explode all trees
21	((amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol)):ti,ab,kw
22	mesh descriptor: [clonazepam] this term only
23	((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
24	mesh descriptor: [ethosuximide] this term only
25	((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
26	mesh descriptor: [lacosamide] this term only
27	((erlosamide or harkoseride or lacosamide or vimpat)):ti,ab,kw
28	mesh descriptor: [lamotrigine] this term only
29	((crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
30	mesh descriptor: [oxcarbazepine] this term only
31	((apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin)):ti,ab,kw
32	mesh descriptor: [acetazolamide] this term only
33	((acetadiazol or acetamox or acetazol amide or acetazolam or acetazolamid* or acetazolamine or acetazoleamid* or acetozolamine or "ak zol" or akzol or albox or apoacetazolamide or azetazolamide or carbinib or "carbonic anhydrase inhibitor" or cidamex or dazamide or defiltran or dehydratin or diacarb or diamox or diluran or diomax or diuramid* or diutazol or edemox or eumicton or fonurit or genephamide or glaucomed* or glauconox or glaupax or huma zolamide or humazolamide or ledamox or lediamox or ledimox or natrionex or nephramid or novozolamide or storzolamide or ulcosilvanil or ulcosylvanil)):ti,ab,kw

#	search
34	((“alpha methylphensuximide” or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin)):ti,ab,kw
35	mesh descriptor: [phenobarbital] explode all trees
36	((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
37	mesh descriptor: [primidone] this term only
38	((“apo-primidone” or cyral or desoxyphenobarbital or desoxyphenobarbitone or hexadiona or lepsiral or liskantin or liskantin or majsolin or midone or misodine or mizodin or mutigan or mylepsin or mylepsinum or mysolin or mysoline or neurosyn or primaclone or primaclone or primadone or primidon* or prysoline or pyrimidone or resimatil or sertan)):ti,ab,kw
39	mesh descriptor: [phenytoin] this term only
40	((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
41	((fycompa or perampanel)):ti,ab,kw
42	((brivaracetam or brivlera or nubriveo or rikelta)):ti,ab,kw
43	((eslicarbazepin* or aptiom or zebinix)):ti,ab,kw
44	{or #4-#43}
45	#3 and #44

Database(s): DARE; HTA database - CRD

Date of last search: 21 April 2021

line	search
1	mesh descriptor epilepsy, generalized explode all trees
2	((((akinetic or atonic or central or diffuse or general or generalised or generalized 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*”))
3	#1 or #2

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

#	searches
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.
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

#	searches
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

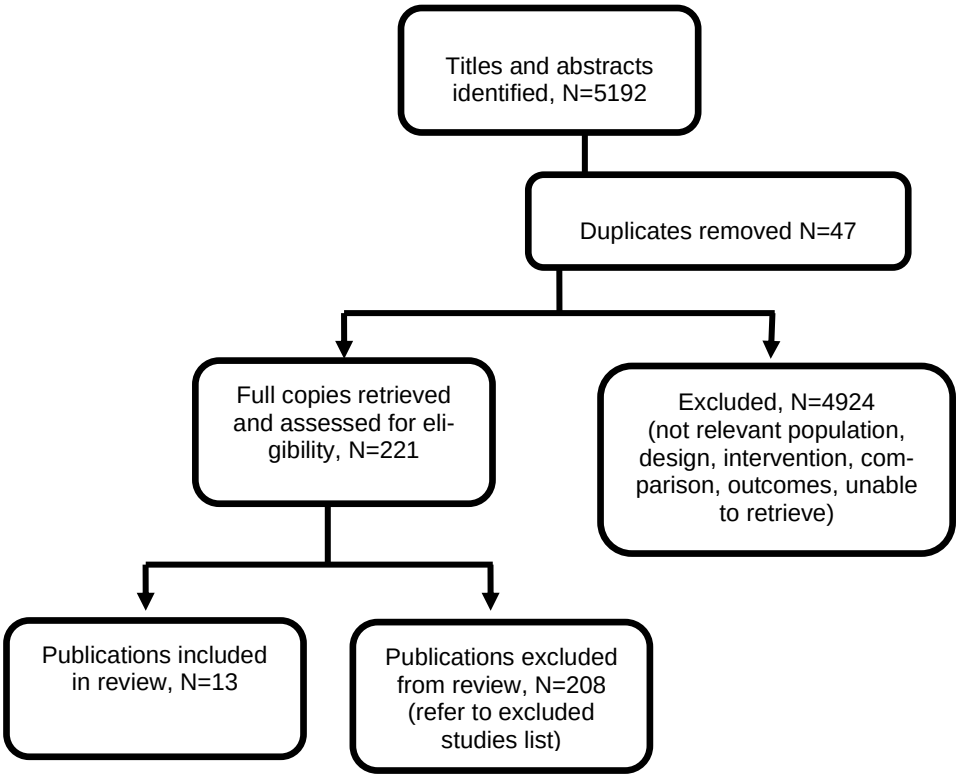
2

3

Appendix C - Clinical evidence study selection

Clinical study selection for: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 10: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes	Comments
Full citation Berkovic, S. F., Knowlton, R. C., Leroy, R. F., Schiemann, J., Falter, U., Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy, Neurology, 69, 1751-1760, 2007 **Ref Id** 1079979 **Country/ies where the study was carried out** Europe, North America, Mexico, Australia, and New Zealand. **Study type** Multi-centre RCT (50 centres across the globe) **Aim of the study** Assess the efficacy and tolerability of adjunctive levetiracetam treatment in adults and children	**Sample size** N=164 levetiracetam N=80, placebo N=84 This included 26 people with absence epilepsy and 7 with unknown syndrome **Characteristics** Age, years, mean (SD) Levetiracetam: 26.9 (11.2), placebo: 30.6 (12.1) Female gender Levetiracetam: 46 (57.5%), placebo: 45 (53.6%) Epilepsy syndrome, n (%) Localization-related—genetic L (levetiracetam): 0 (0) P (placebo): 1 (1.2) Generalized—genetic	**Interventions** Following an 8-week baseline period (comprising a 4-week historical baseline period and a 4-week, prospective, single-blind, placebo baseline period), patients were randomized to treatment with levetiracetam or placebo. The double blind treatment period consisted of a 4-week up-titration period, followed by a 20-week evaluation period. levetiracetam The target levetiracetam dose was 3,000 mg/day PO for adults and 60 mg/kg/day for paediatric patients and adolescents aged under 16 years and weighing under 50 kg. People who could not tolerate the target levetiracetam dose could fall back to a	**Details** Logistic regression analysis compared treatment groups for responder rates in GTC seizure frequency per week and in seizure days per week (all seizures). Follow-up: 24 weeks (maximum study duration: 34 weeks)	**Results** <u>Reduction of seizure frequency >50%</u> Levetiracetam: 57/79; placebo: 38/84 <u>Free of all seizures for the treatment period</u> Levetiracetam: 12/79; placebo: 5/84 <u>Treatment cessation due to adverse drug effects</u> Levetiracetam: 1/79; placebo: 4/84 <u>Serious AEs (SAEs) resulting in hospitalization or disability</u> Levetiracetam: 3;79; placebo: 8/84 <u>Investigators' and patients' global evaluation scores improved on QOLIE- 31-P scale</u> Levetiracetam: 58/73; and 52/67; placebo: 45/79 and 48/75	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, computerised randomisation 1.2: Yes, central randomisation centre ensured concealment 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3. NA 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
with GGE and GTC seizures **Study dates** 2001 to 2005 **Source of funding** UCB Pharma SA, who were involved in the design and conduct of the study; collection, management, and analysis of the data; and preparation and review of the manuscript.	Childhood absence epilepsy L: 3 (3.8) P: 4 (4.8) Juvenile absence epilepsy L: 8 (10.0) P: 11 (13.1) Juvenile myoclonic epilepsy L: 24 (30.0) P: 30 (35.7) Epilepsy with GTC seizures on awakening L: 22 (27.5) P: 27 (32.1) Other genetic generalized epilepsies† L: 18 (22.5) P: 10 (11.9) Epilepsy syndrome unknown L: 5 (6.3) P: 2 (2.4) **Inclusion criteria** 4 to 65 years old and weight ≥20 kg confirmed electroclinical diagnosis consistent with GGE, who were experiencing GTC seizures despite stable treatment with ASMs CT or MRI done in the last 5 years did not show a progressive brain lesion. **Exclusion criteria** Partial-onset seizures, including secondarily generalized TC seizures	dose of 2,000 mg/day (40 mg/kg/day). Placebo Utilising the same routine as intervention group with placebo.			**Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section

Study details	Participants	Interventions	Methods	Outcomes	Comments
	pseudoseizures within the last year seizures occurring only in clustered patterns a history of status epilepticus while taking ASMs within the 3 months before study.				Domain 6: Overall judgment of bias: Low risk of bias The study is judged to be at low risk of bias for all domains for this result.
Full citation Biton, V., Bourgeois, B. F., Topiramate in patients with juvenile myoclonic epilepsy, Archives of Neurology, 62, 1705-1708, 2005 Ref Id 1080000 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of topiramate as an add-on therapy compared to placebo in patients with juvenile myoclonic epilepsy **Study dates** Not reported **Source of funding**	**Sample size** N=22 (n=11 allocated to topiramate and n=11 allocated to placebo) **Characteristics** Age, years, median (range/ IQR not reported): Topiramate: 27 Placebo: 34 Female gender, n (%): 7 (64%) Topiramate: 7 (64%) Placebo: 7 (64%) Epilepsy syndrome, n (%) Primarily generalised tonic-clonic seizures, n (%) Topiramate: 11 (100) Placebo: 11 (100) Myoclonic, n (%) Topiramate: 5 (45) Placebo: 8 (73) Absence, n (%) Topiramate: 4 (36) Placebo: 5 (45)	**Interventions** Patients were randomised to topiramate or placebo. The starting dose of topiramate was 50mg/day during 4 weeks. This was then increased at 2 weeks to target doses of 400mg/day in adults or 6mg/kg/day for children. Treatment was continued for 12 weeks	**Details** Patients and parents/carers had a seizure diary, recording the occurrence of all seizures. The majority of patients (64%) were treated with 2 antiepileptic therapies before topiramate was added. Follow-up: 20 weeks (no measure of variability was reported)	**Results** <u>Reduction of generalised seizure frequency >50%</u> Topiramate: 8/11 Placebo: 5/11 <u>Treatment cessation due to adverse drug effects</u> Topiramate: 2/11 Placebo: 1/11	**Limitations Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: High risk** 1.1: No information 1.2: No information 1.3: No information **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7 : No information **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all

Study details	Participants	Interventions	Methods	Outcomes	Comments
Johnson and Johnson Pharmaceutical Research and development	**Inclusion criteria** Those with at least 3 primarily generalised tonic-clonic seizures during an 8 week baseline period Presence of an EEG consistent with generalised epilepsy **Exclusion criteria** Not reported				participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined 4.2: No information 4.3: Yes, open label study 4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias for all domains.
Full citation French, J. A., Krauss, G. L., Wechsler, R. T., Wang, X. F., Diventura, B., Brandt, C., Trinka,	**Sample size** n=164 people were randomised placebo n=82 perampanel n=82	**Interventions** 3 phases: titration (weeks 1–4), maintenance (weeks 5–17),	**Details** Seizure counts were recorded in patient diaries. The primary efficacy outcome was the	**Results** 50% PGTC seizure responder rate: Perampanel: 52/82; Placebo: 32/82	**Limitations** **Methodological limitations assessed using the Cochrane risk of**

Study details	Participants	Interventions	Methods	Outcomes	Comments
E., O'Brien, T. J., Laurenza, A., Patten, A., Bibbiani, F., Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy, Neurology, 85, 950-957, 2015 **Ref Id** 1114001 **Country/ies where the study was carried out** Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania, Poland, Serbia, South Korea, United States **Study type** Multicentre RCT **Aim of the study** To assess efficacy and safety of adjunctive perampanel in patients with drug-resistant, primary generalized tonic-clonic (PGTC) seizures in genetic generalised epilepsy **Study dates** The first person was enrolled in July 2011,	**Characteristics** Age, years, mean (SD): 28.4 (11.4) Female, n (%): 91 (56.2) Background ASMs at baseline, n (%): 1 : 55 (34) 2: 75 (46) 3: 32 (20) 4: 1 (1) **Inclusion criteria** 12 years and older diagnosed with PGTC seizures and GGE according to the 1981 International League Against Epilepsy (ILAE) classification of epileptic seizures and the 1989 ILAE classification of epilepsies and epileptic syndromes ≥3 PGTC seizures during baseline taking stable doses of 1 to 3 approved ASMs. **Exclusion criteria** Insufficient information to confirm a diagnosis	and follow-up (weeks 18–21). Perampanel During titration, people received an initial daily dose of 2 mg, before uptitration in weekly 2-mg increments to the targeted daily dose of 8 mg or the highest tolerated dose (whichever was lower). People entered the maintenance period at the last dose achieved during titration. Placebo Same procedure as above with placebo	percent change in PGTC seizure frequency per 28 days (titration and maintenance vs baseline). The key secondary endpoint was 50% PGTC seizure responder rate (number of patients achieving ≥50% reduction in PGTC seizure frequency during maintenance vs baseline). Follow-up: 17 weeks (21 weeks for patients not entering an extension phase). No measure of variability was reported	<u>Freedom from all seizures during maintenance period</u> Perampanel: 19/82; Placebo: 4/82 <u>Serious TEAEs</u> Perampanel: 6/82; Placebo: 7/82 <u>Treatment cessation due to AEs</u> Perampanel: 9/82; Placebo: 5/82	**bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, interactive voice response system 1.2: Yes, people had no prior knowledge to allocation 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3. NA 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
and the last in May 2014 **Source of funding** Trial funded by Eisai Inc.					**Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Some concerns** 5.1: Probably no, the study authors do not make reference to any study protocol 5.2: Yes, seizure frequency measured in a number of different outcomes 5.3: No, analysis detailsin the methods section **Domain 6: Overall judgment of bias: Some concerns** The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain

