National Institute for Health and Care Excellence

Final

Epilepsies in children, young people and adults

[L] Effectiveness of antiseizure therapies in the treatment of Lennox-Gastaut syndrome

NICE guideline NG217

Evidence reviews underpinning recommendation section 6.2.1-6.2.9 in NICE guideline

April 2022

Final

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

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Evidence review for effectiveness of antiseizure therapies in the treatment of Lennox-Gastaut syndrome

Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Lennox-Gastaut syndrome?

Introduction

Lennox-Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy of childhood that typically becomes apparent between 1 and 7 years with a peak at 3 to 5 years of age. In up to 30% of cases Lennox-Gastaut syndrome is preceded by an earlier onset epilepsy syndrome such as West syndrome (infantile spasms). It is characterised by multiple seizure types – typically tonic seizures, atonic seizures and atypical absence seizures. The typical EEG pattern during wakefulness shows slow spike and wave activity, but characteristic fast rhythms may be seen during a sleep recording and may be associated with clinically evident tonic seizures. The syndrome has multiple aetiologies with a causal structural abnormality in up to 70%. Overall the prognosis is poor with continuing seizures and severe learning and behaviour difficulties into adult life. The aim of this review is to identify which antiseizure therapies are the most effective in the treatment of Lennox-Gastaut syndrome.

Summary of the protocol

Please 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	• Children, young people and adults with confirmed Lennox-Gastaut syndrome
Intervention	The following anti-epileptic therapies and their combinations will be considered: • Carbamazepine • Clobazam • Clonazepam • Ethosuximide • Felbamate • Gabapentin • Ketogenic diet (included as this is an accepted first or second line treatment for this syndrome) • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Pregabalin • Rufinamide • Sodium valproate • Tiagabine

	• Topiramate • Vigabatrin • Zonisamide
Comparison	• No treatment/placebo • Comparison between the listed interventions (monotherapy or add-on therapy) • Different doses of the listed interventions
Outcomes	**Critical** • Reduction in seizure frequency >50% • Reduction in drop attacks (may also be described as tonic, atonic, or tonic-clonic attacks) • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • Adverse events, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse events) ○ Treatment cessation due to adverse medication effects (dichotomous outcome only) ○ Mortality **Important** • Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS (Vineland Adaptive Behaviour Scale) • Social functioning changes (behaviour reported by parents/caregivers/school or validated tools) • Overall quality of life (reported by caregiver/the individual with Lennox-Gastaut syndrome). Only validated scales will be included

IQ: Intelligence quotient; VABS: Vineland adaptive behaviour scale

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.

Clinical evidence

Included studies

Eight randomised controlled trials (RCTs) and one follow-up study were identified for inclusion in this review (Arzimanoglou 2019, Conry 2009, Dodson 1993, Felbamate study group 1993, Glauser 2008, Motte 1997, Ng 2011, Ohtsuka 2014, Sachdeo 1999).

Two of the included articles provided data from the same population, comparing felbamate with placebo: 1 RCT (Felbamate study group 1993) and 1 follow-up study (Dodson 1993).

One RCT compared add-on rufinamide with any other add-on antiseizure medication (Arzimanoglou 2019); 1 RCT compared add-on low-dose clobazam with add-on high-dose clobazam (Conry 2009); 1 RCT and 1 follow-up study reported results from a study comparing add-on felbamate with placebo (Felbamate study group 1993, Dodson 1993); 2

RCTs compared add-on rufinamide with placebo (Glauser 2008, Ohtsuka 2014); 1 RCT compared add-on lamotrigine with placebo (Motte 1997); 1 RCT compared add-on dose-ranging clobazam with placebo (Ng 2011); and 1 RCT compared add-on topiramate with placebo (Sachdeo 1999).

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 with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

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 rufinamide versus any other add-on antiseizure medication

Study	Population	Intervention	Comparison	Outcomes
Arzimanoglou 2019 RCT Canada, USA, France, Greece, Italy, Poland	N= 37 infants with LGS with inadequate responses to treatment with other ASMs (1-3 ASMs) Age, months, mean (SD): Intervention group = 28.3 (10) Control group = 28.9 (9.9)	Add-on rufinamide n=25 Target maintenance 45mg/kg/day with existing regimen of 1 to 3 ASM	Any other add-on antiseizure medication n=12 In combination with existing regimen of 1 to 3 ASMs	• Time to withdrawal of treatment due to adverse events or lack of seizure efficacy • % of patients with reported serious side effects • Treatment cessation due to adverse medication effects • Social functioning changes: difference in total problems scores

ASMs: antiseizure medications; Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

Table 3. Summary of included studies. Comparison 2: add-on low-dose clobazam versus add-on high-dose clobazam

Study	Population	Intervention	Comparison	Outcomes
Conry 2009 Phase II RCT US	N=68 people with LGS Age, years, median (range): 7.4 (2 to 26)	Add-on low-dose clobazam n=32 Target dose 0.25 mg/kg/day	Add-on high-dose clobazam n=36 Target dose 1.0mg/kg/day	• Reduction in seizure frequency >50% • Reduction in drop attacks • % of patients with reported severe side effects • Treatment cessation due to adverse medication effects • Social functioning changes: % of patients considered to be “improved” or “very much improved” (patient and carer global evaluations)

Study	Population	Intervention	Comparison	Outcomes
				• Social functioning changes: % of patients considered to be "improved" or "very much improved" (investigator evaluation)

Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial

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

Study	Population	Intervention	Comparison	Outcomes
Felbamate study group 1993 RCT US	N=73 people with LGS Age, years, mean (range): Intervention group = 12 (4 to 24) Control group = 14 (4 to 36)	Add-on felbamate n=37 Maximum dose 45mg/kg/day or 3600mg/day, whichever was less	Placebo n=36	• Complete cessation of all seizures¥ • Complete cessation of atonic seizures • Complete cessation of generalised tonic-clonic seizures • Mean change in frequency of all seizures¥ • Mean change in frequency of atonic seizures • Mean change in frequency of generalised tonic-clonic seizures • Treatment cessation due to adverse medication effects • Mortality
Dodson 1993 Follow-up of Felbamate study group 1993 (RCT) US	As above	As above	As above	• Global outcome variable (proxy outcome for quality of life)