Study details	Participants	Interventions	Methods	Outcomes	Comments
Full citation Levisohn, P. M., Holland, K. D., Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison, Epilepsy & Behavior, 10, 547-52, 2007 **Ref Id** 1080743 **Country/ies where the study was carried out** USA **Study type** Open label RCT **Aim of the study** To evaluate clinical response when these topiramate and valproate are titrated to optimal effect in adolescents/adults with juvenile myoclonic epilepsy **Study dates** Unclear **Source of funding** Not stated	**Sample size** N=28 Topiramate: N=19 Valproate: N=9 Characteristics Age, years, median (range) Topiramate: 15 (9-42), Valproate: 16 (12-34) Gender, female (%) Topiramate: 13 (68%), Valproate: 4 (44%) **Inclusion criteria** 12–65 years old >/=25 kg confirmed diagnosis of juvenile myoclonic epilepsy People had active epilepsy in the form of myoclonus or >/=1 PGTCS in the 3 months before study entry. Topiramate or valproate could be initiated as monotherapy or as an adjunct to another ASM (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy. Females of childbearing potential had to be	**Interventions** A 14-week titration phase was followed by a 12-week maintenance phase. Topiramate target dosage was 3–4 mg/kg/day (maximum, 9 mg/kg/day) for people 12–16 years of age and 200 mg/day (maximum, 600 mg/day) for patients >16 years of age. Valproate target dosages were 10 mg/kg/day in patients 12–16 years of age and 750 mg/day in those >16 years (overall maximum, 60 mg/kg/day).	**Details** Seizure counts were captured with seizure diaries maintained by patients and were reviewed at each study visit. Questionnaires were used to assess drug-related systemic toxicity and neurotoxicity. The questionnaires were completed at each post-baseline visit (4, 8, 14, and 26 weeks). Follow-up: 26 weeks (no measure of variability was reported)	**Results** <u>People with over 50% reduction in myoclonic seizure frequency</u> Topiramate: 12/14; Valproate: 9/9 <u>People with over 50% reduction in PGTCS</u> Topiramate: 11/12; Valproate: 3/3 <u>Treatment cessation due to adverse drug effects</u> Topiramate: 1/19; Valproate: 1/9	**Limitations Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Yes, computer generated 1.2: Yes, people had no prior knowledge of allocation 1.3: Yes, some differences between groups at baseline. Topiramate group had higher percentage of women, PGTCS seizures, and people not on baseline ASMs. Valproate group had a higher weight and percentage of people with myoclonic seizures. **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, open label 2.2: Yes, open label 2.3. Probably no, no indication the context affected recruitment or engagement 2.4 NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
	premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception. **Exclusion criteria** Previous discontinuation of topiramate or valproate due to an adverse event abnormal cranial CT or MRI scan dementia or mental retardation progressive myoclonic epilepsy clinically unstable medical conditions history of nephrolithiasis SGPT levels greater than two times the upper limit of the normal range co-therapy with a carbonic anhydrase inhibitor or barbiturate ASM use of an experimental medication or device within 30 days of study entry.				2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Some concerns** 3.1: No, a number of people dropped out prior to the trial ending 3.2: Probably not, no analysis methods used to correct for bias 3.3: Yes, adverse events and seizure control were often reasons for leaving the study 3.4: No, Similar numbers and reasoning in each group for leaving the study **Domain 4: Measurement of the outcome: Some concerns** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, outcomes standardised though there was no blinding 4.3: Yes, open label study 4.4: No, the outcomes appear to be objective

Study details	Participants	Interventions	Methods	Outcomes	Comments
					Domain 5: Selection of the reported result: Some concerns 5.1: Probably no, the study authors do not make reference to any study protocol 5.2: No, single measurements 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Full citation Machado, R. A., Garcia, V. F., Astencio, A. G., Cuartas, V. B., Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial, Seizure, 22, 846-55, 2013 **Ref Id** 1100264 **Country/ies where the study was carried out** Cuba	**Sample size** N=82 Lamotrigine n=43, valproate n=39 Eight people randomized to valproate regimen and 2 patients randomized to the lamotrigine group were not treated, and were excluded because they did not pick up their medication. Analysed numbers: lamotrigine n=41, valproate n=31	**Interventions** Although the prescribed drug was determined by randomization, drug dose was that prescribed by the physicians in their everyday practice. The initial maintenance dose, and any subsequent increment or decrement was decided by the epileptologists, but the rate of titration was aided by guidelines. People on carbamazepine or phenytoin were instructed to drop the	**Details** The primary end points of the study were: time from randomization to treatment withdrawal time from randomization to seizure remission. Frequency of clinically important adverse events and side-effects emerging after randomization quality of life outcomes Follow-up: 24 months (Authors attempted to follow all patients for at least 2 years, but those	**Results** ITT analysis used. <u>Median (range) time to withdrawal for any reason</u> Lamotrigine 11 (3 to 20) Valproate 12 (3 to 20) <u>Percentage of patients with reported side effects</u> Lamotrigine: 7/41; valproate: 11/31	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: No information 1.2: No information 1.3: No, groups similar at baseline

Study details	Participants	Interventions	Methods	Outcomes	Comments
Study type Open label RCT **Aim of the study** To determine the efficacy and tolerability of lamotrigine in adult patients with juvenile myoclonic epilepsy **Study dates** 2008 to 2010 **Source of funding** It was stated that no funding was received from pharmaceutical companies for this study	**Characteristics** Age, years, mean (SD) Lamotrigine 26 (11), valproate 27 (13) Gender, female (%) Lamotrigine 26 (63%), valproate 21 (67) Prior treatment 63 of 82 people had been treated with carbamazepine. 2 people had received phenytoin. 17 people had never received any medication before. **Inclusion criteria** Juvenile myoclonic epilepsy **Exclusion criteria** insufficient documentation of seizure frequency poor compliance progressive neurological diseases severe psychiatric disorders drug or alcohol abuse systemic disorders laboratory abnormalities pregnant or breastfeeding	doses out slowly during the following 3 weeks and afterwards, they should enter the study. Lamotrigine Highest guideline dose was 300mg per day and could be reached after 25 weeks. Valproate Highest dose was 3000mg per day and this could be reached after 9 weeks	who did not return to the outpatient clinic were included until the date of their last follow-up). No measure of variability was reported	<u>Difference in QOLIE-31 from start of study to end of study (mean ± 2.5 SD)</u> Lamotrigine 7.3, valproate 12.3: no measure of variance provided	**Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes, open label study 2.2: Yes, open label study 2.3. No, none reported 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Some concerns** 4.1: Probably no, median change often used and this can obscure the more extreme results 4.2: Probably no, outcomes appear well defined 4.3: Yes, open label study 4.4: Yes, there were subjective outcomes

Study details	Participants	Interventions	Methods	Outcomes	Comments
					4.5: Possibly not, no reason to think it would **Domain 5: Selection of the reported result: Some concerns** 5.1: No mention of a study protocol 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Full citation Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., Cramp, C., Cockerell, O. C., Cooper, P. N., Doughty, J., Eaton, B., Gamble, C., Goulding, P. J., Howell, S. J., Hughes, A., Jackson, M., Jacoby, A., Kellett, M., Lawson, G. R., Leach, J. P., Nicolaides, P., Roberts, R., Shackley, P., Shen, J.,	**Sample size** N=716 total population in the study (n=239 allocated to lamotrigine, n= 239 allocated to topiramate, and n=238 allocated to valproate) N = 450 with genetic generalised epilepsy (63% of total population) (n=145 allocated to lamotrigine, n= 151 allocated to topiramate,	**Interventions** Valproate, topiramate, lamotrigine; drug dose and preparation was done by the clinician in their own practice. As such, dose adjustments were decided by the clinician, with the main goal being to control the seizures experienced by the patient with the minimum effective dose.	**Details** Patients were randomised in a 1:1:1 ratio to valproate, lamotrigine or topiramate. HR estimates and 95% CIs were calculated with Cox regression models and adjusted for drug, epilepsy syndrome and drug-syndrome interaction terms. Time to treatment failure was defined as "stopping the randomised drug because of	**Results** *Data for patients with genetic generalised epilepsy only- data taken from HTA report* <u>Time to treatment failure, HR (95% CI)</u> Topiramate vs Valporate 1.90 (1.33 to 2.71) Lamotrogine vs. Valporate: 1.56 (1.08 2 to 2.25)	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, telephone based randomisation 1.2: Yes, central randomisation centre ensured concealment

Study details	Participants	Interventions	Methods	Outcomes	Comments
Smith, D. F., Smith, P. E., Smith, C. T., Vanoli, A., Williamson, P. R., The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial, Lancet, 369, 1016-1026, 2007 **Ref Id** 1114590 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the long-term outcomes of patients with generalised onset seizures taking valproate, topiramate or lamotrigine **Study dates** 12th January 1999 to 31st August 2004. Follow-up data were obtained up to Jan 13, 2006 **Source of funding**	and n=154 allocated to valproate) **Characteristics** Of whole study population Age, years, mean (SD)* Lamotrigine: 22.8 (14.3) Topiramate: 22.3 (13.3) Valproate: 22.5 (14.5) Female gender* Lamotrigine: 97 (40.6) Topiramate: 97 (40.6) Valproate: 95 (39.9) Epilepsy syndrome, n (%)* Genetic partial, n (%) Lamotrigine: 1 (0.4) Topiramate: 2 (0.8) Valproate: 0 (0) Symptomatic or cryptogenic partial, n (%) Lamotrigine: 18 (7.5) Topiramate: 11 (4.6) Valproate: 20 (8.4) Genetic generalised, n (%) Lamotrigine: 145 (60.7) Topiramate: 151 (63.5) Valproate: 154 (64.7) Other syndrome, n (%) Lamotrigine: 9 (3.8)		inadequate seizure control, intolerable side effects, or the addition of other anti-epileptic drug". The time to first seizure was defined as "time from randomisation to first seizure of any type". Follow-up: Up to 6 years (patients lost to follow-up were included until the date of their last follow-up). No measure of variability was reported	<u>Time to 12 month remission, HR (95% CI)</u> Topiramate vs Valporate 0.83 (0.64 to 1.07) Lamotrogine vs. Valporate: 0.69 (0.53 to 0.89) <u>Time to 24 month remission, HR (95% CI)</u> Topiramate vs Valporate 0.69 (0.50 to 0.94) Lamotrogine vs. Valporate: 0.60 (0.43 to 0.83) <u>Time to first seizure, HR (95% CI)</u> Topiramate vs Valporate 1.26 (0.96 to 1.65) Lamotrogine vs. Valporate: 1.73 (1.32 to 2.26)	1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was not blinded 2.2: Yes, the study was not blinded 2.3. No, there were no deviations from the intended intervention 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined 4.2: Probably yes, outcome assessors were

Study details	Participants	Interventions	Methods	Outcomes	Comments
Health Technology Assessment Programme; with additional contributions from GlaxoSmithKline, Janssen-Cilag, Novartis Pfizer, Sanofi-Synthelabo, and the Wellcome Trust	Topiramate: 8 (3.4) Valproate: 5 (2.1) Unclassified, n (%) Lamotrigine: 66 (27.6) Topiramate: 66 (27.7) Valproate: 59 (24.8) **Inclusion criteria** Those with newly diagnosed epilepsy Those who had failed treatment with previous monotherapy (as long as the drug failure did not include one of the drugs present in the randomisation) Those in remission of epilepsy who had relapsed after withdrawal of treatment **Exclusion criteria** Those who themselves or the clinical thought the treatment was contraindicated Those in whom all their seizures had been acute symptomatic seizures (including febrile seizures) Those ≤4 years old Those with a history of progressive neurological disease				aware of treatment allocation, although outcomes were standardised 4.3: NA 4.4: NA **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: Some concerns** **Other information** *Note that only results for those with genetic generalised epilepsy have been reported, however demographic characteristics have been included to all patients. Those with genetic generalised epilepsy 15% (n=66) had childhood absence epilepsy, 10% (n=45) had juvenile absence epilepsy,

Study details	Participants	Interventions	Methods	Outcomes	Comments
					26% (n=119) had juvenile myoclonic epilepsy, 9% (n=42) had generalise epilepsy with tonic clonic seizures on waking and 37% (n= 168) had an unspecified genetic generalised epilepsy.
Full citation Marson, A. G., Appleton, R., Baker, G. A., Chadwick, D. W., Doughty, J., Eaton, B., Gamble, C., Jacoby, A., Shackley, P., Smith, D. F., et al.,, A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial, Health technology assessment (winchester, england), 11, iii-iv, ix-x, 1-134, 2007 **Ref Id** 1080831 **Country/ies where the study was carried out** UK **Study type** see Marson 2007 **Aim of the study** see Marson 2007	**Sample size** see Marson 2007 **Characteristics** see Marson 2007 **Inclusion criteria** see Marson 2007 **Exclusion criteria** see Marson 2007	**Interventions** see Marson 2007	**Details** see Marson 2007	**Results** see Marson 2007	**Limitations** see Marson 2007

Study details	Participants	Interventions	Methods	Outcomes	Comments
Study dates see Marson 2007 **Source of funding** see Marson 2007					
Full citation Marson, Anthony, Burnside, Girvan, Appleton, Richard, Smith, Dave, Leach, John Paul, Sills, Graeme, Tudur-Smith, Catrin, Plumpton, Catrin, Hughes, Dyfrig A., Williamson, Paula, Baker, Gus A., Balabanova, Silviya, Taylor, Claire, Brown, Richard, Hindley, Dan, Howell, Stephen, Maguire, Melissa, Mohanraj, Rajiv, Smith, Philip E., Lanyon, Karen, Manford, Mark, Chitre, Manali, Parker, Alasdair, Swiderska, Nina, Appleton, Richard, Pauling, James, Hughes, Adrian, Gupta, Rajat, Hanif, Sadia, Awadh, Mostafa, Ragunathan, Sharmini, Cable, Nicola, Cooper, Paul, Hindley, Daniel, Rakshi, Karl, Molloy, Sophie, Reuber, Markus, Ayonrinde, Kunle, Wilson, Martin,	**Sample size** Total included population: N=520 Valproate: n=260; Levetiracetam: n=260 Population with generalised epilepsy: n=397 Valproate: n=201; Levetiracetam: n=196 **Characteristics** Of whole study population Age, years, median (IQR) Valproate: 13·6 (8·8–19·7) Levetiracetam: 14·1 (9·1–19·8) Female gender, n (%) Valproate: 93 (36%) Levetiracetam: 90 (35%) Epilepsy syndrome - unclassified epilepsy, n (%) Valproate: 59 (23%) Levetiracetam: 64 (25%)	**Interventions** Valproate and levetiracetam dose and preparation were done by the clinician as per routine NHS practice and dispensed by hospital and community pharmacies. The initial recommended treatments and dosages were: For participants aged 12 years or more: • 500mg twice per day of valproate • 500mg twice per day of levetiracetam For participants aged 5-12 years: • 25 mg/kg daily maintenance dose of valproate • 40 mg/kg daily maintenance dose of levetiracetam	**Details** Patients were randomised with a computer program in a 1:1 ratio to valproate or levetiracetam. Participants continued in follow-up even if they did not continue with the allocated treatment, with outcome data sought from their GP if data from hospital follow-up were no longer available. HR estimates and 95% CIs were calculated with Cox proportional hazard regression models, with subgroup effects explored in a post-hoc analysis. Data were presented separately for participants with absence epilepsies, other generalised epilepsies, and unclassified epilepsy only for the outcome time to 12-month remission from seizures. This outcome was calculated	**Results** Data reported for patients with generalised epilepsy (including absence and other generalised epilepsies) only Time to 12-month remission from seizures HR (95% CI) Absence epilepsy: Valproate vs Levetiracetam 0.90 (0.60 to 1.35) Other generalised epilepsy: Valproate vs Levetiracetam 1.55 (1.14, 2.11)	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, computerised randomisation 1.2: Yes, central randomisation centre ensured concealment 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes, open-label study 2.2: Yes, open-label study 2.3. Probably no, authors reported 6 (1%) major treatment protocol deviations, however protocol implies these deviations are defined as due to randomised

Study details	Participants	Interventions	Methods	Outcomes	Comments
Saladi, Satyanarayana, Gibb, John, Funston, Lesley-Ann, Cassidy, Damhait, Boyd, Jonathan, Ratnayaka, Mal, Faza, Hani, Sadler, Martin, Al-Moasseb, Hassan, Galtrey, Clare, Wren, Damien, Olabi, Anas, Fuller, Geraint, Khan, Muhammed, Kallappa, Chetana, Chinthapalli, Ravi, Aji, Baba, Davies, Rhys, Foster, Kathryn, Hitiris, Nikolas, Maguire, Melissa, Hussain, Nahin, Dowson, Simon, Ellison, Julie, Sharrack, Basil, Gandhi, Vandna, Powell, Rob, Tittensor, Phil, Summers, Beatrice, Shashikiran, Sastry, Dison, Penelope J., Samarasekera, Shanika, McCorry, Doug, White, Kathleen, Nithi, Kannan, Richardson, Martin, Brown, Richard, Page, Rupert, Deekollu, David, Slaght, Sean, Warriner, Stephen, Ahmed, Mansoor, Chaudhuri, Abhijit, Chow, Gabriel, Artal, Javier, Kucinskiene, Danute, Sreenivasa, Harish, Velmurugan,	<u>Epilepsy syndrome - generalised epilepsy*</u> <u>Childhood absence, n (%)</u> Valproate: 52 (26%) Levetiracetam: 52 (27%) <u>Juvenile absence, n (%)</u> Valproate: 22 (11%) Levetiracetam: 14 (7%) <u>Juvenile myoclonic, n (%)</u> Valproate: 24 (12%) Levetiracetam: 27 (14%) <u>Epilepsy with tonic-clonic seizures on awakening, n (%)</u> Valproate: 11 (5%) Levetiracetam: 12 (6%) <u>Other genetic generalised epilepsy not specified, n (%)**</u> Valproate: 90 (45%) Levetiracetam: 90 (46%) <u>Other epilepsy syndrome, n (%)</u> Valproate: 10 (5%) Levetiracetam: 7 (4%)	Treatment and dosage adjustments were subsequently made by the clinician according to treatment response and standard clinical practice.	as days from randomisation to the first date at which a period of 12 months had elapsed without any seizures, captured using seizure diaries and reports at clinic visits. Follow-up range: 2 to 6.5 years		treatment not starting within 7 days of randomisation which is consistent with what might occur outside of trial context 2.4 NA 2.5. NA 2.6 Yes, ITT used for the relevant outcome 2.7 NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for the relevant outcome for all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined 4.2: Probably no, comparable methods of outcome measurement 4.3: Yes, open label study 4.4: Probably no, outcomes assessed using seizure diaries 4.5: NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
Singara, Zipitis, Christos S., McLean, Brendan, Lal, Vaithianathar, Gregoriou, Angelous, Maddison, Paul, Pickersgill, Trevor, Anderson, Joseph, Lawthom, Charlotte, Howell, Stephen, Whitlingum, Gabriel, Rakowicz, Wojtek, Kinton, Lucy, McLellan, Alisa, Vora, Nitish, Zuberi, Sameer, Kelso, Andrew, Hughes, Imelda, Martland, John, Emsley, Hedley, de Goede, Christian, Singh, R. P., Moor, Carl-Christian, Aram, Julia, Mohanraj, Rajiv, Sakthivel, Kumar, Nelapatla, Suresh, Rittey, Chris, Pinto, Ashwin, Leach, John Paul, Cock, Hannah, Richardson, Anna, Houston, Erika, Cooper, Christopher, Lawson, Geoff, Massarano, Albert, Burness, Christine, Marson, Anthony, Smith, Dave, Wieshmann, Udo, Dey, Indranil, Sivakumar, Puthuval, Yeung, Lap-Kong, Smith, Philip, Bentur, Hemalata, Heafield, Tom, Mathew, Anna,	*For all generalised epilepsy syndromes, participants could be classified as belonging to multiple groups **150/180 (83%) patients in this group reported tonic-clonic seizures **Inclusion criteria** • Those aged 5 years or older • Those with a history of at least 2 unprovoked epileptic seizures requiring treatment • Those with a clinical diagnosis of either a generalised epilepsy syndrome or unclassified epilepsy • Those who had not been treated with anti-seizure medicine other than emergency treatment in the 2 week period before enrolment				**Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: Low risk of bias**

Study details	Participants	Interventions	Methods	Outcomes	Comments
Smith, David, Jauhari, Praveen, The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial, The Lancet, 397, 1375-1386, 2021 **Ref Id** 1313570 **Country/ies where the study was carried out** UK **Study type** Multi-centre, open-label, randomised controlled trial. **Aim of the study** To "compare the long term clinical effectiveness and cost-effectiveness of levetiracetam compared with valproate in participants with newly diagnosed generalised or unclassifiable epilepsy." **Study dates**	**Exclusion criteria** • Those with provoked or acute symptomatic seizures only • Those currently taking anti-seizure medication • Those with known progressive neurological diseases				

Study details	Participants	Interventions	Methods	Outcomes	Comments
April 2013 - Jan 2019 **Source of funding** National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 09/144/09). Author AG Marson part funded by the NIHR Applied Research Collaboration North West Coast. Co-sponsored by the University of Liverpool and the Walton Centre NHS Foundation Trust.					
Full citation Nejad, S. E. M., Nikpour, M. R. A., Rahim, F., Naghibi, S. N., Bahrammi, M. A., A randomized open-label comparison of lamotrigine and valproate in patients with juvenile myoclonic epilepsy, International Journal of Pharmacology, 5, 313-318, 2009 **Ref Id** 1080944 **Country/ies where the study was carried out** Iran **Study type**	**Sample size** N=46 women (n=23 randomised to lamotrigine and n=23 randomised to valproate) **Characteristics** Age, years, mean (SD), n (%): age 8-30 years Female gender, n (%): 46 (100%) Epilepsy syndrome, n (%) Juvenile myoclonic epilepsy, n (%) 46 (100%) Tonic-clonic seizures, n (%)	**Interventions** Lamotrigine was started at the dose of 500 mg day and was progressively increased to a mean dose of 1500-2000 mg day in a time course of 8 weeks. The target maintenance dose for valproate was 800 mg day after starting valproate at the dose of 200 mg/12 h. The mean dose was reached within 4 weeks. Patients were clinically observed every 3 months.	**Details** Clinical records were analysed. Efficacy The basis for comparison was defined as the myoclonic seizure frequency in the 6 months prior to the commencement of treatment. We classified patients post-treatment into three categories: those achieving seizure freedoms, those achieving between 50 and 99% reduction in seizures and those with worsening. We observed the reduction of massive or	**Results** Mean seizure reduction from baseline **Juvenile myoclonic** Mean seizure frequency at baseline (SD) Valproate: 5.10 (1.51), n=23 Lamotrigine: 4.77 (1.63), n=23 Mean seizure frequency at follow-up (SD) Valproate: 0.60 (1.31), n=20	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: High risk** 1.1: No information 1.2: No information 1.3: No information **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was open label 2.2: Yes, the study was open label

Study details	Participants	Interventions	Methods	Outcomes	Comments
Randomised open label trial **Aim of the study** To assess the effectiveness of lamotrigine compared with valproate in patients with juvenile myoclonic epilepsy **Study dates** 2007 to 2008 **Source of funding** Not reported	43 (93.48%) Myoclonic absences, n (%) 5 (11%) **Inclusion criteria** Women with juvenile myoclonic epilepsy **Exclusion criteria** Not reported		focal epileptic myoclonus and other generalized seizures (e.g., absence, tonic-clonic). Follow-up: 28 weeks (no measure of variability was reported)	Lamotrigine: 0.86 (1.69), n=22 **Tonic-clonic** <u>Mean seizure frequency at baseline (SD)</u> Valproate: 2.26 (1.09), n=19 Lamotrigine: 2.3 (1.26), n=20 <u>Mean seizure frequency at follow-up (SD)</u> Valproate: 0.36 (0.68), n=19 Lamotrigine: 0.45 (0.94), n=20	2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7 : No information **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined 4.2: No information 4.3: Yes, open label study 4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section

Study details	Participants	Interventions	Methods	Outcomes	Comments
					Domain 6: Overall judgment of bias: High risk of bias The study is judged to be at high risk of bias for all domains.
Full citation 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 **Ref Id** 1080960 **Country/ies where the study was carried out** 14 countries (Australia, New Zealand, Europe, and North and Central America) **Study type** Multi-centre RCT **Aim of the study** To assess the efficacy, safety, and tolerability of levetiracetam as adjunctive therapy for people with myoclonic seizures that were not fully controlled despite treatment with an ASM.	**Sample size** N=121 Levetiracetam n=61, placebo n=60 113 had Juvenile myoclonic epilepsy and 8 had Juvenile absence epilepsy **Characteristics** Age, years, mean (SD) Levetiracetam 25 (7.4), placebo 26.8 (9.5) Female gender, n (%) Levetiracetam 39 (63.9%), placebo 38 (63.3%) Epilepsy syndrome, n (%) Juvenile myoclonic epilepsy: Levetiracetam 54 (88.5%), placebo 59 (98.3%) Juvenile absence epilepsy: Levetiracetam 7 (11.5%), placebo 1 (1.7%) Concomitant ASM, n (%)	**Interventions** Following an 8-week, single-blind, prospective, placebo baseline period, patients were randomly assigned to receive levetiracetam or placebo. Levetiracetam 4 week titration period where dose was increased to 3,000 mg/day. This was continued for 12 weeks. 1 concomitant ASM was to be taken with the study treatment at a stable dose. People were discontinued from the study if they withdrew consent for any reason or for lack of efficacy or safety reasons, as judged by the investigator. Placebo: Followed same pattern as intervention group with placebo.	**Details** Daily record cards used by people or their families to record seizures. Follow-up: 16 weeks (no measure of variability was reported)	**Results** <u>Reduction of myoclonic seizure frequency >50%</u> Levetiracetam 35 of 60, placebo 14 of 60 <u>Short term seizure freedom during 16-week treatment period</u> Levetiracetam 8 of 61, placebo 0of 60 <u>Improvement in overall HRQoL via QoLIE-31-P</u> Levetiracetam 88.3%, placebo 60.4%. No measure of variance provided. <u>Treatment cessation due to adverse drug effects</u> Levetiracetam 3 of 61, placebo 1 of 60 <u>Serious adverse events</u> Levetiracetam 4 of 61, placebo 1 of 60	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: some concerns** 1.1: Yes, central randomization centre 1.2: Yes, central randomisation centre ensured concealment 1.3: Yes, more people with juvenile absence epilepsy in the levetiracetam group **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3. NA 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
Study dates From 2001 to 2004 **Source of funding** This study was funded by UCB Pharma SA, Braine-l'Alleud, Belgium.	Valproic acid: levetiracetam 37 (61%), placebo 33 (55%) Lamotrigine levetiracetam 15 (25%), placebo 17 (28%) Other: levetiracetam 15 (14%), placebo 17 (17%) **Inclusion criteria** 12 to 65 years old a diagnosis of GGE with myoclonic seizures receiving a stable dose of one ASM for at least 4 weeks before study entry females of childbearing potential were eligible if they used a medically accepted contraceptive method. **Exclusion criteria** nonepileptic seizures within the previous year signs suggestive of a progressive brain lesion history of partial-onset seizures status epilepticus within the previous 3 months previous or current treatment with levetiracetam current use of vigabatrin or tiagabine				**Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: Some concerns**

Study details	Participants	Interventions	Methods	Outcomes	Comments
	current use of felbamate with less than 18 months exposure				The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
Full citation Park, K. M., Kim, S. H., Nho, S. K., Shin, K. J., Park, J., Ha, S. Y., Kim, S. E., A randomized open-label observational study to compare the efficacy and tolerability between topiramate and valproate in juvenile myoclonic epilepsy, Journal of Clinical Neuroscience, 20, 1079-1082, 2013 **Ref Id** 1081001 **Country/ies where the study was carried out** Republic of Korea **Study type** Randomised controlled trial **Aim of the study** To compare topiramate and valporate **Study dates** July 2006 to August 2008 **Source of funding** Study partially supported by a grant from	**Sample size** N=33 (n=16 allocated to topiramate and n=17 allocated to valproate) **Characteristics** Age, years, median (range) Topiramate: 19 (13 to 42), valproate: 17 (range 14 to 36) Sex (male:female) Topiramate: 1:1, valproate: 1:1.1 Epilepsy syndrome, n (%) Absence seizure Topiramate: 5 (31) Valproate: 8 (47) Generalised tonic clonic seizure Topiramate: 14 (88) Valproate: 14 (82) Absence seizure + generalised tonic clonic seizure Topiramate: 4 (25) Valproate:5 (29) **Inclusion criteria** Those with newly or previously diagnosed	**Interventions** Patient's medication was titrated for 8 weeks, followed by a 24-week maintenance phase. Valproate was titrated up to 1200 mg/day and topiramate up to 100 mg/day. The dose of valproate was titrated up to 300mg/day for 2 weeks, and the dose of topiramate was increased 25mg/day for 2 weeks.	**Details** Patients were randomised with a computer program in a 1:1 ratio to topiramate or valproate. Patients were withdrawn from the study in they continued to present with seizures after researching the maximal dose. Patients were requested to record seizure frequency in a diary, which was reviewed at each visit. Because counting myoclonic seizures can be difficult, the number of days without myoclonic seizures was counted. Follow-up: 24 weeks (no measure of variability was reported)	**Results** Number of participants who were seizure-free during the 24 week maintenance period Topiramate:7/11 Valproate: 9/16	**Limitations Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, computerised randomisation 1.2: No information 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7 : No information **Domain 3: Missing outcome data: Low risk**

Study details	Participants	Interventions	Methods	Outcomes	Comments
Janssen Pharmaceuticals, Korea	juvenile myoclonic epilepsy with a history, poor response or adverse events to other antiepileptic drugs **Exclusion criteria** Those who had previously taken topiramate or valproate Those with absence of myoclonic seizures Significantly abnormal cranial CT scans or MRI Presence of a progressive neurological condition History of nephrolithiasis Abnormal liver enzymes test Pregnancy				3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined 4.2: No information 4.3: Yes, open label study 4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias for all domains.
Full citation Sundqvist, A., Tomson, T., Lundkvist, B.,	**Sample size** N=18 (2 of these people were excluded from analysis due to adverse	**Interventions** Enteric-coated sodium valproic acid tablets:	**Details** Patients went on to the next part of the study before planned cross-	**Results** Seizure frequency increase of 50% or more	**Limitations** **Methodological limitations assessed using the Cochrane risk of**

Study details	Participants	Interventions	Methods	Outcomes	Comments
Valproate as monotherapy for juvenile myoclonic epilepsy: Dose-effect study, Therapeutic Drug Monitoring, 20, 149-157, 1998 **Ref Id** 1081290 **Country/ies where the study was carried out** Sweden **Study type** Single centre crossover RCT **Aim of the study** To study the correlation between dose and effect, and plasma concentration and effect of VPA as monotherapy in people with juvenile myoclonic epilepsy. **Study dates** Unclear **Source of funding** Karolinska Institute Research Funds and Orion Pharma AB giving support and providing study medication.	events not considered to be in relation to epileptic seizures) Low dose to start: N=10 High dose to start: N=8 Of the 16 people who completed the study: 4 were de novo patients and 12 were switched from other antiepileptic drugs because of poor seizure control **Characteristics** Age, years, median (range) 25 (15-46) Males, n (%) 9 (56%) **Inclusion criteria** over 14 years old newly diagnosed and previously untreated JME or people with JME and not seizure-free treated with antiepileptic drug(s) other than VPA. Consecutive people with JME meeting the inclusion criteria at an outpatient epilepsy clinic were included. **Exclusion criteria**	500 mg VPA b.i.d. (low dose). Enteric-coated sodium valproic acid tablets: 1000 mg b.i.d. (high dose). No titration period was used. Observation time of each dose was 6 months.	over or study completion if they experienced unacceptable seizure control, defined as having >1 generalised tonic-clonic seizure on the given dose, or if they had intolerable side effects, which were defined subjectively by the patient. Patients used specially-designed calendars to keep records of their seizures and reported their seizure frequency at their monthly appointment. Each tonic-clonic seizure was registered separately as 1 event, whereas the occurrence of repetitive myoclonic or absence seizures in 1 day was counted as 1 myoclonic, 1 absence event, or both, even if the patient had suffered more than 1 seizure of each type. This was due to the difficulty to count repetitive myoclonic or absence seizures. A drop in total seizure event frequency between the two doses of ≥50% was considered clinically	low dose: 0, high dose: 4. <u>Treatment cessation due to adverse drug effects</u> low dose: 0, high dose: 2	**bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: High risk** 1.1: No information 1.2: No, provided by the pharmaceutical company providing medication 1.3: No information **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3. NA 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Some concerns** 3.1: Probably no, 2 of 18 randomised did not have data 3.2: Probably no, not related to interventions 3.3: Probably no, people withdrew prior to 1 intervention being used 3.4: NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
	Taking medication other than ASM planned pregnancy blood chemistry showing hepatic enzymes more than two times the hospital's upper normal limit.		significant. The first 30 days of treatment on each dose was omitted from the seizure count. Patients were asked at each monthly visit how they would classify their side-effects from the following: none, slight, moderate, or severe. The following side-effects were actively asked for: gastritis, diarrhea, sedation, hand tremor, numbness, hair loss, increased appetite, need for change of daily routines, as well as any other patient-reported side-effects. Follow-up: 6 months per dose (no measure of variabil-ity was reported)		**Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Some concerns** 5.1: Probably no, the study authors do not make reference to any study protocol 5.2: Yes, seizure frequency measured in a number of different outcomes 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias in at least one domain for this result.
Full citation Wu, L., Yagi, K., Hong, Z., Liao, W., Wang, X., Zhou, D., Inoue, Y.,	**Sample size** N=117, n=59 allocated to levetiracetam and	**Interventions** Levetiracetam 1000 mg/day for those who had no GTC seizures	**Details** Patients were randomised 1:1 using central randomisation via an	**Results** Median (IQR) percent reduction from combined baseline in GTC	**Limitations** **Methodological limitations assessed using the Cochrane risk of**