¥All seizures: atonic, tonic, generalised tonic-clonic, atypical absence, and complex partial
Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial

Table 5: Summary of included studies. Comparison 4: add-on rufinamide versus placebo

Study	Population	Intervention	Comparison	Outcomes
Glauser 2008 RCT Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and US	N=138 people with LGS Age, years, median (range): Intervention group = 13 (4 to 35) Control group = 10.5 (4 to 37)	Add-on rufinamide n=74 Maximum dose 45mg/kg/day	Placebo n=64	• Reduction in total seizure frequency >50% • Improvement in seizure severity • Reduction in drop attacks • Treatment cessation due to adverse medication effects • % of patients with reported serious side effects
Ohtsuka 2014	N=59 people with	Add-on	Placebo	• Reduction in seizure

Study	Population	Intervention	Comparison	Outcomes
RCT Japan	LGS Age, years, mean (SD): Intervention group = 16 (7.1) Control group = 13.9 (6.1)	rufinamide n=29 Maximum dose was 3200mg/day	n=30	frequency > 50% • Reduction in tonic seizures • Reduction in atonic seizures • Reduction in tonic-clonic seizures • % of patients with a dose reduction due to safety concerns • Treatment cessation due to adverse medication effects • % of patients with reported serious side effects

Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

Table 6: Summary of included studies. Comparison 5: add-on lamotrigine versus placebo

Study	Population	Intervention	Comparison	Outcomes
Motte 1997 RCT France, US, Spain, UK	N= 169 people with LGS Age, years, mean (SD): Intervention group = 9.6 (5.2) Control group = 10.9 (5.9)	Add-on lamotrigine n=79 Maximum dose was 400mg/day	Placebo n=90	• Reduction in seizure frequency > 50% • Reduction in drop attacks • Treatment cessation due to adverse medication effects

LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

Table 7: Summary of included studies. Comparison 6, 7, and 8: dose-ranging clobazam (add-on) versus placebo

Study	Population	Intervention	Comparison	Outcomes
Ng 2011 RCT US, Europe, India and Australia	N=238 people with LGS Age, years, mean (SD): placebo group = 13 (9.2) low-dose group = 10.9 (7.2) medium-dose group = 14.1 (10.4) high-dose group = 11.7 (8.5)	Add-on dose-ranging clobazam n=58 randomised to clobazam 0.25 mg/kg/day [low dose]; n=62 randomised to clobazam 0.5 mg/kg/day [medium dose]; and n=59 randomised	Placebo n=59	• Reduction in seizure frequency > 50% • Complete reduction in drop attacks • % of patients with a change in medication dose • % of patients with reported serious side effects • Mortality • Treatment cessation due to adverse medication effects

Study	Population	Intervention	Comparison	Outcomes
		to clobazam 1 mg/kg/day [high dose]		

Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

Table 8: Summary of included studies. Comparison 9: add-on topiramate versus placebo

Study	Population	Intervention	Comparison	Outcomes
Sachdeo 1999 RCT US	N=98 people with LGS Age, years, mean (SD) in the intervention group 11.2 (6.2) and in the control group 11.2 (7.70	Add-on topiramate n=48 Target dose was 6mg/kg/day	Placebo n=50	• Reduction in major seizure frequency (drop attacks and tonic-clonic seizures) >50% • Complete cessation of drop attacks • % of patients with reported severe adverse side effects • Treatment cessation due to adverse medication effects • % of patients with dose reduction or temporary discontinuation of treatment

Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

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

Summary of the evidence

No evidence regarding monotherapy or first-line therapies were identified in this review. Amongst the second-line interventions identified, add-on lamotrigine, add-on rufinamide, add-on high-dose and medium-dose clobazam, add-on topiramate and add-on felbamate showed important differences with the interventions they were compared with, usually placebo. The majority of the evidence from these studies was very low to moderate quality; most outcomes had very serious imprecision and were at risk of bias due to lack of information regarding randomisation and allocation concealment.

For instance, add-on lamotrigine was associated with clinically important benefits in relation to reduction in seizure frequency >50%, and reduction in drop attacks when compared to placebo; add-on rufinamide was associated with clinically important benefits in relation to reduction in seizure frequency >50%, improvement in seizure severity, reduction in drop attacks and reduction in tonic seizures when compared to placebo; add-on high-dose and medium-dose clobazam were associated with reduced seizure frequency when compared to lo-dose clobazam. Finally, add-on topiramate was associated with clinically important reductions in seizure frequency >50%, and complete reduction in drop attacks when compared with placebo; and add-on felbamate was associated with clinically important benefis in relation to mean reduction of seizure frequency (all, atonic, generalised tonic-clonic) and quality of life when compared to placebo.

No clinically important differences were found for add-on rufinamide versus any other add-on antiseizure medication (note that only paediatric patients were included) and add-on low dose clobazam versus placebo.

No evidence was found for the following antiseizure therapies: carbamazepine, clonazepam, ethosuximide, gabapentin, ketogenic diet, lacosamide, levetiracetam, oxcarbazepine, pregabalin, sodium valproate, tiagabine, vigabatrin and zonisamide.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

Two relevant papers were identified in the literature review of published economic evidence on this topic (Benedict 2010; Verdian 2010; see appendix H and appendix I for summary and full evidence tables). Both papers considered the cost effectiveness of rufinamide compared to topiramate and lamotrigine as an adjunctive treatment in children with Lennox-Gastaut syndrome. Benedict 2010 also included standard therapy alone as a comparator.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See supplementary materia 2 for details.

Summary of studies included in the economic evidence review

Benedict 2010 was a cost effectiveness analysis which reported outcomes in terms of cost per 1% increase in successfully treated patients in terms of tonic-atonic (drop attack) frequency and cost per 1% increase in successfully treated patients in terms of total seizure. Success was defined as a greater than 50% reduction in frequency.

Verdian 2010 was a cost utility analysis which reported outcomes in terms of incremental cost per QALY. Utility values were estimated using time trade off methodology from 119 members of the UK general population.

Both studies adopted the perspective of the NHS & PSS. Both studies received funding from the manufacturer of rufinamide.