Study details	Participants	Interventions	Methods	Outcomes	Comments
Ohtsuka, Y., Sasagawa, M., Terada, K., Du, X., Muramoto, Y., Sano, T., Adjunctive levetiracetam in the treatment of Chinese and Japanese adults with generalized tonic-clonic seizures: A double-blind, randomized, placebo-controlled trial, Epilepsia Open, 3, 474-484, 2018 **Ref Id** 1081483 **Country/ies where the study was carried out** China **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of adjunctive levetiracetam in the treatment of patients with genetic generalised epilepsy **Study dates** October 2010 to May 2014 **Source of funding** UCB Pharma	n=58 allocated to placebo Whole study: N=251 GGE population: N = 117 **Characteristics** Characteristics reported for the whole population Age, years, mean (SD) Levetiracetam: 31.5 (11.3), placebo: 32.8 (12.5) Male gender Levetiracetam: 79 (62.7%), placebo: 76 (60.8%) Epilepsy syndrome, n (%) Focal: L (levetiracetam): 1 (0.8), P (placebo): 0 (0) Generalized: L: 120 (95.2), P: 120 (96) Genetic: L: 59 (46.8), P: 59 (46.8) Juvenile myoclonic epilepsy: L: 3 (2.4), P: 3 (2.4) Epilepsy with grand mal seizures of awakening: L: 2 (1.6), P:6 (4.8) Other: L: 54 (42.9), P: 49 (39.2)	up to week 8 after randomization. For those who had ≥1 GTC seizure, levetiracetam was increased to 3,000 mg/day in steps of 1,000 mg/day/2 weeks. The control group received placebo utilising the same routine as with the intervention group. Doses remained stable during the evaluation period.	interactive voice response system. After randomisation, a 12-week dose adjustment period was followed by a 16-week evaluation period. Once the evaluation period was completed, patients entered a 6-week withdrawal period with a final safety visit 2 weeks after the last dose. Follow-up: 28 weeks (no measure of variability was reported)	<u>seizures/week during the treatment period (for those with genetic generalised epilepsy)</u> Levetiracetam: 73.9% (54.7 to 94.8) Placebo: 27.0% (-7.2 to 57.9)	**bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, central randomisation via an interactive voice response system. 1.2: Yes, central randomisation centre ensured concealment 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3. NA 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised with genetic generalised epilepsy 3.2: NA 3.3: NA

Study details	Participants	Interventions	Methods	Outcomes	Comments
	Symptomatic: L: 61 (48.4), P: 62 (49.6) Specific syndromes: L: 0 (0), P: 2 (1.6) Other: L: 61 (48.4), P: 60 (48) Undertermined: L: 61 (4.8), P: 4 (3.2) **Inclusion criteria** ≥16 years old Uncontrolled GTC seizures (ILAE classification) despite treatment with 1 or 2 anti-epileptic drugs Those with idipathic generalised epilepsy, symptomatic generalized epilepsy, cryptogenic generalized epilepsy or undetermined epilepsy with GTC seizures ≥3 GTC seizures during the combined baseline period, with ≥1 GTC seizure occurring during both the retrospective and prospective baseline periods **Exclusion criteria** Focal epilepsy confirmed by EEG and magnetic resonance imaging				3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgement of bias: Low risk of bias** The study is judged to be at low risk of bias for all domains for this result.

Study details	Participants	Interventions	Methods	Outcomes	Comments
	Signs suggesting a progressive brain lesion History of status epilepticus within 3 months prior to trial enrolment Previous treatment with levetiracetam Those with psychogenic nonepileptic seizures or clinically significant acute or chronic illness Those with Lennox-Gastaut				

GTCS: Generalised tonic clonic seizures; PGTC: Primary generalised tonic clonic seizures; RCT: Randomised controlled trial; TEAEs: Treatment emergent adverse event; VAL: Valproate

Appendix E – Forest plots

Forest plots for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 1: levetiracetam versus placebo

Figure 2: Reduction of seizure frequency >50%

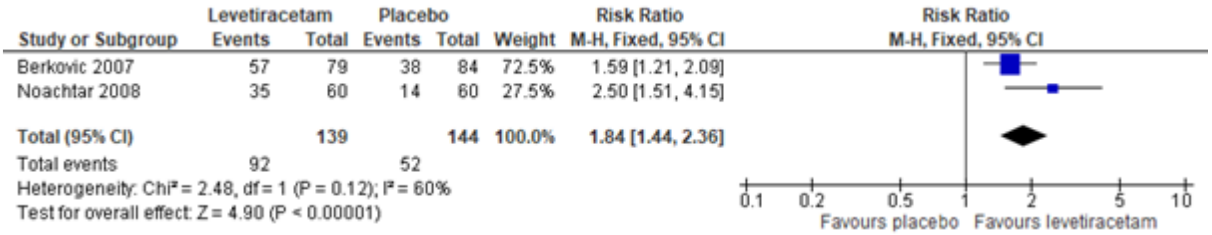


Figure 3: Serious adverse events

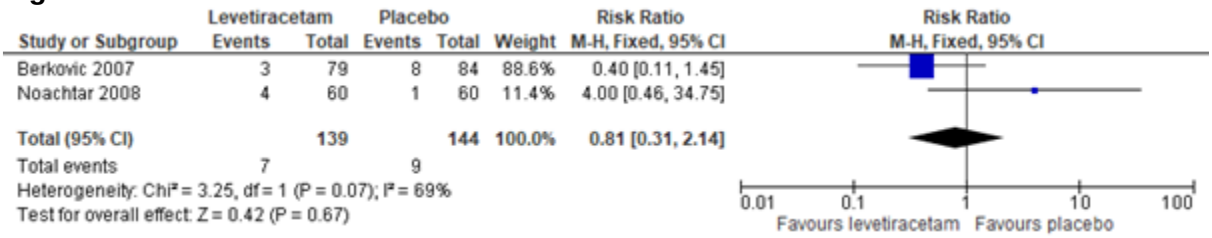
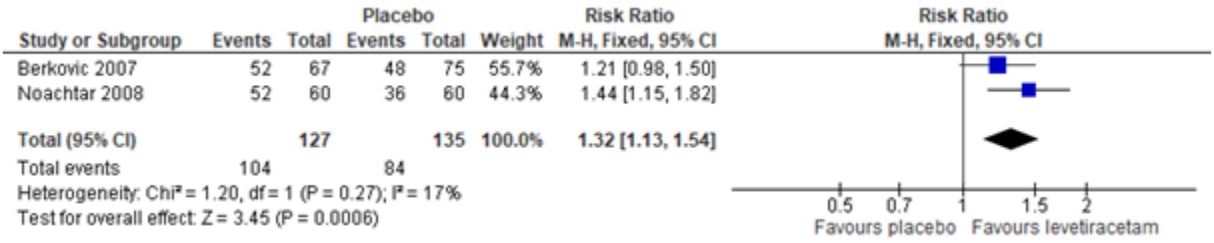


Figure 4: Patients global evaluation scores improved on QOLIE-31-P scale



Appendix F - GRADE tables

GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 11: Clinical evidence profile. Comparison 1: add-on levetiracetam versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on levetiracetam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction of seizure frequency >50%												
2 (Berkovic 2007, Noachtar 2008)	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	92/139 (66.2%)	52/144 (36.1%)	RR 1.84 (1.44 to 2.36)	303 more per 1000 (from 159 more to 491 more)	⊕⊕OO LOW	CRITICAL
Short-term seizure freedom during the 16 week treatment period												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	8/61 (13.3%)	0/60 (0%)	RR 17 (1 to 288.07)	POR 8.22 (1.97 to 34.29)	⊕⊕OO LOW	CRITICAL
Free of all seizures for the treatment period												
1 (Berkovic 2007)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	12/79 (15.2%)	5/84 (6%)	RR 2.55 (0.94 to 6.92)	92 more per 1000 (from 4 fewer to 352 more)	⊕⊕⊕O MODERATE	CRITICAL
Median percent reduction from combined baseline in GTC seizures/week during the treatment period (Better indicated by lower values)												
1 (Wu 2018)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Median: 73.9% IQR: 54.7 to 94.8	Median: 27.0% IQR: -7.2 to 57.9	-	not calculable	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
2 (Berkovic 2007, Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/139 (5%)	9/144 (6.3%)	RR 0.81 (0.31 to 2.14)	12 fewer per 1000 (from 43 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug events												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on levetiracetam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2 (Berkovic 2007, No-achtar 2008)	RCT	serious[1]	serious[2]	no serious indirectness	very serious[5]	none	4/139 (2.9%)	5/144 (3.5%)	RR 0.83 (0.22 to 3.07)	6 fewer per 1000 (from 27 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL
Investigators global evaluation scores improved on QOLIE-31-P scale												
1 (Berkovic 2007)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	58/73 (79.5%)	45/79 (57%)	RR 1.39 (1.11 to 1.75)	222 more per 1000 (from 63 more to 427 more)	⊕⊕⊕O MODERATE	IMPORTANT
Patients global evaluation scores improved on QOLIE-31-P scale												
2 (Berkovic 2007, No-achtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	104/127 (81.9%)	84/135 (62.2%)	RR 1.32 (1.13 to 1.54)	199 more per 1000 (from 81 more to 336 more)	⊕⊕OO LOW	IMPORTANT

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Serious heterogeneity unexplained by subgroup analysis*
[3] *95% CI crosses 1 MID (1.25)*
[4] *Due to low event rate, and to prevent quality inflation this was downgraded by one for imprecision*
[5] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 12: Clinical evidence profile. Comparison 2: add-on topiramate versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction of generalised seizure frequency >50%												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Biton 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/11 (72.7%)	5/11 (45.5%)	RR 1.6 (0.76 to 3.36)	273 more per 1000 (from 109 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug events												
1 (Biton 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/11 (18.2%)	1/11 (9.1%)	RR 2 (0.21 to 18.98)	91 more per 1000 (from 72 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 13: Clinical evidence profile. Comparison 3: add-on perampanel versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on perampanel	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction of primarily generalised tonic-clonic seizures (PGTC) >50%												
1 (French 2015)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/82 (63.4%)	32/82 (39%)	RR 1.62 (1.18 to 2.23)	242 more per 1000 (from 70 more to 480 more)	⊕⊕OO LOW	CRITICAL
Freedom from all seizures during treatment period												
1 (French 2015)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/82 (23.2%)	4/82 (4.9%)	RR 4.75 (1.69 to 13.36)	183 more per 1000 (from 34	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on perampanel	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										more to 603 more)		
% of patients with reported side effects (trial reported serious)												
1 (French 2015)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/82 (7.3%)	7/82 (8.5%)	RR 0.86 (0.3 to 2.44)	12 fewer per 1000 (from 60 fewer to 123 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug events												
1 (French 2015)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/82 (11%)	5/82 (6.1%)	RR 1.8 (0.63 to 5.14)	49 more per 1000 (from 23 fewer to 252 more)	⊕OOO VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *95% CI crosses 1 MID (1.25)*
[3] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 14: Clinical evidence profile. Comparison 4: topiramate versus valproate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Valproate	Relative (95% CI)	Absolute	Quality	Importance
Time to treatment failure												
1 (Marson 2007)	RCT	serious[1]	no serious in-consistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.90 (1.33 to 2.17)	-	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Valproate	Relative (95% CI)	Absolute	Quality	Importance
Reduction of myoclonic seizure frequency >50%												
1 (Levisohn 2007)	RCT	very serious[2]	no serious in-consistency	no serious indirectness	serious[3]	none	12/14 (85.7%)	9/9 (100%)	RR 0.88 (0.67 to 1.15)	120 fewer per 1000 (from 330 fewer to 150 more)	⊕OOO VERY LOW	CRITICAL
Reduction of primarily generalised tonic-clonic seizure (PGTCS) frequency >50%												
1 (Levisohn 2007)	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/12 (91.7%)	3/3 (100%)	RR 1.01 (0.66 to 1.54)	10 more per 1000 (from 340 fewer to 540 more)	⊕OOO VERY LOW	CRITICAL
Number of participants who were seizure free during the 24 week treatment period												
1 (Park 2013)	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/11 (63.6%)	9/16 (56.3%)	RR 1.13 (0.61 to 2.11)	73 more per 1000 (from 219 fewer to 624 more)	⊕OOO VERY LOW	CRITICAL
Time to 12 month remission												
1 (Marson 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.83 (0.64 to 1.08)	-	⊕⊕OO LOW	CRITICAL
Time to 24 month remission												
1 (Marson 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.69 (0.50 to 0.95)	-	⊕⊕OO LOW	CRITICAL
Time to first seizure												
1 (Marson 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.26 (0.96 to 1.65)	-	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse drug events												
1 (Levisohn 2007)	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/19 (5.3%)	1/9 (11.1%)	RR 0.47 (0.03 to 6.74)	59 fewer per 1000 (from 108 fewer to 638 more)	⊕OOO VERY LOW	CRITICAL

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[3] 95% CI crosses 1 MID (0.8 or 1.25)
[4] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 15: Clinical evidence profile. Comparison 5: lamotrigine versus valproate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Valproate	Relative (95% CI)	Absolute	Quality	Importance
Time to withdrawal for any reason (median)												
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	41	31	-	Median (range) in lamotrigine: 11 (3-20), valproate: 12 (3-20)	⊕OOO VERY LOW	CRITICAL
Mean seizure reduction from baseline (juvenile myoclonic) (Better indicated by lower values)												
1 (Nejad 2009)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23	23	-	MD 0.6 lower (1.85 lower to 0.65 higher)	⊕OOO VERY LOW	CRITICAL
Mean seizure reduction from baseline (tonic-clonic) (Better indicated by lower values)												
1 (Nejad 2009)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	19	19	-	MD 0.04 higher (0.84 lower to 0.92 higher)	⊕OOO VERY LOW	CRITICAL
Time to 12 month remission												
1 (Marson 2007)	RCT	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.69 (0.53 to 0.90)	-	⊕⊕OO LOW	CRITICAL
Time to 24 month remission												
1 (Marson 2007)	RCT	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.60 (0.43 to 0.84)	-	⊕⊕OO LOW	CRITICAL
Time to first seizure												
1 (Marson 2007)	RCT	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.73 (1.32 to 2.27)	-	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Valproate	Relative (95% CI)	Absolute	Quality	Importance
Percentage of patients with reported side effects												
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	7/41 (17.1%)	11/31 (35.5%)	RR 0.48 (0.21 to 1.10)	185 fewer (from 280 fewer to 35 more)	⊕OOO VERY LOW	CRITICAL
Mean QOLIE-31 change score from baseline to end of the study (Better indicated by higher values)												
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	31	-	MD 5 lower (6.17 to 3.83 lower)	⊕⊕OO LOW	IMPORTANT

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Evidence downgraded by 2 as ranges are subjectively very wide*
[3] *95% CI crosses 1 MID (+/-0.5 x control group SD for outcome 'mean seizure reduction from baseline (juvenile myoclonic)= +/-0.75*
[4] *95% CI crosses 2 MIDs (+/-0.5 x control group SD for outcome 'mean seizure reduction from baseline (tonic-clonic) = +/-0.54*
[5] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[6] *95% CI crosses 1 MID (0.8)*

Table 16: Clinical evidence profile. Comparison 6: valproate versus levetiracetam

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Levetiracetam	Relative (95% CI)	Absolute	Quality	Importance
Time to 12 month remission in absence epilepsy[a]												
1 (Marson 2021)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 0.9 (0.6 to 1.35)	-	⊕⊕OO LOW	CRITICAL
Time to 12 month remission in other generalised epilepsy[b]												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Levetiracetam	Relative (95% CI)	Absolute	Quality	Importance
1 (Marson 2021)	RCT	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 1.55 (1.14 to 2.11)	-	⊕⊕OO LOW	CRITICAL

[a] *Absence epilepsy defined as including participants with childhood absence epilepsy and juvenile absence epilepsy*
[b] *Other generalised epilepsy defined as including participants with juvenile myoclonic epilepsy, epilepsy with tonic-clonic seizures on awakening, other genetic generalised epilepsy not specified, and/ or other epilepsy syndrome*
[1] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[2] *Population is indirect due to the study including participants with multiple different syndromes in the subgroup 'other generalised epilepsy'. For example, 150/180 (83%) participants defined as having genetic generalised epilepsy reported tonic-clonic seizures*
[3] *95% CI crosses 1 MID (1.25)*

Table 17: Clinical evidence profile. Comparison 7: low-dose valproate versus high-dose valproate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-dose valproate	High-dose valproate	Relative (95% CI)	Absolute	Quality	Importance
Seizure frequency increase of 50% or more												
1 (Sundqvist 1998)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/10 (0%)	4/8 (50%)	RR 0.09 (0.01 to 1.47)	455 fewer per 1000 (from 495 fewer to 235 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug events												
1 (Sundqvist 1998)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/10 (0%)	2/8 (25%)	RR 0.16 (0.01 to 2.99)	210 fewer per 1000 (from 248 fewer to 498 more)	⊕OOO VERY LOW	CRITICAL

1 [1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Appendix G - Economic evidence study selection

Economic evidence study selection for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

Appendix H - Economic evidence tables

Economic evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 18: Economic evidence tables

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Marson 2007a & Marson 2007b **Country:** United Kingdom **Type of economic analysis:** Cost Utility Analysis **Source of funding:** UK NHS Research and Development Health Technology Assessment Programme	**Interventions in detail:** Sodium valproate (VPA) Topiramate (TPM) Lamotrigine (LTG)	**Population characteristics:** People with epilepsy for whom sodium valproate was the better standard treatment option than carbamazepine. 63% of the population had genetic generalised epilepsy. 27% of the cohort had unclassified epilepsy with the remainder either symptomatic or cryptogenic partial epilepsy or other epilepsy syndrome (outside of the scope of the review question). Male:59.6% Mean age :22.5 years **Modelling approach:** With-in trial economic evaluation. **Source of base-line and effectiveness data:**	**Total Costs-questionnaire responders [n=165] (95%CI):** • VPA: £1390 (£369-£2411) • TPM: £1568 (£1303-£1842) • LTG: £1906 (£1405-£2408) **Total Costs -Adults and children for which seizure and resource use evidence is available [n=299] (95%CI):** • VPA: £1136 (£529-£1743) • TPM: £1568 (£1378-£1757) • LTG: £1906 (£1466-£2055) **Mean total number of seizures** • VPA: 44.1 (17.4-70.9) • TPM: 75.1 (19.8-130.3) • LTG: 120.9 (59.2-182.6)	**Perspective:** • UK NHS **Currency:** • UK pound sterling (£) **Cost year:** • 2005 **Time horizon:** • 2 years **Discounting:** • 3.5% per annum **Applicability:** Despite being a UK NHS study it was deemed only partially applicable to the decision problem. This was because only 63% of the population had GGE. The study is now relatively old with both TPM and LTG being significantly cheaper having come off patent.

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		All effectiveness data was taken from the accompanying RCT reported in detail in accompanying clinical evidence review. **Source of cost data:** Resource use was collected from patient records and from responses to resource use questions in the QoL questionnaire. ASM drug prices were taken from the BNF and other resource use costed using national unit costs for social care and from the Finance Department of Walton NHS Hospital Trust. Costs of adverse events were taken from TFR2A and TFR2B specialty and programme costs returns to the Department of Health by Trusts. Where necessary prices were inflated to 2005 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index **Source of QoL data:** Utility estimates were based on EQ-5D questionnaires	**QALYs (95% CI)** • VPA: 1.648 (1.51-1.79) • TPM: 1.809 (1.74-1.88) • LTG: 1.701 (1.61-1.79) **Incremental Costs-questionnaire responders [n=165] (vs VPA):** • TPM: £178 • LTG: £516 **Incremental Costs -Adults and children for which seizure and resource use evidence is available [n=299] (vs VPA):** • TPM: £432 • LTG: £770 **Incremental QALYs (vs VPA)** • TPM:0.161 • LTG:0.053 **ICER (cost seizure avoided):** • TPM: Dominated vs VPA • LTG: Dominated vs VPA **ICER (cost per QALY)** • TPM: £1,106 vs VPA • LTG: Dominated vs TPM **Deterministic sensitivity analysis:**	**Limitations:** The study meets most quality criteria. The study did not present a probabilistic sensitivity analysis comparing all three potential interventions. **Other comments:** It is unclear how representative those who returned QoL questionnaires are of the rest of the population and whether this impacted upon the QALY outcomes.

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		completed by 165 adults (children were not given QoL questionnaires) from the accompanying RCT. Responses were scored using UK population tariffs.	*Varying drug costs between high and low (range of ICER [cost per QALY estimates] estimates)* • TPM: £692-£1,106 • LTG: Dominated vs TPM for all values *Alternative assumptions around AUC analysis (range of ICER [cost per QALY estimates] estimates)* • TPM: £1,035-£1,633 • LTG: Dominated vs TPM for all assumptions **Probabilistic sensitivity analysis (probability cost effective at £20,000 per QALY threshold compared to VPA):** • TPM: 95% • LTG: 63% No probabilistic sensitivity analysis presented comparing all three interventions simultaneously	

ASM: Antiseizure medication; CUA: cost utility analysis; EQ-5D: EuroQol- 5 Dimension; ICER: incremental cost effectiveness ratio; LTG: Lamotrigine; QALY: quality adjusted life year; QoL: quality of life. TPM: Topiramate; VPA: Sodium Valproate; VS: Versus

Appendix I - Economic evidence profiles

Economic evidence profiles for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 19: Economic evidence profiles

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Author & year: Marson 2007a & Marson 2007b C**ountry:** United Kingdom **Interventions:** Sodium valproate (VPA) Topiramate (TPM) Lamotrigine (LTG) **Population:** People with epilepsy for whom valproate was the better standard treatment option than carbamazepine.	**Minor limitations**[1]	**Partially applicable**[2]	**Type of economic analysis:** CUA **Time horizon:** 2 years **Primary measure of outcome:** QALY	*Versus VPA* TPM: £178 LTG: £516	*Versus VPA (QALYS)* TPM:0.161 LTG:0.053	TPM: £1,106 vs VPA LTG: Dominated vs TPM	**Deterministic sensitivity analyses:** Conclusions were not sensitive to alternate assumptions around drug pricing and QALY estimates **PSA:** Probability cost effective at £20,000 per QALY threshold compared to VPA • TPM: 95% • LTG: 63%

ASM: Antiseizure medication; CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; LTG: Lamotrigine; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; TPM: Topiramate; VPA: Sodium Valproate.

1. The study met the majority of quality criteria. The study did not present a probabilistic sensitivity analysis comparing all three potential interventions.

2. Only 63% of the study cohort had Generalised Genetic Epilepsy. The study is over 10 years old and drug pricing has changed significantly in that time.

Appendix J - Economic analysis

Economic evidence analysis for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

No economic analysis was conducted for this review question.

Appendix K - Excluded studies

Excluded clinical studies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

Table 20: Excluded studies and reasons for their exclusion

Clinical studies

Study	Reason for Exclusion
Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Canadian Study Group for Childhood Epilepsy, Epilepsia, 39, 952â€• 959, 1998	Incorrect population: partial epilepsies or generalised tonic-clonic seizures without subgroup analysis
Topiramate as long-term therapy in generalised tonic-clonic seizures of non-focal origin, Epilepsia, 38 Suppl 3, 60, 1997	Conference abstract
A double-blind trial of topiramate in patients with generalised tonic-clonic seizures of non-focal origin, Epilepsia, 38 Suppl 3, 60, 1997	Conference abstract
A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta neurologica Scandinavica, 137, 152â€• 154, 2018	Incorrect population
Perampanel in treatment of refractory partial epilepsy in adolescents and adults: results of international multicenter randomized, double-blind, placebo-controlled phase III studies, 2014	Not in English language
Effect of levetiracetam on cognitive function and clonic seizure frequency in children with epilepsy, Current Molecular Medicine, 2019	Does not include data on GGE population
Akter, N., Rahman, M. M., Akhter, S., Fatema, K., A Randomized Controlled Trial of Phenobarbital and Levetiracetam in Childhood Epilepsy, Mymensingh Medical Journal: MMJ, 27, 776-784, 2018	Childhood epilepsy population without GGE subgroup analysis
Al-Bajalan, S. J., Kamil, M. W., Levetiracetam in the treatment of epilepsy as add on or monotherapy, Epilepsia, 1), 33, 2015	Conference abstract
Arnold, S., Blatt, I., Clark, A. M., Halvorsen, M. B., Nagaraddi, V. N., Usl255, a once-Daily, extended-Release topiramate, has positive effects on clinical outcomes and quality of life: Results from the phase 3 prevail clinical trial, Epilepsy Currents, 1), 105, 2014	Conference abstract
Arpita, A., Chandrakanta,, Kumar, R., Singh, S. N., Efficacy of intravenous valproate versus intravenous phenytoin in children with status epileptICUs: A randomized controlled trial in tertiary care centre, Pediatric Critical Care Medicine, 1), 11, 2014	Conference abstract
Arroyo, S., Dodson, W. E., Privitera, M. D., Glauser, T. A., Naritoku, D. K., Dlugos, D. J., Wang, S., Schwabe, S. K., Twyman, R. E., Randomized dose-controlled study of topiramate as	Epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
first-line therapy in epilepsy, Acta Neurologica Scandinavica, 112, 214-222, 2005	
Arya, R., Anand, V., Garg, S. K., Michael, B. D., Clobazam monotherapy for partial-onset or generalized-onset seizures, Cochrane Database of Systematic Reviews, 2014 (10) (no pagination), 2014	Systematic review - does not include data on GGE population
Arya, R., Giridharan, N., Anand, V., Garg, S. K., Clobazam monotherapy for focal or generalized seizures, Cochrane Database of Systematic Reviews, 2018	Systematic review - does not include data on GGE population
Banu, S. H., Jahan, M., Koli, U. K., Ferdousi, S., Khan, N. Z., Neville, B., Side effects of phenobarbital and carbamazepine in childhood epilepsy: Randomised controlled trial, British Medical Journal, 334, 1207-1210, 2007	Incorrect population
Barcs, G., Walker, E. B., Elger, C. E., Scaramelli, A., Stefan, H., Sturm, Y., Moore, A., Flesch, G., Kramer, L., D'Souza, J., Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy, Epilepsia, 41, 1597-1607, 2000	Incorrect population
Baulac, M., Patten, A., Giorgi, L., Long-term efficacy of zonisamide vs. carbamazepine monotherapy for treatment of adults with newly diagnosed partial epilepsy: Analysis by baseline seizure types, Epilepsia, 2), 180, 2014	Conference abstract
Bawden, H. N., Camfield, C. S., Camfield, P. R., Cunningham, C., Darwish, H., Dooley, J. M., Gordon, K., Ronen, G., Stewart, J., van Mastrigt, R., The cognitive and behavioural effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy, Epilepsy Research, 33, 133-43, 1999	Childhood epilepsy population without GGE subgroup analysis
Belousova, E. D., Perampanel in treatment of refractory partial epilepsy in adolescents and adults: results of international multicenter randomized, double-blind, placebo-controlled phase III studies, Zhurnal nevrologii i psihiatrii imeni S.S. Korsakova, 2014, 32-38, 2014	Not in English
Ben-Menachem, E., Henriksen, O., Dam, M., Mikkelsen, M., Schmidt, D., Reid, S., Reife, R., Kramer, L., Pledger, G., Karim, R., Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures, Epilepsia, 37, 539-543, 1996	Incorrect population
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	Childhood epilepsy population without subgroup analysis
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	Results not reported by study arm

Study	Reason for Exclusion
generalised epilepsy, Epilepsia, 39, 1329-1333, 1998	
Berg, I., Butler, A., Ellis, M., Foster, J., Psychiatric aspects of epilepsy in childhood treated with carbamazepine phenytoin or sodium valproate: A random trial, Developmental Medicine and Child Neurology, 35, 149-157, 1993	Childhood epilepsy population without GGE subgroup analysis
Bermeo-Ovalle, A., Dietary treatments for epilepsy: Why is this so hard for us to swallow?, Epilepsy Currents, 16, 312-313, 2016	Epilepsy population without GGE subgroup analysis
Betts, T., Waegemans, T., Crawford, P., A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy, Seizure, 9, 80-87, 2000	Epilepsy population without GGE subgroup analysis
Beydoun, A., Sachdeo, R. C., Rosenfeld, W. E., Krauss, G. L., Sessler, N., Mesenbrink, P., Kramer, L., D'Souza, J., Oxcarbazepine monotherapy for partial-onset seizures: A multicenter, double-blind, clinical trial, Neurology, 54, 2245-2251, 2000	Incorrect population
Biton, V., Berkovic, S. F., Abou-Khalil, B., Sperling, M. R., Johnson, M. E., Lu, S., Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial, Epilepsia, 55, 57â€• 66, 2014	Incorrect population â€“ sample not comprosed solely of people who experience generalised seizures and subgroup analyses not included
Biton, V., Di Memmo, J., Shukla, R., Lee, Y. Y., Poverennova, I., Demchenko, V., Saiers, J., Adams, B., Hammer, A., Vuong, A., et al.,, Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study, Epilepsy & Behavior, 19, 352â€• 358, 2010	Incorrect population
Biton, V., Mirza, W., Montouris, G., Vuong, A., Hammer, A. E., Barrett, P. S., Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy, Neurology, 56, 172-177, 2001	Epilepsy population without GGE subgroup analysis
Biton, V., Montouris, G. D., Ritter, F., Riviello, J. J., Reife, R., Lim, P., Pledger, G., A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures, Neurology, 52, 1330-1337, 1999	Incorrect population
Biton, V., Sackellares, J. C., Vuong, A., Hammer, A. E., Barrett, P. S., Messenheimer, J. A., Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures, Neurology, 65, 1737-1743, 2005	Incorrect population
Boas, J., Dam, M., Friis, M. L., Kristense, O., Pedersen, B., Gallagher, J., Controlled trial of lamotrigine (Lamictalregistered trade mark) for treatment-resistant partial seizures, Acta neurologica scandinavica., 94, 247â€• 252, 1996	Incorrect population