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 effectiveness analysis showing rufinamide cost an extra £62 and £2151 per 1% reduction in drop attacks and total seizures respectively compared to lamotrigine, topiramate andstandard therapy in children with Lennox-Gastaut syndrome. It was deemed partially applicable to the decision problem because whilst it took a UK NHS & PSS perspective it did not report outcomes in terms of quality adjusted life years (QALYs). It was deemed to have potentially serious methodological limitations as there was a lack of transparency around some parameters. It was deemed directly applicable to the decision problem but was deemed to have potentially serious methodological limitations.
- There was evidence from 1 UK cost utility model comparing rufinamide ith lamotrigine and topiramate in children with Lennox_Gastaut syndrome. The study estimated a cost per QALY for RUF of £20,538 and £154,831 compared to TPM and LTG respectively. There was a 52% and 8% probability that RUF was cost effective at a £20,000 per QALY threshold.

Summary of the economic evidence

Two economic evaluations relevant to the decision problem were identified (Benedict 2010, Verdian 2010).

Benedict 2010 was a patient simulation model comparing rufinamide (RUF) to lamotrigine (LTG), topiramate (TPM) and standard therapy in people with Lennox-Gastaut syndrome (LGS). It was deemed partially applicable to the decision problem because whilst it took a UK NHS & PSS perspective it did not report outcomes in terms of quality adjusted life years (QALYs). It was deemed to have potentially serious methodological limitations as it was funded by the manufacturer of RUF and there was a lack of transparency around some parameters. The study presented 2 analyses one considering reduction in drop attacks and the other reduction in total seizures. RUF was associated with a £62 cost per 1% reduction in drop attacks (compared to TPM) and £2151 per reduction in total seizures (compared to LTG). There was an 80% probability that RUF was the optimal treatment when willingness to pay for a 1% reduction in drop attacks and total seizures was £250 and £900 respectively.

Verdian 2010 was a Markov model comparing RUF to LMG and TPM as an adjunctive treatment in children with LGS. It was deemed directly applicable to the decision problem as it took a NHS & PSS perspective and reported outcomes in terms of cost per QALY. It was deemed to have potentially serious methodological limitations due to being funded by the manufacturer of RUF and lack of transparency around estimates of key parameters. The study estimated a cost per QALY for RUF of £20,538 and £154,831 compared to TPM and LTG respectively. There was a 52% and 8% probability that RUF was cost effective at a £20,000 per QALY threshold.See appendix H and appendix I for summary and full evidence tables.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The main objective of treatment for children with Lennox-Gastaut syndrome is to control seizures as much as possible whilst minimising the risk of adverse events. The committee therefore agreed that reduction in seizure frequency >50%, time to withdrawal of treatment or change of medication, and adverse events (as assessed by trial-defined adverse and serious adverse events and mortality) should be designated as critical outcomes for this review. As 'drop attacks' (also described as tonic, atonic, or tonic-clonic attacks) are a key feature of Lennox-Gastaut syndrome, reduction in drop attacks specifically was also included as a critical outcome in this review.

Balancing the need to control seizures with the need to maintain (or improve) quality of life is a key issue in the treatment of children with Lennox Gastaut syndrome and the committee therefore agreed that overall quality of life should be included as an important outcome. The committee also agreed to include neurodevelopment outcomes and social functioning changes as important outcomes as better seizure control is expected to lead to improvements in a child's developmental abilities.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The majority of outcomes were considered very low, low or moderate quality evidence, indicating high uncertainly in the reliability of the data. This was with the exception of some of the outcomes reported by Glauser 2008, Ng 2011 and Ohtsuka 2014, which were considered high quality.

Data was generally downgraded due to risk of bias, with limited information provided regarding randomisation and allocation concealment. Data was also downgraded due to imprecision. The included studies only included a small number of participants; therefore, overall the data should be regarded with some caution.

Benefits and harms

The committee considered the evidence included within this evidence review and used the evidence and their expertise to make recommendations.

Lennox-Gastaut syndrome is a severe developmental and epileptic encephalopathy that is characterised by different types of seizures, intellectual disability and abnormal EEG features. Diagnosis is often difficult to establish because the seizure types and EEG features it presents with are not specifically indicative of this syndrome, and because these tend to evolve over time. The committee highlighted that treatment is also likely to have been initiated before the diagnosis is established, often because it is challenging to distinguish this epilepsy syndrome from others, particularly in the early stages of the presentation. For these reasons, and based on their experience and expertise, the committee agreed that the involvement of an adult or paediatric neurologist is needed to guide the care of people with Lennox-Gastaut. This is standard current practice, therefore the committee did not think this recommendation would lead to increased costs or resource use.

The committee agreed that, prior to starting antiseizure therapy there should be a discussion with the person, their family and carers, if appropriate, about an individualised antiseizure therapy strategy according to their syndrome 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.

No evidence was found assessing the effectiveness of monotherapy or first-line therapy, so the expert opinion of the committee was that sodium valproate should be the first-line medication in people with Lennox-Gastaut syndrome because it is effectively used in clinical practice for generalised seizures, including Lennox-Gastaut syndrome, and because the severity of the syndrome and the lack of evidence for alternative first-line options. The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children, yet agreed that it should be considered as first-line treatment as approximately two thirds of children outgrow this syndrome and its neurodevelopmental consequences mean that pregnancy is unusual. However the committee agreed that, for women and girls who are able to have children, sodium valproate should only be prescribed after a full and clear discussion with them or their families/carers, as appropriate, ensuring they understand all the potential risks and benefits. If sodium valproate is prescribed to women and girls able to have children, clinicians must follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a pregnancy prevention programme, if appropriate.

Based on the available evidence, which showed that, when used as an add-on therapy, lamotrigine reduced seizure frequency, the committee agreed to recommend that lamotrigine should be used as an add-on or alternative therapy if sodium valproate is unsuccessful. The committee agreed that it was appropriate to extrapolate from the add-on evidence on lamotrigine as it is commonly used in clinical practice as monotherapy in Lennox-Gastaut syndrome.

The evidence suggested that lamotrigine was as effective as clobazam when compared to placebo, however the committee recommended lamotrigine as second-line therapy in

preference to clobazam because, according to their experience, it is better tolerated. The committee acknowledged that, due to the extended time required to titrate lamotrigine safely, clobazam is sometimes used in the short term to ameliorate seizures involving injuries. Once lamotrigine has reached adequate treatment doses, the decision to wean clobazam can be made on an individual basis. Clobazam is not licenced for children under 6 years old in the UK, but it can be used on a named-patient basis.

The evidence suggested that clobazam, rufinamide and topiramate reduce seizure frequency and drop-attacks, therefore the committee recommended these if first- and second-line therapy were unsuccessful or if seizures continue. One of the studies assessing the effectiveness of clobazam conducted analysis by low-, medium- and high-dose, however the committee did not think that it was appropriate to recommend a specific dose of clobazam as this is decided on an individual basis. Furthermore, according to their clinical experience, high doses of clobazam can worsen tonic seizures, although this is rare.

Although there was no evidence assessing the effectiveness of clobazam, rufinamide and topiramate as a monotherapy, the committee agreed that it was appropriate to extrapolate from the add-on evidence as these ASMs are commonly used in clinical practice for tonic or atonic seizures/drop attacks. The recommendations regarding cannabidiol were adopted from the NICE technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome.

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. The committee warned about the potential sedative effects of cannabidiol, clobazam, rufinamide and topiramate. They agreed that these medications should be carefully titrated, in line with the BNF guidance, adverse events monitored, and there should be a frequent treatment review.

The committee noted that ketogenic diets are successfully used in clinical practice in cases of Lennox-Gastaut syndrome difficult to treat and recommended these as a fourth-line treatment based on their expert opinion. The committee emphasised that these should only be prescribed under the guidance or supervision of a neurologist with expertise in epilepsy as these are calculated individually, and the person's weight and ketone levels need to be monitored.

The evidence supported the committee's experience that felbamate reduced seizure frequency. The committee emphasised that felbamate should only be used in severe drug-resistant cases and should only be considered under the supervision of an epilepsy specialist. This is due to the monitoring required for haematological and hepatic adverse events associated with felbamate, and because it is not licenced for use in the UK.

Although no evidence was identified which reported on any of the other ASMs included in the protocol for this review, the committee agreed that, whilst these may benefit some patients, clinical experience also suggests that they may exacerbate seizures. Therefore, they agreed to draft a recommendation stating this.

In the absence of evidence for monotherapy or first-line therapy, the committee agreed to make a recommendation for future research (see Appendix L).

Cost effectiveness and resource use

The committee considered 2 previously published economic evaluations which considered rufinamide compared to lamotrigine and topiramate. The committee highlighted limitations with the evidence which prevented them making strong recommendations based upon it. Most significantly that both studies were funded by the manufacturer of rufinamide and the

lack of transparency around key parameters. Both studies took a NHS & PSS perspective. One study also did not report outcomes in terms of cost per QALY.

The committee also highlighted the age of the studies (>10 years) and that since these analyses were completed all drugs considered are now off patent and relatively inexpensive. It was therefore considered that the most effective treatment would also be the most cost effective. Given this and the identified weaknesses in the included economic evaluations recommendations were made in line with the clinical evidence.

The recommendations made for this review question are unlikely to change current practice and therefore no resource impact is anticipated.

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 section 6.2.1-6.2.9 and the research recommendation on complex epilepsy syndromes.

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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 Lennox-Gastaut syndrome?

Table 9: Review protocol for effectiveness of antiseizure therapies in the management of Lennox-Gastaut syndrome

Field	Content
PROSPERO registration number	CRD42020164489
Review title	Effectiveness of antiseizure therapies in treatment of seizures in those with Lennox-Gastaut syndrome
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Lennox-Gastaut syndrome?
Objective	The objective of this review is to determine which anti-epileptic therapies improve outcomes in those with seizure in Lennox-Gastaut syndrome. This review will determine the effectiveness of therapies given alone or in combination (add-on therapy).
Searches	Databases to be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by: • Date limit: no date limit • English language studies • Human studies • RCT and systematic review study design filter

Field	Content
Condition or domain being studied	Lennox-Gastaut syndrome
Population	• Inclusion: children, young people and adults with confirmed Lennox-Gastaut syndrome • Exclusion: newborn babies (under 28 days) with acute symptomatic seizures
Intervention	The following anti-epileptic therapies and their combinations will be considered: • Carbamazepine • Clobazam • Clonazepam • Ethosuximide • Felbamate • Gabapentin • Ketogenic diet (included as this is an accepted first or second line treatment for this syndrome) • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Pregabalin • Rufinamide • Sodium valproate • Tiagabine • Topiramate • Vigabatrin • Zonisamide
Comparator/Reference standard/Confounding factors	• No treatment/placebo • Comparison between the listed interventions (monotherapy or add-on therapy) • Different doses of the listed interventions

Field	Content
Types of study to be included	• Systematic Reviews 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 (this is, including children, young people and adults with Lennox-Gastaut syndrome and other types of epilepsy) will be excluded, unless subgroup analysis for Lennox-Gastaut syndrome has been reported. • Conference abstracts will not be included because these do not typically provide sufficient information to fully assess the risk of bias • Studies including surgery as part of the interventions will not be included
Context	Recommendations will apply to those receiving care in healthcare settings (for example, community, primary, secondary care).
Primary outcomes (critical outcomes)	• Reduction in seizure frequency >50% • Reduction in drop attacks ((may also be described as tonic, atonic, or tonic-clonic attacks) • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • 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
Secondary outcomes (important outcomes)	• Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS (vineland Adaptive Behaviour Scale) • Social functioning changes (behaviour reported by parents/caregivers/school or validated tools) • Overall quality of life (reported by caregiver/the individual with Lennox-Gastaut syndrome). Only validated scales will be included *NB: Outcomes are in line with those described in the core outcome set for epilepsy (http://www.comet-initiative.org/studies/searchresults)*
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated.