Study	Reason for Exclusion
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	Incorrect population
Braathen, G., Andersson, T., Gylje, H., Melander, H., Naglo, A. S., Noren, L., Persson, A., Rane, A., Sjors, K., Theorell, K., Wigertz, A., Comparison between one and three years of treatment in uncomplicated childhood epilepsy: A prospective study. I. Outcome in different seizure types, Epilepsia, 37, 822-832, 1996	Epilepsy population without GGE subgroup analysis
Bresnahan, R., Martin-Mcgill, K. J., Williamson, 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	Systematic review - does not include data on GGE population
Bresnahan, R., Martinâ€• McGill, K. J., Williamson, J., Michael, B. D., Marson, A. G., Clobazam addâ€• on therapy for drugâ€• resistant epilepsy, Cochrane Database of Systematic Reviews, 2019	Does not include data on GGE population
Bresnahan, R., Panebianco, M., Marson, A. G., Lamotrigine add-on therapy for drugâ€• resistant generalised tonicâ€• clonic seizures, Cochrane Database of Systematic Reviews, 2020	Systematic review - does not include data on GGE population
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 - does not include data on GGE population
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 â€“ does not include data on GGE population
Brigo, F., Igwe, S. C., Bragazzi, N. L., Lattanzi, S., Clonazepam monotherapy for treating people with newly diagnosed epilepsy, Cochrane Database of Systematic Reviews, 2019	Systematic review - does not include data on GGE population
Brigo, F., Igwe, S. C., Lattanzi, S., Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents, Cochrane Database of Systematic Reviews, 2019	Systematic review - does not include data on GGE population
Brodie, M. J., Perucca, E., Ryvlin, P., Ben-Menachem, E., Meencke, H. J., Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy, Neurology, 68, 402-408, 2007	Incorrect population
Brodie, M. J., Richens, A., Yuen, A. W., Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group, Lancet, 345, 476-9, 1995	Epilepsy population without GGE subgroup analysis
Buchanan, N., Clobazam in the treatment of epilepsy: prospective follow-up to 8 years, Journal	Uncontrolled study

Study	Reason for Exclusion
of the Royal Society of Medicine, 86, 378-80, 1993	
Bülau, P., Fröscher, W., Schuchardt, V., Kreiten, K., Prospective randomized study of the effectiveness of clonazepam and diazepam in petit mal status, Der nervenarzt, 57, 667â€• 671, 1986	Not in English
Callaghan, N., Kenny, R. A., O'Neill, B., Crowley, M., Goggin, T., A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy, Journal of neurology, neurosurgery, and psychiatry, 48, 639â€• 644, 1985	Epilepsy population without GGE subgroup analysis
Callaghan, N., O'Hare, J., O'Driscoll, D., O'Neill, B., Daly, M., Comparative study of ethosuximide and sodium valproate in the treatment of typical absence seizures (petit mal), Developmental Medicine and Child Neurology, 24, 830-836, 1982	Incorrect population it does not report on GGE group specifically (covered in NGA review on absence seizures)
Camfield, P., Booth, F., Buckley, D., Camfield, C., Darwish, H., Dooley, J., Farrell, K., Gordon, K., Hwang, P., Langevin, P., Larbrisseau, A., Lowry, N., Meek, D., Munn, R., Reggin, J., Ronen, G., Sinclair, B., Tibbles, J., Whiting, S., Wilfong, A., Yager, J., Stewart, J., Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy, Epilepsia, 39, 952-959, 1998	Childhood epilepsy population without GGE subgroup analysis
Campos, M. S. A., Ayres, L. R., Morelo, M. R. S., Carizio, F. A. M., Pereira, L. R. L., Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses, International Journal of Clinical Pharmacy, 40, 589-598, 2018	Does not include data on GGE population
Chakravarty, A., Mukherjee, A., Roy, D., Observations on juvenile myoclonic epilepsy amongst ethnic Bengalees in West Bengal--an Eastern Indian State, Seizure, 16, 134-41, 2007	Not a randomised controlled trial
Chung, S., Sperling, M. R., Biton, V., Krauss, G., Hebert, D., Rudd, G. D., Doty, P., Lacosamide as adjunctive therapy for partial-onset seizures: A randomized controlled trial, Epilepsia, 51, 958-967, 2010	Incorrect population
Cnaan, A., Shinnar, S., Arya, R., Adamson, P. C., Clark, P. O., Dlugos, D., Hirtz, D. G., Masur, D., Glauser, T. A., Second monotherapy in childhood absence epilepsy, Neurology, 88, 182â€• 190, 2017	Incorrect population it does not report on GGE group specifically (covered in NGA review on absence seizures)
Colleran, N., O. Connor T, O. Brien J.J, Anti epileptic drug trials for patients with drug resistant idiopathic generalised epilepsy: A meta-analysis, Seizure, 51, 145-156, 2017	Does not report on GGE group specifically
Coppola, G., Auricchio, G., Federico, R., Carotenuto, M., Pascotto, A., Lamotrigine versus valproic acid as first-line monotherapy in newly	Incorrect population it does not report on GGE group specifically (covered in NGA review on absence seizures)

Study	Reason for Exclusion
diagnosed typical absence seizures: An open-label, randomized, parallel-group study, Epilepsia, 45, 1049-1053, 2004	
Crawford, P., Chadwick, D., A comparative study of progabide, valproate, and placebo as add-on therapy in patients with refractory epilepsy, Journal of Neurology Neurosurgery and Psychiatry, 49, 1251-1257, 1986	Epilepsy population without GGE subgroup analysis
Cross, J. H., Epilepsy (generalised seizures), BMJ clinical evidence, 2015	Systematic review: studies checked for inclusion in this review
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	Childhood epilepsy population without GGE subgroup analysis
Dahlin, M., Knutsson, E., Amark, P., Nergårdh, A., Reduction of epileptiform activity in response to low-dose clonazepam in children with epilepsy: a randomized double-blind study, Epilepsia, 41, 308â€• 315, 2000	Childhood epilepsy population without GGE subgroup analysis
Dam, M., Oxcarbazepine in monotherapy, Behavioural neurology, 3, 31-4, 1990	Population did not include patients with genetic generalised epilepsy.
De Silva, M., MacArdle, B., McGowan, M., Hughes, E., Stewart, J., Neville, B. G. R., Johnson, A. L., Reynolds, E. H., Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy, Lancet, 347, 709-713, 1996	Childhood epilepsy population without GGE subgroup analysis
de Silva, M., MacArdle, B., McGowan, M., Hughes, E., Stewart, J., Neville, B. G., Johnson, A. L., Reynolds, E. H., Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy, Lancet (london, england), 347, 709â€• 713, 1996	Childhood epilepsy population without GGE subgroup analysis
Dozieres-Puyravel, B., Auvin, S., An evidence-based review on the use of perampanel for the treatment of focal-onset seizures in pediatric patients, Neuropsychiatric Disease and Treatment, 15, 2789-2798, 2019	Does not include data on GGE population
Duchowny, M., Pellock, J. M., Graf, W. D., Billard, C., Gilman, J., Casale, E., Womble, G., Risner, M., Manasco, P., A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children, Neurology, 53, 1724-1731, 1999	Incorrect population
Dumitrascu, V., Matusz, A. A., Vlad, D. C., Barac, B., Cheveresan, A., Safety and efficacy of Topiramate, in pediatric epileptic Patients, Basic and Clinical Pharmacology and Toxicology, 1), 129, 2009	Conference abstract
Elterman, R. D., Glauser, T. A., Wyllie, E., Reife, R., Wu, S. C., Pledger, G., A double-blind randomized trial of topiramate as adjunctive therapy	Incorrect population

Study	Reason for Exclusion
for partial-onset seizures in children, Neurology, 52, 1338-1344, 1999	
Epina-garza, J., Rosenfeld, W., Saeki, K., Villanueva, V., Yoshinaga, H., Bibbiani, F., Yang, H., Patten, A., Williams, B., Laurenza, A., Efficacy and tolerability of perampanel in adolescent patients with generalised seizure types: A pooled analysis of six randomised studies, Developmental Medicine and Child Neurology, 59 (Supplement 1), 55, 2017	Conference abstract
Eriksson, A. S., Nergardh, A., Boreus, L., Knutsson, E., Double-blind cross-over study with lamotrigine in children with Lennox-Gastaut syndrome and other types of generalized intractable epilepsy, Epilepsia, 36 Suppl 3, S110â€• 11, 1995	Conference abstract
Eriksson, A. S., Nergardh, A., Hoppu, K., The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: A randomized, double-blind, crossover study, Epilepsia, 39, 495-501, 1998	Epilepsy population without GGE subgroup analysis
Eun, S. H., Eun, B. L., Lee, J. S., Hwang, Y. S., Kim, K. J., Lee, Y. M., Lee, I. G., Lee, M., Ko, T. S., Kim, J. T., et al.,, Effects of lamotrigine on cognition and behavior compared to carbamazepine as monotherapy for children with partial epilepsy, Brain & development, 34, 818â€• 823, 2012	Incorrect population
Eun, S. H., Kim, H. D., Eun, B. L., Lee, I. K., Chung, H. J., Kim, J. S., Kang, H. C., Lee, Y. M., Suh, E. S., Kim, D. W., Eom, S., Lee, J. S., Moon, H. K., Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy, Seizure, 20, 558-563, 2011	Epilepsy population without GGE subgroup analysis
Eun, S. H., Kim, H. D., Lee, I. K., Chung, H. J., Eun, B. L., Lee, J. S., Kim, J. S., Kang, H. C., Suh, E. S., Kim, D. W., Eom, S., Moon, H. K., A multicenter comparative trial of low and high dose zonisamide in children with newly diagnosed epilepsy as monotherapy, Epilepsia, 4), 147, 2010	Conference abstract
Eun, S., Kim, H., Lee, I., Chung, H., Eun, B., Lee, J., Kim, J., Kang, H., Suh, E., Kim, D., Eom, S., Moon, H., A multi-center comparative trial of low and highdose zonisamide in children with newly diagnosed epilepsy as monotherapy, Epilepsia, 11), 244, 2009	Conference abstract
Fattore, C., Boniver, C., Capovilla, G., Cerminara, C., Citterio, A., Coppola, G., Costa, P., Darra, F., Vecchi, M., Perucca, E., A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy, Epilepsia, 52, 802-809, 2011	Incorrect population does not report on GGE group specifically
Faught, E., Wilder, B. J., Ramsay, R. E., Reife, R. A., Kramer, L. D., Pledger, G. W., Karim, R. M., Topiramate placebo-controlled dose-ranging	Incorrect population

Study	Reason for Exclusion
trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages, Neurology, 46, 1684-1690, 1996	
Ferlazzo, E., Trenite, D. K. N., de Haan, G. J., Nitschke, F., Ahonen, S., Gasparini, S., Minassian, B. A., Update on pharmacological treatment of progressive myoclonus epilepsies, Current Pharmaceutical Design, 23, 5662-5666, 2017	Narrative review. Studies checked for inclusion
Feyissa, A. M., Brivaracetam in the treatment of epilepsy: A review of clinical trial data, Neuropsychiatric Disease and Treatment, 15, 2587-2600, 2019	Not a systematic review/no methodology reported
Fletcher, M. L., Sarangarm, P., Smolinske, S., Nash, J., Alunday, R. L., Seifert, S. A., Warrick, B., A systematic review of second-line therapies in toxic seizures, Clinical Toxicology, 57 (10), 928, 2019	Conference abstract
Ford, L., Shi, Y., Manitpisitkul, P., Effects of topiramate on growth and development in children with new or recent-onset epilepsy: A phase-4 randomized, active-controlled study, Epilepsy Currents, 1), 143-144, 2015	Conference abstract
Forsythe, I., Butler, R., Berg, I., McGuire, R., Cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate, Developmental Medicine & Child Neurology, 33, 524-34, 1991	Childhood epilepsy population without GGE subgroup analysis
Forsythe, W. I., Owens, J. R., Toothill, C., Effectiveness of acetazolamide in the treatment of carbamazepine-resistant epilepsy in children, Developmental Medicine & Child Neurology, 23, 761-9, 1981	Incorrect study design
Frank, L. M., Enlow, T., Holmes, G. L., Manasco, P., Concannon, S., Chen, C., Womble, G., Casale, E. J., Lamictal (lamotrigine) monotherapy for typical absence seizures in children, Epilepsia, 40, 973-979, 1999	Incorrect population â€“ does not report on GGE group specifically
French, J. A., Krauss, G. L., Biton, V., Squillacote, D., Yang, H., Laurenza, A., Kumar, D., Rogawski, M. A., Adjunctive perampanel for refractory partial-onset seizures: Randomized phase III study 304, Neurology, 79, 589-596, 2012	Epilepsy population without GGE subgroup analysis
French, J. A., Krauss, G. L., Steinhoff, B. J., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305, Epilepsia, 54, 117-125, 2013	Epilepsy population without GGE subgroup analysis
French, J. A., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T. J., Laurenza, A., Patten, A., Bibbiani, F., Adjunctive perampanel (PER) for treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients (PTS) with idiopathic generalized epilepsy (IGE): A double-	Conference abstract

Study	Reason for Exclusion
blind, randomized, placebo-controlled phase III trial, Epilepsy Currents, 1), 367, 2015	
French, J., Elger, C., Goldberg-Stern, H., Thomson, A., Krauss, G., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., Global phase iii trial of perampanel, a selective, non-competitive AMPA receptor antagonist, as adjunctive therapy in patients with refractory partial-onset seizures, Neurology, 77 (2), 199-200, 2011	Conference abstract
French, J., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T. J., Laurenza, A., Patten, A., Bibbiani, F., 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. Conference: 67th American Academy of Neurology Annual Meeting, AAN, 84, 2015	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	Abstract
French, J., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T., Laurenza, A., Patten, A., Bibbiani, F., Adjunctive perampanel RCT for PGTC seizures, Journal of Neurology, Neurosurgery and Psychiatry. Conference: Association of British Neurologists, ABN, 86, 2015	Conference abstract
French, J., Krauss, G., Wechsler, R., Wang, X., DiVentura, B., Brandt, C., Trinka, E., O'Brien, T., Laurenza, A., Patten, A., et al.,, Adjunctive perampanel RCT for PGTC seizures, Journal of neurology, neurosurgery and psychiatry. Conference: association of british neurologists, ABN 2015. London united kingdom. Conference start: 20150910. Conference end: 20150910. Conference publication: (var.pagings), 86, 2015	Conference abstract
Fritz, N., Glogau, S., Hoffmann, J., Rademacher, M., Elger, C. E., Helmstaedter, C., Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy, Epilepsy and Behavior, 6, 373-381, 2005	Incorrect population
Geng, H., Wang, C., Efficacy and safety of oxcarbazepine in the treatment of children with epilepsy: A metaanalysis of randomized controlled trials, Neuropsychiatric Disease and Treatment, 13, 685-695, 2017	Does not report on GGE group specifically
Gibberd, F. B., Park, D. M., Scott, G., Gawel, M. J., Fry, D. E., Page, N. G., Engler, C., English, J. R., Rose, F. C., A comparison of phenytoin and pheneturide in patients with epilepsy: a double-	Incorrect population