Field	Content
	Titles and abstracts of the retrieved citations will be screened. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria outlined in the review protocol. 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. Draft included and excluded study lists will be circulated to the committee for their comments, resolution of any disputes will be by discussion between the senior reviewer, topic advisor and chair. Duplicate screening will not be undertaken for this question. A standardised form will be used to extract data from studies (see Developing NICE guideline: the manual section 6.4) and will include: study setting; study design; study aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of intervention and control groups; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. All data extraction will be quality assured by a senior reviewer.
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 and quasi-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 and <1% events in the other. Risk difference will be used for outcomes with zero events in both arms. 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,

Field	Content
	respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • 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 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, results will be presented separately by: • Age (split by adult and children)
Type and method of review	☒ Intervention

Field	Content		
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	03 February 2020		
Anticipated completion date	02 June 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact National Guideline Alliance 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	National Guideline alliance (NGA) technical team		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the		

Field	Content
	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/gid-ng10112/documents/committee-member-list
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020164489
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Epilepsy, Lennox-Gastaut, children, adults, young people, anti-epileptic drug.
Details of existing review of same topic by same authors	Not applicable
Additional information	
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: The Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IQ: intelligence quotient; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; ROBIS: risk of bias in systematic reviews; 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 Lennox-Gastaut syndrome?

Clinical

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

EMCare 1995 to January 15, 2020; Embase Classic+Embase 1947 to 2020 January 15; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2020 January 15, 2020
Date of last search: 15 January 2020

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	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
2	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
3	1 or 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	gabapentin/ use emczd, emcr or gabapentin/ use ppez or gabapentin*.sh. or (apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin).ti,ab.
9	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
10	9 use emczd, emcr
11	diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycerides/
12	11 use ppez
13	((adequate adj3 protein*) or atkin* or keto* or kd* or (carbohydrate* adj5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) adj5 (index or treat* or modulat*)) or (high fat* adj5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or low glyc* index treatment* or lgit or (medium chain adj (tryglyceride* or triglyceride*)) or mct*).ti,ab.
14	or/10,12-13
15	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
16	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.
17	levetiracetam/ use emczd, emcr, ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
18	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.
19	rufinamide/ use emczd, emcr or rufinamide*.sh. or (banzel or inovelon or rufinamid* or xilep).ti,ab.
20	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

#	Searches
	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.
21	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.
22	vigabatrin/ use emczd, emcr, ppez or (4 vinyl 4 aminobutyric acid or 4 vinylaminobutyric acid or 4 vinylgaba or gamma vinyl 4 aminobutyric acid or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid or gamma vinylgaba or n vinyl 4 aminobutyric acid or n vinyl gaba or n vinyl gamma aminobutyric acid or sabril sabrilex or vigadrone or sabril or sabrilex or vigabatrin or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid).ti,ab.
23	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
24	felbamate/ use emczd, emcr, ppez or (felbamate or felbamyl or felbatol or taloxa).ti,ab.
25	pregabalin/ use emczd, emcr, ppez or (lyrica or pregabalin).ti,ab.
26	tiagabine/ use emczd, emcr, ppez or (gabitril or tiabex or tiagabine).ti,ab.
27	((anti epilep* or antiepilep* or anti convul* or anticonvuls* or anti seizure* or antiseizure*) adj2 (drug* or treatment*)).ti,ab.
28	or/4-8,14-27
29	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.
30	29 use ppez
31	(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.
32	31 use ppez
33	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.
34	33 use emczd, emcr
35	or/30,32,34
36	meta-analysis/
37	meta-analysis as topic/ or systematic reviews as topic/
38	"systematic review"/
39	meta-analysis/
40	(meta analy* or metanaly* or metaanaly*).ti,ab.
41	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
42	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
43	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45	(search* adj4 literature).ab.
46	(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.
47	cochrane.jw.
48	((pool* or combined) adj2 (data or trials or studies or results)).ab.
49	(or/36-37,40,42-48) use ppez
50	(or/38-41,43-48) use emczd, emcr
51	or/49-50
52	or/35,51
53	3 and 28 and 52
54	53
55	limit 54 to english language
56	((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.)
57	56 use emez

#	Searches
58	((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.)
59	58 use mesz
60	57 or 59
61	55 not 60

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 01 of 12, January 2020; Cochrane Central Register of Controlled Trials, Issue 1 of 12, January 2020
Date of last search: 15 January 2020

#	searches
1	mesh descriptor: [lennox gastaut syndrome] explode all trees
2	((“childhood epileptic encephalopathy” or (lennox near/1 (gastaut or syndrome*)) or lgs)):ti,ab,kw
3	#1 or #2
4	mesh descriptor: [carbamazepine] explode all trees
5	mesh descriptor: [clobazam] this term only
6	mesh descriptor: [clonazepam] this term only
7	mesh descriptor: [ethosuximide] this term only
8	mesh descriptor: [gabapentin] this term only
9	mesh descriptor: [diet, carbohydrate-restricted] explode all trees
10	mesh descriptor: [dietary fats] explode all trees
11	mesh descriptor: [glycemic index] this term only
12	mesh descriptor: [diet, ketogenic] this term only
13	mesh descriptor: [triglycerides] explode all trees
14	mesh descriptor: [lacosamide] this term only
15	mesh descriptor: [lamotrigine] this term only
16	mesh descriptor: [levetiracetam] this term only
17	mesh descriptor: [oxcarbazepine] this term only
18	mesh descriptor: [topiramate] this term only
19	mesh descriptor: [valproic acid] this term only
20	mesh descriptor: [vigabatrin] this term only
21	mesh descriptor: [zonisamide] this term only
22	mesh descriptor: [felbamate] this term only
23	mesh descriptor: [pregabalin] this term only
24	mesh descriptor: [tiagabine] this term only
25	((amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol)):ti,ab,kw
26	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab,kw
27	((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
28	((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
30	(((adequate near/1 protein*) or atkin* or keto* or kd or (carbohydrate* near/1 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) near/1 (index or treat* or modulat*)) or (“high fat*” near/1 (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
31	((erlosamide or harkoseride or lacosamide or vimpat)):ti,ab,kw
32	((crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
33	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
34	((apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin)):ti,ab,kw
35	((banzel or inovelon or rufinamid* or xilep)):ti,ab,kw
36	((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

#	searches
	topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)):ti,ab,kw
37	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or “di n propylacetate” or “di n propylacetate sodium” or “di n propylacetic acid” or diplexil or “dipropyl acetate” or “dipropyl acetic acid” or dipropylacetate or “dipropylacetate sodium” or “dipropylacetatic acid” or “dipropylacetic acid” or diprosin or divalproex or epilam or epilex or “epilim chrono” or “epilim chromosphere” or “epilim enteric” or epilim or episenta or “epival cr” or ergenyl or “espa valept” or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or “myproic acid” or “n dipropylacetic acid” or orfil or orfiril or orlept or petilin or “propylisopropylacetic acid” or propymal or “semisodium valproate” or “sodium 2 propylpentanoate” or “sodium 2 propylvalerate” or “sodium di n propyl acetate” or “sodium di n propylacetate” or “sodium dipropyl acetate” or “sodium dipropylacetate” or “sodium n dipropylacetate” or stavzor or “valberg pr” or valcote or valepil or valeptol or valerin or “valhel pr” or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or “valproic acid” or valprosid or valprotek or valsup or vupral)):ti,ab,kw
38	((“4 vinyl 4 aminobutyric acid” or “4 vinylaminobutyric acid” or “4 vinylgaba” or “gamma vinyl 4 aminobutyric acid” or “gamma vinyl gaba” or “gamma vinyl gamma aminobutyric acid” or “gamma vinylgaba” or “n vinyl 4 aminobutyric acid” or “n vinyl gaba” or” n vinyl gamma aminobutyric acid” or “sabril sabrilex” or vigadrone or sabril or sabrilex or vigabatrin or “gamma vinyl gaba” or “gamma vinyl gamma aminobutyric acid”)):ti,ab,kw
39	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
40	((felbamate or felbamyl or felbatol or taloxa)):ti,ab,kw
41	((lyrica or pregabalin)):ti,ab,kw
42	(((antiepilep* or anticonvul* or antiseizure*) near/1 (drug* or treatment*)) or ((“anti epilep*” or “anti convul*” or “anti seizure*”) near/1 (drug* or treatment*))):ti,ab,kw
43	{or #4-#42}
44	#3 and #43

Database(s): DARE; HTA database - CRD
Date of last search: 15 January 2020

#	searches
1	mesh descriptor lennox gastaut syndrome explode all trees
2	((“childhood epileptic encephalopathy” or (lennox near1 (gastaut or syndrome*)) or lgs))
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

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

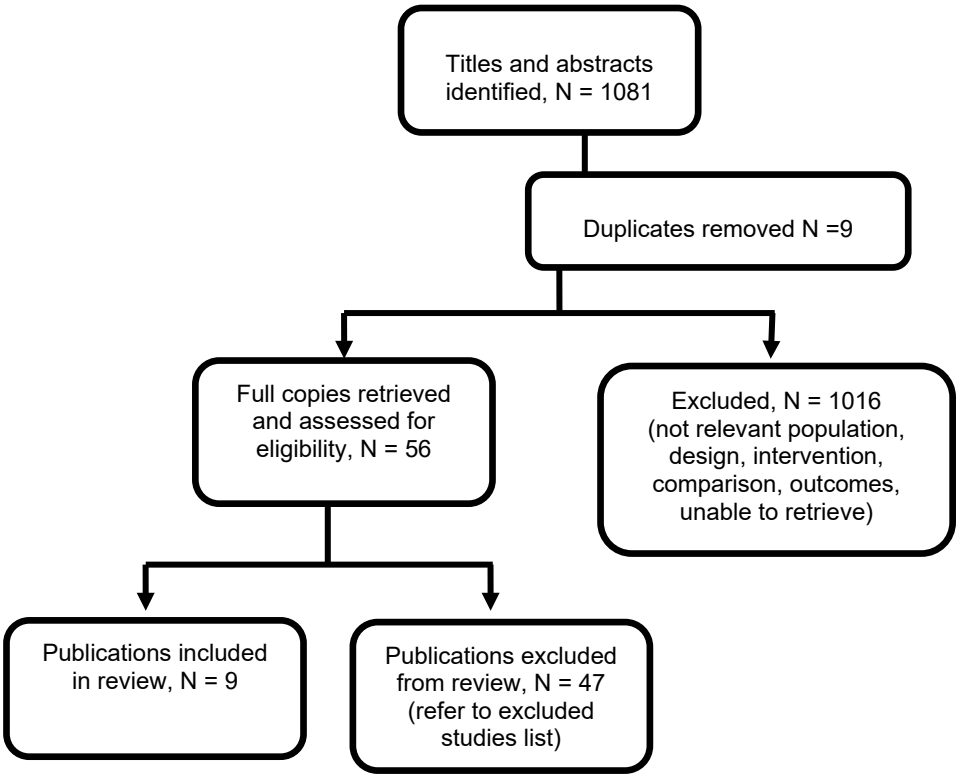
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees

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

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 Lennox-Gastaut syndrome?

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 Lennox-Gastaut syndrome?

Table 10: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Arzimanoglou, A., Ferreira, J., Satlin, A., Olhaye, O., Kumar, D., Dhadda, S., Bibbiani, F., Evaluation of long-term safety, tolerability, and behavioral outcomes with adjunctive rufinamide in pediatric patients (>=1 to <4 years old) with Lennox-Gastaut syndrome: Final results from randomized study 303, European Journal of Paediatric Neurology, 23, 126-135, 2019 **Ref Id** 1113441 **Country/ies where the study was carried out** Canada, France, Greece, Italy, Poland, USA **Study type** Randomised controlled trial	**Sample size** N= 37 (N=25 in the rufinamide group and n= 12 in the 'any other antiepileptic drug' group) **Characteristics** Age, months, mean (SD) Intervention: 28.3 (10) Control: 29.8 (9.9) Males, n (%) Intervention: 14 (56) Control: 10 (83.3) Time since diagnosis, mean months (SD) Intervention:19.9 (9.9) Control: 23 (9.5) **Inclusion criteria** • 1 to 4 years of age • Clinical diagnosis of Lennox-Gastaut syndrome	**Interventions** Oral suspension rufinamide (45 mg/kg/day) versus any other investigator-chosen antiepileptic drug	**Details** After a baseline period where participants were monitored to assess whehter they displayed Lennox-Gastaut syndrome, participants were randomised to rufinamide or to an ASM chosen by the investigator as adjunctive of the participant's existing 1 to 3 antiepileptic drugs. Randomisation method was not reported. Study was open label Follow-up: 106 weeks (no measure of variability was reported)	**Results** *Primary outcomes* Time to withdrawal of treatment due to adverse events or lack of seizure efficacy; median (weeks) Intervention group: 142 weeks Control group: 28 weeks (no IQR or p-value were reported) % of patients with reported serious side effects Intervention group: 10/25 Control group: 5/12 Treatment	**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 was provided to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, study was open label 2.2: Yes, study was open