Study	Reason for Exclusion
blind cross-over trial, Journal of Neurology, Neurosurgery & Psychiatry, 45, 1113-8, 1982	
Gillham, R., Kane, K., Bryant-Comstock, L., Brodie, M. J., A double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure, Seizure, 9, 375-379, 2000	Incorrect population
Gilliam, F. G., Veloso, F., Bomhof, M. A. M., Gazda, S. K., Biton, V., Ter BruIGEn, J. P., Neto, W., Bailey, C., Pledger, G., Wu, S. C., Alving, J., Arroyo, S., Arts, R., Ayala, R., Barbano, R., Ben-Menachem, E., Blume, W., Brodtkorb, E., Browne, T. R., Chadwick, D., Couch, C., Crumrine, P. K., Dam, M., De Deyn, P. P., Dellaportas, C., Desai, H., Edwards, K. R., Engelsen, B., Farran, R. D., Frank, L. M., French, J., Friedman, A. J., Gelbum, J., Harden, C. L., Hart, C., Henriksen, O., Hoffstetter, M. D., Holt, P. J., Hulihan, J. F., Hull, R. P., Husainy, T., Kang, H., Kern, R., Kirzinger, S. S., Lee, M. A., Leroy, R. F., Licht, J., Mai, J., Michelucci, R., Morris, G. L., Mutani, R., Narus, M., Nieto Barrera, M., Nisman-Safirstein, M., Ogunyemi, A., Pak, J., Pennell, P. B., Phillips, S. G., Pillay, N., Ramsay, R. E., Ritter, F. J., Rogers-Neame, N. T., Rosenfeld, W. E., Schneiderman, J., Singer, R., So, N. K., Soederfeldt, B., Soryall, I. N., Sperling, M., Starreveld, E., Steinhoff, B. J., Stodiek, S. R. G., Tans, J. T. J., Todorov, A. B., Van Orman, C. B., Veilleux, M., Waltimo, O., Wannamaker, B. B., Weaver, D., Zagnoni, P., A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy, Neurology, 60, 196-202, 2003	Incorrect population
Gimigliano, F., Is clobazam monotherapy effective and safe in people with focal or generalized seizures? A Cochrane Review summary with commentary, Developmental Medicine & Child Neurology, 62, 670-672, 2020	Commentary
Gjerloff, I., Arentsen, J., Alving, J., Secher, B. G., Monodose versus 3 daily doses of sodium valproate: A controlled trial, Acta Neurologica Scandinavica, 69, 120-124, 1984	Epilepsy population without GGE subgroup analysis
Glauser, A. T., Dlugos, J. D., Dodson, E. W., Grinspan, A., Wang, S., Wu, S. C., Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents, Journal of Child Neurology, 22, 693-699, 2007	Epilepsy population without GGE subgroup analysis
Glauser, T. A., Ayala, R., Elterman, R. D., Mitchell, W. G., Van Orman, C. B., Gauer, L. J., Lu, Z., Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures, Neurology, 66, 1654-1660, 2006	Epilepsy population without GGE subgroup analysis
Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., Masur, D., Clark, P. O., Adamson, P. C., Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: Initial	Epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
monotherapy outcomes at 12 months, Epilepsia, 54, 141-155, 2013	
Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., Masur, D., Clark, P. O., Capparelli, E. V., Adamson, P. C., Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy, New England Journal of Medicine, 362, 790-799, 2010	Epilepsy population without GGE subgroup analysis
Glauser, T. A., Dlugos, D. J., Dodson, W. E., Grinspan, A., Wang, S., Wu, S. C., Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents, Journal of Child Neurology, 22, 693â€• 699, 2007	Epilepsy population without GGE subgroup analysis
Glauser, T. A., Nigro, M., Sachdeo, R., Pasteris, L. A., Weinstein, S., Abou-Khalil, B., Frank, L. M., Grinspan, A., Guarino, T., Bettis, D., et al.,, Adjunctive therapy with oxcarbazepine in children with partial seizures, Neurology, 54, 2237â€• 2244, 2000	Epilepsy population without GGE subgroup analysis
Gram, L., Flachs, H., Würtz-Jørgensen, A., Parnas, J., Andersen, B., Sodium valproate, serum level and clinical effect in epilepsy: a controlled study, Epilepsia, 20, 303â€• 311, 1979	Epilepsy population without GGE subgroup analysis
Guerreiro, M., Better seizure control and tolerability over the long term with oxcarbazepine (Trileptal (R)) monotherapy compared with phenytoin in newly diagnosed children and adolescents with partial and generalised tonic-clonic seizures, Epilepsia, 44 Suppl 8, 148â€• 149, 2003	Conference abstract
Guerreiro, M. M., Vigonius, U., Pohlmann, H., De Manreza, M. L. G., Fejerman, N., Antoniuk, S. A., Moore, A., A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy, Epilepsy Research, 27, 205-213, 1997	Epilepsy population without GGE subgroup analysis
Gunawan, C., Seneviratne, U., D'Souza, W., The effect of antiepileptic drugs on epileptiform discharges in genetic generalized epilepsy: A systematic review, Epilepsy and Behavior, 96, 175-182, 2019	Does not include data on GGE subgroup
Hee Seo, J., Mock Lee, Y., Soo Lee, J., Chul Kang, H., Dong Kim, H., 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	Childhood epilepsy population with no GGE subgroup analysis
Herranz, J. L., Arteaga, R., Adin, J., Armijo, J. A., Conventional and sustained-release valproate in children with newly diagnosed epilepsy: A randomized and crossover study comparing clinical effects, patient preference and pharmacokinetics, European Journal of Clinical Pharmacology, 62, 805-815, 2006	Epilepsy population without GGE subgroup analysis
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	Epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
possible alternative to carbamazepine?, Epilepsia, 28, 693â€• 698, 1987	
Huang, T. S., Zhu, J. L., Li, B., Hu, Y., Chen, L., Liao, J. X., Valproic acid versus lamotrigine as a monotherapy for absence epilepsy in children, Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics], 11, 653â€• 655, 2009	Not in English
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	Epilepsy population without GGE subgroup analysis
Ijff, D. M., Postulart, D., Lambrechts, Daje, Majoie, Mhjm, de Kinderen, R. J. A., Hendriksen, J. G. M., Evers, Smaa, Aldenkamp, A. P., Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial, Epilepsy & behavior, 60, 153â€• 157, 2016	Childhood epilepsy population without GGE subgroup analysis
Irct138803051949N,, Comparison the effect of Modified Atkins diet in decreasing frequency of seizure in adult patients with refractory epilepsy with using Modified Atkins diet and patients with refractory epilepsy control without using Modified Atkins diet group, http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT138803051949N1, 2013	Does not include data on GGE population
Jawad, S., Richens, A., Goodwin, G., Yuen, W. C., Controlled trial of lamotrigine (Lamictal^a) for refractory partial seizures, Epilepsia, 30, 356-363, 1989	Does not include data on GGE subgroup
Junemann, I., Wolf, S., Tergau, F., Nitsche, M. A., Cognitive performance in patients with focal and primary generalized epilepsy under levetiracetam or topiramate monotherapy: A prospective pseudo-randomized study, Epilepsia, 6), 47, 2009	Conference abstract
Kalviaiinen, R., Genton, P., Andermann, E., Magaudda, A., Frucht, S., Schlit, A., Gerard, D., Van Otterdijk, E., Von Rosenstiel, P., Brivaracetam in patients with Unverricht-Lundborg disease: Results from two randomized, placebo-controlled, double-blind studies, Epilepsia, 10), 47, 2009	Conference abstract
Kanner, A. M., Ashman, E., Gloss, D., Harden, C., Bourgeois, B., Bautista, J. F., Abou-Khalil, B., Burakgazi-Dalkilic, E., Park, E. L., Stern, J., Hirtz, D., Nespeca, M., Gidal, B., Faught, E., French, J., Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy, Neurology, 91, 82-90, 2018	Practice guideline summary - studies checked for inclusion in this review

Study	Reason for Exclusion
Karimzadeh, P., Moosavian, T., Moosavian, H. R., Effects of a formula-based ketogenic diet on refractory epilepsy in 1 to 3 year-old patients under classic ketogenic diet, Iranian Journal of Child Neurology, 13, 83-90, 2019	Unclear whether sample includes patients with GGEs and no subgroup analysis for this population is included.
Kerr, M. P., Baker, G. A., Brodie, M. J., A randomized, double-blind, placebo-controlled trial of topiramate in adults with epilepsy and intellectual disability: Impact on seizures, severity, and quality of life, Epilepsy and Behavior, 7, 472-480, 2005	Epilepsy population without GGE subgroup analysis
Kim, J. A., Yoon, J. R., Lee, E. J., Lee, J. S., Kim, J. T., Kim, H. D., Kang, H. C., Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy, Epilepsia, 57, 51-58, 2016	Intervention not relevant
Kim, J. A., Yoon, J. R., Lee, E., Lee, J. S., Kim, H. D., Kang, H. C., Comparison of efficacy between a modified atkins diet and a classic ketogenic diet in childhood intractable epilepsy, Epilepsy Currents, 1), 95-96, 2015	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	Epilepsy population without GGE subgroup analysis
Knott, C., Panayiotopoulos, C. P., Carbamazepine in the treatment of generalised tonic clonic seizures in juvenile myoclonic epilepsy, Journal of Neurology, Neurosurgery & Psychiatry, 57, 503, 1994	Letter
Kosteljanetz, M., Christiansen, J., Dam, A. M., Hansen, B. S., Lyon, B. B., Pedersen, H., Dam, M., Carbamazepine vs phenytoin. A controlled clinical trial in focal motor and generalized epilepsy, Archives of Neurology, 36, 22-4, 1979	Epilepsy population without GGE subgroup analysis
Kosteljanetz, M., Christiansen, J., Dam, A. M., Hansen, B. S., Lyon, B. B., Pedersen, H., Dam, M., Carbamazepine (Tegretol) or phenytoin in the treatment of focal motor epilepsy or generalized epilepsy? A controlled clinical trial, Ugeskrift for laeger, 141, 989â€• 991, 1979	Not in English
Krauss, G. L., Serratosa, J. M., Villanueva, V. E., Endziniene, M., Hong, Z., French, J., Yang, H., Squillacote, D., Zhu, J., Laurenza, A., Efficacy and safety of perampanel, an AMPA receptor antagonist, as an adjunctive therapy in a phase III study of patients with refractory partial-onset seizures, Epilepsy Currents. Conference: 64th Annual Meeting of the American Epilepsy Society, AES and 3rd Biennial North American Regional Epilepsy Congress. San Antonio, TX United States. Conference Publication:, 11, 2011	Conference abstract
Krauss, G., Wang, X. F., Haldre, S., Yang, H., Squillacote, D., Zhu, J., Laurenza, A., Randomized, double-blind, placebo-controlled phase III	Conference abstract

Study	Reason for Exclusion
study of perampanel, a selective, noncompetitive AMPA receptor antagonist, as adjunctive therapy in patients with refractory partial-onset seizures: Efficacy by seizure type, Epilepsia, 6), 253, 2011	
Krauss, G., Wechsler, R. T., Bibbiani, F., Patten, A., Williams, B., Yang, H., Gidal, B., Hussein, Z., Relationship between perampanel exposure, seizure outcomes and treatment-emergent adverse events (TEAEs) in patients with primary generalized tonic-clonic (PGTC) seizures in idiopathic generalized epilepsy (IGE): A randomized, double-blind phase III study, Epilepsia, 1), 132, 2015	Conference abstract
Kuersten, M., Tacke, M., Gerstl, L., Hoelz, H., Stulpnagel, C. V., Borggraefe, I., Antiepileptic therapy approaches in KCNQ2 related epilepsy: A systematic review, European Journal of Medical Genetics, 63 (1) (no pagination), 2020	Does not include data on GGE population
Kurth, C., Gaida-Hommernick, B., Hagemann, C., Kerling, F., Kowalik, A., Tergau, F., Impact of low-dose topiramate monotherapy for epilepsy in adults with focal and generalised seizures, Aktuelle neurologie, 34, 276â€• 282, 2007	Not in English
Kutt, H., Solomon, G., Wasterlain, C., Peterson, H., Louis, S., Carruthers, R., Carbamazepine in difficult to control epileptic out-patients, Acta Neurologica Scandinavica. Supplementum, 60, 27-32, 1975	Does not include data on GGE subgroup
Kwan, P., Johnson, M. E., Merschhemke, M., Lu, S., Adjunctive brivaracetam in adults with uncontrolled generalized seizures: Subpopulation analysis of the results of a randomized, double-blind, placebo-controlled trial, Epilepsy Currents. Conference: 64th Annual Meeting of the American Epilepsy Society, AES and 3rd Biennial North American Regional Epilepsy Congress. San Antonio, TX United States. Conference Publication:, 11, 2011	Conference abstract
Kwan, P., Johnson, M. E., Merschhemke, M., Lu, S., Safety and tolerability of adjunctive brivaracetam in adults with uncontrolled epilepsy: Randomized, double-blind, placebo-controlled trial, Epilepsia, 4), 152, 2010	Conference abstract
Kwan, P., Johnson, M., Merschhemke, M., Lu, S., Adujunctive brivaracetam in adults with uncontrolled generalized seizures: sub-population analysis of the results of a randomized, double-blind, placebo-controlled trial, Proceedings of the 64th annual meeting of the american epilepsy society, 2010	Conference abstract
Kwan, P., Trinka, E., Van Paesschen, W., Rektor, I., Johnson, M. E., Lu, S., Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: Results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial, Epilepsia, 55, 38-46, 2014	Epilepsy population without GGE subgroup analysis