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effectiveness of rufinamide in the treatment of Lennox-Gastaut Syndrome **Study dates** June 2011 and November 2015 **Source of funding** Eisai Inc.	**Exclusion criteria** • Those with epilepsy syndromes not suggesting the electroclinical profile of patients within the LGS (this is, benign myoclonic epilepsy of infancy, atypical benign partial epilepsy) • Those with an inadequate response to treatment after a fixed dose of 1 to 3 concomitant ASMs for a minimum of 4 weeks prior randomisation • Those with familial short QT syndrome • Those who had previously received rufinamide			cessation due to adverse drug effects Intervention group: 2/25 Control group: 1/12 *Secondary outcomes* Social functioning changes: difference in total problems scores, mean difference between groups (95% CI) 1.197 (-7.6 to 5.3), p =0.7083	label 2.3: No information whether there were deviations from the intended intervention **Domain 3: Missing outcome data: High risk** 3.1: No information 3.2: No evidence 3.3: No information 3.4: No information **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgment of bias: High**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					risk The study is judged to be at high risk of bias in at least one domain for this result
Full citation Conry, J. A., Ng, Y. T., Paolicchi, J. M., Kernitsky, L., Mitchell, W. G., Ritter, F. J., Collins, S. D., Tracy, K., Kormany, W. N., Abdulnabi, R., et al.,, Clobazam in the treatment of Lennox-Gastaut syndrome, Epilepsia, 50, 1158-1166, 2009 **Ref Id** 1176847 **Country/ies where the study was carried out** USA **Study type** Phase II RCT **Aim of the study** To assess the effectiveness of clobazam in the treatment of people with LGS **Study dates**	**Sample size** N=68 (n=32 in the low-dose clobazam group and n=36 in the high-dose clobazam group) **Characteristics** Age, years, median (range): 7.4 (2 to 26) Male:female: 42:26 Patients randomised to each treatment group were comparable. No p-values were reported **Inclusion criteria** • EEG with slow spike and wave and multifocal spikes • ≥ 1 type of generalised seizure for at least 6 months • <11 years old at the onset of LGS • >12.5 kgs • Up to 3 antiepileptic grugs • At least 2 drop	**Interventions** Low-dose clobazam (target dose of 25 mg/kg/day to a maximumof 10mg/day) or high-dose clobazam(target dose 1.0mg/kg/day to amaximum of 40mg/day)	**Details** The study consisted of a 3 week titration period and a 4-week maintenance period. Method of randomisation was not reported. Patients and assessors were blinded to treatment allocation. Seizures were parental or carer reported. Analyses were "intention to treat" Follow-up: 7 weeks (no measure of variability was reported)	**Results** *Primary outcomes* Reduction in seizure frequency >50% Low-dose group: 12/32 High-dose group: 30/36 Reduction in drop attacks, mean (SD) Low-dose group at baseline: 141 (188) Low-dose group during maintenance: 91 (122) High-dose group at baseline: 207 (229) High-dose group during maintenance: 32 (57) % of patients with reported severe side effects Low-dose group: 1/32 High-dose group:	**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 was provided to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported, study published in 2009 **Source of funding** Ovation Pharmaceuticals, Deerfield, IL	seizures per week **Exclusion criteria** • Those with an episode of status epilepticus within 12 weeks of baseline • Those in whom the aetiology of the seizures was a progressive neurologic disease (except tuberous sclerosis) • Those who had taken corticotropins in the 6 months before screening			2/36 Treatment cessation due to adverse drug effects Low-dose group: 3/32 High-dose group: 6/36 *Secondary outcomes* Social functioning changes: % of patients considered to be "improved" or "very much improved" at 3 weeks (patient/ carer global evaluations) Low-dose group: 16/29 High-dose group: 30/32 Social functioning changes: % of patients considered to be "improved" or "very much improved" at 3 weeks (investigator evaluations) Low-dose group: 13/29 High-dose group:	**outcome data: Low risk** 3.1: Nearly all, n=7 did not have at least one measurement during the maintenance period **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: High risk** 5.1: No information. Trial protocol was not available 5.2: No information. Trial protocol was not available 5.3: No information. Trial protocol was not available **Domain 6: Overall judgment of bias: High risk** The study is judged to be at high risk of bias in at least one domain for this result

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				30/32	
Full citation Dodson, W. E., Felbamate in the treatment of Lennox-Gastaut syndrome: Results of a 12- month open-label study following a randomized clinical trial, Epilepsia, 34, S18-S24, 1993 **Ref Id** 1162839 **Country/ies where the study was carried out** See Felbamate Study Group 1993 **Study type** See Felbamate Study Group 1993 **Aim of the study** See Felbamate Study Group 1993 **Study dates** See Felbamate Study Group 1993 **Source of funding** See Felbamate Study Group 1993	**Sample size** See Felbamate Study Group 1993 **Characteristics** See Felbamate Study Group 1993 **Inclusion criteria** See Felbamate Study Group 1993 **Exclusion criteria** See Felbamate Study Group 1993	**Interventions** See Felbamate Study Group 1993	**Details** See Felbamate Study Group 1993	**Results** Secondary outcomes Global outcome variable (proxy outcome for quality of life) during the maintenance period, mean (SD) Intervention group: 0.823 (0.756), n=37 Control group: 0.256 (0.685), n=36	**Limitations** See Felbamate Study Group 1993