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	Epilepsy population without GGE subgroup analysis
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, 135, 231-239, 2017	Epilepsy population without GGE subgroup analysis
Lee, B. I., No, S. K., Yi, S. D., Lee, H. W., Kim, O. J., Kim, S. H., Kim, M. K., Kim, S. E., Kim, Y. S., Kim, J. M., et al.,, Unblinded, randomized multicenter trial comparing lamotrigine and valproate combination with controlled-release carbamazepine monotherapy as initial drug regimen in untreated epilepsy, Seizure, 55, 17â€• 24, 2018	Incorrect population
Lee, S. A., Lee, H. W., Heo, K., Song, H. K., Kim, O. J., Lee, S. M., Kim, S. O., Lee, B. I., Cognitive and behavioral effects of lamotrigine and carbamazepine monotherapy in patients with newly diagnosed or untreated partial epilepsy, Epilepsia, 4), 116, 2010	Conference abstract
Levisohn, P. M., Holland, K. D., Hulihan, J. F., Fisher, A. C., Topiramate versus valproate in patients with juvenile myoclonic epilepsy, Epilepsia, 44 Suppl 9, 267â€• 268, 2003	Conference abstract
Liu, J., Wang, L. N., Wang, Y. P., Topiramate for juvenile myoclonic epilepsy, Cochrane Database of Systematic Reviews, 2019 (1) (no pagination), 2019	Does not include data on GGE subgroup
Liu, X., Lee, N., Han, T., Wang, X., The new antiepileptic drugs (levetiracetam and oxcarbazepine) compared with traditional antiepileptic drugs (carbamazepine and valproate) in the initial 52 weeks of monotherapy for epilepsy induced by melas - an open-label, prospective, randomised controlled multicenter study, Neurology. Conference: 65th American Academy of Neurology Annual Meeting. San Diego, CA United States. Conference Publication:, 80, 2013	Conference abstract
Livingston, S., Treatment of grand mal epilepsy: phenobarbital versus diphenylhydantoin sodium, Clinical Pediatrics, 7, 444-5, 1968	Survey
Lu, Y., Xiao, Z., Yu, W., Xiao, F., Xiao, Z., Hu, Y., Chen, Y., Wang, X., Efficacy and safety of adjunctive zonisamide in adult patients with refractory partial-onset epilepsy: a randomized, double-blind, placebo-controlled trial, Clinical drug investigation, 31, 221â€• 229, 2011	Incorrect population
Manitpisitkul, P., Shalayda, K., Todd, M., Wang, S. S., Ness, S., Ford, L., Pharmacokinetics and safety of adjunctive topiramate in infants (1-24	Childhood epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
months) with refractory partial-onset seizures: A randomized, multicenter, open-label phase 1 study, Epilepsia, 54, 156-164, 2013	
Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., Cramp, C., Cockerell, O. C., Cooper, P. N., Doughty, J., et al.,, The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial, Lancet (london, england), 369, 1016â€• 1026, 2007	Study included - duplicate report
Marson, A. G., Chadwick, D. W., Report of a pragmatic trial comparing clobazam and "standard" treatment in childhood epilepsy, Epilepsia, 40, 531â€• 533, 1999	Letter
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 valproate or levetiracetam in generalised and unclassifiable epilepsy: an un-blinded randomised controlled trial, Epilepsia, 60, 25â€• , 2019	Conference Abstract
Marson,A.G., Appleton,R., Baker,G.A., Chadwick,D.W., Doughty,J., Eaton,B., Gamble,C., Jacoby,A., Shackley,P., Smith,D.F., Tudur-Smith,C., Vanoli,A., Williamson,P.R., A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial, Health Technology Assessment, 11, 1-108, 2007	Epilepsy population without GGE subgroup analysis
Mattson, R. H., Cramer, J. A., Collins, J. F., Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures, New England Journal of Medicine, 313, 145-151, 1985	Incorrect population
Mattson, R. H., Cramer, J. A., Collins, J. F., A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group, New England Journal of Medicine, 327, 765â€• 771, 1992	Incorrect population
Mbizvo, G. K., Chandrasekar, B., Nevitt, S. J., Dixon, P., Hutton, J. L., Marson, A. G., Levetiracetam addâ€• on for drugâ€• resistant focal epilepsy, Cochrane Database of Systematic Reviews, 2020	Does not include data on GGE population
McAuley, C., McShane, T., Ethosuximide was superior to valproate and lamotrigine in controlling absence seizures and minimising side effects, Archives of Disease in Childhood: Education and Practice Edition, 96, 119, 2011	Does not include patients with GGE
Mikkelsen, B., Birket-Smith, E., Bradt, S., Holm, P., Bparm, null, Lung, M., Thorn, I., Vestermark, S., Olsen, P. Z., Clonazepam in the treatment of	Childhood epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
epilepsy. A controlled clinical trial in simple absences, bilateral massive epileptic myoclonus, and atonic seizures, Archives of Neurology, 33, 322â€• 325, 1976	
Milichap, J. G., Aymat, F., Controlled evaluation of primidone and diphenyllhydantoin sodium. Comparative anticonvulsant efficacy and toxicity in children, JAMA, 204, 738-9, 1968	Epilepsy population without GGE subgroup analysis
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
Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., Whitney, A., Cross, J. H., A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy, Epilepsia, 50, 1109-1117, 2009	Childhood epilepsy population without GGE subgroup analysis
Neal,E., Chaffe,H., Fitzsimmons,G., Edwards,N., Lawson,M., Schwartz,R., Cross,H., A randomized trial of classical and medium-Chain triglyceride ketogenic diets in the treatment of childhood epilepsy - Efficacy and tolerability after 12 months, Epilepsia, 50, 86-87, 2009	Conference abstract
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	Childhood epilepsy population without GGE subgroup analysis
Nevitt, S. J., Marson, A. G., Smith, C. T., Carbamazepine versus phenytoin monotherapy for epilepsy: An individual participant data review, Cochrane Database of Systematic Reviews, 2019 (7) (no pagination), 2019	Does not include data on GGE population
Nolan, S. J., Marson, A. G., Weston, J., Tudur Smith, C., Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review, Cochrane Database of Systematic Reviews, 4, CD001769, 2016	Does not include data on patients with GGE
Nolan, S. J., Tudur Smith, C., Pulman, J., Marson, A. G., Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalised onset tonic-clonic seizures, Cochrane Database of Systematic Reviews, 2013 (1) (no pagination), 2013	Does not include data on patients with GGE
O'Brien, T. J., Steinhoff, B. J., Laurenza, A., Patten, A., Bibbiani, F., Yang, H., Myoclonic and absence seizures in patients with idiopathic generalized epilepsy (IGE): Exploratory outcomes in a phase III PGTC study with adjunctive perampanel, Epilepsia, 57 (Supplement 2), 32, 2016	Conference abstract

Study	Reason for Exclusion
O'Brien, T. J., Steinhoff, B. J., Yang, H., Laurenza, A., Patten, A., Bibbiani, F., Efficacy of adjunctive perampanel in idiopathic generalised epilepsy: Subgroup analysis of patients with absence and myoclonic seizures in a double-blind placebo-controlled Phase 3 trial, European Journal of Neurology, 1), 343, 2015	Conference abstract
Pal, D. K., Das, T., Chaudhury, G., Johnson, A. L., Neville, B. G., Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India, Lancet (london, england), 351, 19â€• 23, 1998	Does not include patients with GGE
Potschka, H., Trinka, E., Perampanel: Does it have broad-spectrum potential?, Epilepsia, 60, 22-36, 2019	Narrative review. References checked.
Ramsay, R. E., Wilder, B. J., Berger, J. R., Bruni, J., A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults, Neurology, 33, 904-910, 1983	Does not include patients with GGE
Ramsay, R. E., Wilder, B. J., Murphy, J. V., Holmes, G. L., Uthman, B., Slater, J., Morris, D. D., Shu, V. S., Pierce, M. W., Efficacy and safety of valproic acid versus phenytoin as sole therapy for newly diagnosed primary generalized tonic-clonic seizures, Journal of Epilepsy, 5, 55-60, 1992	Does not include patients with GGE
Reunanen, M., Dam, M., Yuen, A. W., A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy, Epilepsy Research, 23, 149â€• 155, 1996	Does not include patients with GGE
Rho, J. M., Arroyo, S., Squires, L., Wang, S., Jacobs, D., Topiramate as first-line therapy: findings from children/adolescents with newly diagnosed epilepsy, Epilepsia, 44 Suppl 9, 93â€• 94, 2003	Conference abstract
Rosati, A., Ilvento, L., Lucenteforte, E., Pugi, A., Crescioli, G., McGreevy, K. S., Virgili, G., Mugelli, A., De Masi, S., Guerrini, R., Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis, Epilepsia, 59, 297-314, 2018	Does not include data on patients with GGE
Sachdeo, R. C., Reife, R. A., Lim, P., Pledger, G., Topiramate monotherapy for partial onset seizures, Epilepsia, 38, 294-300, 1997	Epilepsy population without GGE subgroup analysis
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	Epilepsy population without GGE subgroup analysis
Sato, S., White, B. G., Penry, J. K., Valproic acid versus ethosuximide in the treatment of absence seizures, Neurology, 32, 157-163, 1982	Does not include patients with GGE
Schapel, G. J., Beran, R. G., Vajda, F. J. E., Berkovic, S. F., Mashford, M. L., Dunagan, F.	Epilepsy population without GGE subgroup analysis

Study	Reason for Exclusion
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	
Schäuble, B., Levisohn, P., Holland, K., Wiegand, F., Open label study to evaluate the effectiveness of topiramate in patients with juvenile myoclonic epilepsy, Epilepsia, 48 Suppl 3, 42, Abstract No: P186, 2007	Conference abstract
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	Epilepsy population without GGE subgroup analysis
Severi, S., Muscas, G. C., Bianchi, A., Zolo, P., Efficacy and safety of Lamotrigine monotherapy in partial epilepsy, Bollettino - Lega Italiana contro l'Epilessia, 149â€• 151, 1994	Article not in English
Song, L., Liu, F., Liu, Y., Zhang, R., Ji, H., Jia, Y., Clonazepam addâ€• on therapy for drugâ€• resistant epilepsy, Cochrane Database of Systematic Reviews, 2020	Does not include data on patients with GGE
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	Does not include data on patients with GGE
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	Does not include data on patients with GGE
Sperling, M. R., Abou-Khalil, B., Harvey, J., Rogin, J. B., Biraben, A., Galimberti, C. A., Kowacs, P. A., Hong, S. B., Cheng, H., Blum, D., Nunes, T., Soares-Da-Silva, P., Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: Results of a phase III, double-blind, randomized, placebo-controlled trial, Epilepsia, 56, 244-253, 2015	Incorrect population
Sperling, M., Williams, B., Laurenza, A., Ma, T., Yang, H., Efficacy of perampanel by baseline seizure frequency in patients with partial seizures, Epilepsia, 57 (Supplement 2), 181, 2016	Conference abstract
Stefan, H., Schafer, H., Kuhnen, C., Schneider, S., Clinical monitoring during carbamazepine slow-release, once-daily monotherapy, Epilepsia, 29, 571-7, 1988	Epilepsy population without GGE subgroup analysis
Steinhoff, B. J., Krauss, G. L., Majoie, M., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., Efficacy of perampanel in complex partial and secondary generalized seizures: A phase III study in patients with refractory partial seizures, Epilepsy Currents. Conference: 65th Annual Meeting of the American Epilepsy Society, AES.	Conference abstract

Study	Reason for Exclusion
Baltimore, MD United States. Conference Publication:, 12, 2012	
Steinhoff, B. J., O'Brien, T. J., Yang, H., Laurenza, A., Patten, A., Bibbiani, F., Efficacy of adjunctive perampanel in idiopathic generalised epilepsy patients with drug-resistant primary generalised tonic-clonic seizures by age, sex, race: A double-blind PBO-controlled phase 3 trial, European Journal of Neurology, 1), 64-65, 2015	Conference abstract
Steinhoff, B., O'Brien, T., Yang, H., Laurenza, A., Patten, A., Bibbiani, F., Efficacy of adjunctive perampanel in idiopathic generalized epilepsy patients with drug-resistant primary generalized tonic-clonic seizures by age, sex, and race: Double-blind placebo-controlled phase III study, Neurology. Conference: 68th American Academy of Neurology Annual Meeting, AAN, 86, 2016	Conference abstract
Sun, M. Z., Deckers, C. L. P., Liu, Y. X., Wang, W., Comparison of add-on valproate and primidone in carbamazepine-unresponsive patients with partial epilepsy, Seizure, 18, 90-93, 2009	Epilepsy population without GGE subgroup analysis
Sundqvist, A., Nilsson, B. Y., Tomson, T., Valproate monotherapy in juvenile myoclonic epilepsy: dose-related effects on electroencephalographic and other neurophysiologic tests, Therapeutic Drug Monitoring, 21, 91-6, 1999	Same study as Sundqvist 2008 but this study does not contain any relevant outcomes
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	Does not include data on GGE population
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	Not randomised
Tang, L., Ge, L., Wu, W., Yang, X., Rui, P., Wu, Y., Yu, W., Wang, X., Lamotrigine versus valproic acid monotherapy for generalised epilepsy: A meta-analysis of comparative studies, Seizure, 51, 95-101, 2017	Does not include data on patients with GGE
Thilothammal, N., Banu, K., Ratnam, R. S., Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study, Indian Pediatrics, 33, 549â€• 555, 1996	Incorrect population
Thilothammal, N., Kannan, null, Krishnamurthy, P. V., Kamala, K. G., Ahamed, S., Banu, K., Role of phenobarbitone in preventing recurrence of febrile convulsions, Indian pediatrics, 30, 637â€• 642, 1993	Incorrect population
Timmings, P., Kasteleijn-Nolst Trenite, D. G. A., Use of change in eeg photo-paroxysmalresponse (ppr) to predict chronic AED efficacy:	Conference abstract

Study	Reason for Exclusion
Does the surrogate endpoint model work? A double blind placebo controlled study of lamotrigine vs. Valproate modelled in jme, Epilepsia, 2), 30-31, 2014	
Toledo, M., Baulac, M., Rosenow, F., Terada, K., Li, T., De Backer, M., Brock, M., Werhahn, K., Efficacy of lacosamide monotherapy in patients with newly diagnosed epilepsy stratified by baseline disease severity: sub-analysis of data from a prospective non-inferiority trial versus controlled-release carbamazepine, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Toledo, M., Baulac, M., Rosenow, F., Terada, K., Li, T., De Backer, M., Brock, M., Werhahn, K. J., Efficacy of lacosamide monotherapy in patients with newly diagnosed epilepsy stratified by baseline disease severity: Subanalysis of data from a prospective noninferiority trial versus controlledrelease carbamazepine, Epilepsia, 57 (Supplement 2), 179, 2016	Conference abstract
Trevathan, E., Kerls, S. P., Hammer, A. E., Vuong, A., Messenheimer, J. A., Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures, Pediatrics, 118, e371-e378, 2006	Incorrect population
Trevathan, E., Kerls, S. P., Hammer, A. E., Vuong, A., Messenheimer, J. A., Lamotrigine for juvenile myoclonic epilepsy: analysis of data from a randomized controlled clinical trial, Epilepsia, 46 Suppl 8, 219, 2005	Conference abstract
Trinka, E., Tsong, W., Toupin, S., Patten, A., Wilson, K., Isojarvi, J., James, D., A systematic review and indirect treatment comparison of perampanel versus brivaracetam as adjunctive therapy in patients with focal-onset seizures with or without secondary generalization, Epilepsy Research, 166 (no pagination), 2020	Does not include data on GGE population
Troupin, A., Ojemann, L. M., Halpern, L., Dodrill, C., Wilkus, R., Friel, P., Feigl, P., Carbamazepine--a double-blind comparison with phenytoin, Neurology, 27, 511-9, 1977	Incorrect population
Verity, C. M., Hosking, G., Easter, D. J., A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The Paediatric EPITEG Collaborative Group, Developmental Medicine & Child Neurology, 37, 97-108, 1995	Epilepsy population without GGE subgroup analysis
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Warnock, R., Yates, S., Schmid, M., Werhahn, K., Doty, P., Rationale and study design for a	Conference abstract

Study	Reason for Exclusion
novel phase 3, randomized, double-blind trial of adjunctive lacosamide in patients with idiopathic generalized (genetic) epilepsy and uncontrolled primary generalized tonic-clonic seizures, Epilepsia, 1), 215, 2015	
Werhahn, K., Rosenow, F., Toledo, M., Baulac, M., Terada, K., Li, T., Brock, M., De Backer, M., Randomized double-blind noninferiority trial of lacosamide versus controlled-release carbamazepine monotherapy-subgroup analysis of unclassified patients with initial generalized tonic-clonic seizures only, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Wilkus, R. J., Dodrill, C. B., Troupin, A. S., Carbamazepine and the electroencephalogram of epileptics: a double blind study in comparison to phenytoin, Epilepsia, 19, 283-91, 1978	Epilepsy population without GGE subgroup analysis
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 not in English
Zhou, S., Zhan, Q., Wu, X., Effect of levetiracetam on cognitive function and clonic seizure frequency in children with epilepsy, Current molecular medicine., 29, 2019	Childhood epilepsy population without GGE subgroup analysis

Excluded economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix L - Research recommendations

Research recommendations for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in idiopathic generalised epilepsies (IGEs), including juvenile myoclonic epilepsy?

No research recommendations were made for this review question.