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Felbamate study group in Lennox-Gastaut Syndrome.Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome), New England Journal of Medicine, 328, 29-33, 1993 **Ref Id** 1176788 Country/ies where the study was carried out USA **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of felbamate in people with LGS **Study dates** Not reported, study published in 1993 **Source of funding** Not reported	**Sample size** N=73 (n=37 randomised to the felbamate group and n=36 randomised to the placebo group) **Characteristics** Age, months, mean (range) Intervention:12 (4 to 24) Control:14 (4 to 36) Males, n (%) Intervention: 27 (72.9) Control: 24 (66.66) Total number of antiepileptic drugs taken previously, mean (range) Intervention: 8 (3 to 16) Control: 8 (4 to 12) Total seizure frequency during baseline phase Intervention group: 1617 (no SD/ range reported) Control group: 716 (no SD/ range reported) No p-values were reported **Inclusion criteria** • Those with a history of multiple seizure types and a minimum of 90 atonic seizures or	**Interventions** Felbamate (15mg/kg/day) versus placebo. Felbamate was increased to 30 mg/kg/day after 7 days and the maximal dose after 14 days. The maximum dose could be either 45 mg/kg/day or 3600 mg/day, whichever was lower. During the maintenance period, participants continued to receive the maximal tolerated dose.	**Details** The trial had a 14 day titration period and a 56 day maintenance period. Participants were randomised in blocks of 2 to receive either felbamate or placebo. Randomisation was done by a separate computer-generated randomisation schedule at each participating centre. Felbatamate or placebo were added to the standard antiepileptic drug regimen. Follow-up: 70 days (no measure of variability was reported)	**Results** *Primary outcomes* Complete cessation of all seizures during the maintenance period Intervention group: 4/37 Control group: 1/36 Complete cessation of atonic seizures during the maintenance period Intervention group: 5/28 Control group: 0/22 Complete cessation of tonic-clonic seizures during the maintenance period Intervention group: 7/16 Control group: 1/13 Mean change (range) % in frequency of all seizures (atonic, tonic, generalised tonic-clonic, atypical absence, and complex partial) Intervention group: -26 (-100 to 521), SD= -58, n=37	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: High risk** 1.1: Yes, computer generated random numbers 1.2: No information was provided regarding randomisation concealment 1.3: Yes, the total seizure frequency in the felbamate group is higher than in the placebo group (1617 versus 716, respectively) **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	atypical absence seizures/ month during an 8 weeks prior to baseline • Those between 4 and 25 years **Exclusion criteria** • Those taking more than 2 antiepileptic drugs • Those with evidence of progressive central nervous system lesions on magnetic resonance imaging or computed tomography • Those pregnant or not taking adequate contraception • Those with a history of identifiable progressive neurologic disorders, anoxic episodes within the previous year, or other major medical illness • Those with previous suicide attempts • Those with poor compliance with past antiepileptic therapy • Those with a history of			Control group: 5 (-100 to 321), SD=11, n=36 p<0.001 <u>Mean change (range) % in frequency of atonic seizures</u> Intervention group: -44 (-100 to 145), SD=94, n=28 Control group: -7 (-88 to 57), SD=13, n=22 p=0.02 <u>Mean change (range) % in frequency of generalised tonic-clonic seizures</u> Intervention group: -40 (-100 to 206), SD=59, n=16 Control group: 12 (-100 to 293), SD=15, n=13 p=0.017 <u>Treatment cessation due to adverse drug effects during the</u>	participants randomised **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined 4.2: Probably no 4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **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 **Other information** Raw data was not provided for the change from baseline among the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	drug or alcohol abuse • Those who had recently received corticotropin, were following ketogenic diets • Those with inadequate supervision from parents/ guardians			maintenance period Intervention group: 1/37 Control group: 1/36 Mortality during the maintenance period Intervention group: 0/37 Control group: 0/36	neuropsychological tests performed, therefore it has not been reported
Full citation Glauser, T., Kluger, G., Sachdeo, R., Krauss, G., Perdomo, C., Arroyo, S., Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome, Neurology, 70, 1950-1958, 2008 **Ref Id** 1080418 **Country/ies where the study was carried out** Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and USA **Study type**	**Sample size** N=138 (n=74 allocated to rufinamide and n=64 allocated to placebo) **Characteristics** Age, years, median (range) Intervention: 13 (4 to 35) Control: 10.5 (4 to 37) Males, n (%) Intervention: 46 (62.2) Control: 40 (62.5) Duration of LGS, median years (range) Intervention: 7.9 (0.1 to 32.7)	**Interventions** Rufinamide versus placebo	**Details** The study consisted of a 28 day baseline period followed by a 84 day double blind phase. For the ITT analyses, all 84 days were included (14 day titration period + 70 day maintenance period). Randomisation was produced at the country/center level and were assigned with sequential numbers during the first visit. Patients and assessors were blinded to treatment	**Results** *Primary outcomes* Reduction in total seizure frequency >50% after 28 days Intervention group: 23/74 Control group: 7/64 Improvement in seizure severity at the end of the double-blind phase Intervention group: 39/73 Control group: 19/62 Reduction in drop-attacks Median (range)	**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, computer generated random numbers 1.2: No information was provided regarding randomisation concealment 1.3: No baseline differences between intervention groups suggesting a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To assess the effectiveness of rufinamide in people with LGS **Study dates** March 1998 and November 2000 **Source of funding** Eisai Pharmaceutical, conducted by Novartis Pharmaceutical	Control: 7.5 (0.1 to 34.1) **Inclusion criteria** • Those aged between 4 and 30 years • Those with a history of multiple seizure types, including atypical absence seizures and drop attacks • Those with a minimum of 90 seizures in the month prior to trial entry • EEG showing a pattern of slow spike and wave complexes • > 18kgs • 1 to 3 ASMs in a fixed dose **Exclusion criteria** • Not reported		allocation. Follow-up: median 84 days (no measure of variability was reported)	reduction in the intervention group -42.5 (-100.0 to 1190.8), n=73 Median (range) reduction in the control group 1.4 (-100 to -709.6), n=60 p<0.0001 <u>% of patients with reported serious side effects</u> Intervention group: 2/74 Control group: 2/64 <u>Treatment cessation due to adverse drug effects</u> Intervention group: 6/74 Control group: 1/64	randomisation problem **Domain 2: Deviations from intended** interventions: Low risk 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for all participants randomised **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined 4.2: Probably no 4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 6: Overall judgment of bias: Low risk of bias The study is judged to be at low risk of bias for all domains **Other information** Social functioning could not be reported because SD of the mean was not reported
Full citation Motte, J., Trevathan, E., Arvidsson, J. F. V., Barrera, M. N., Mullens, E. L., Manasco, P., Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome, New England Journal of Medicine, 337, 1807-1812, 1997 **Ref Id** 1080908 **Country/ies where the study was carried out** France, USA, UK, Spain **Study type** Randomised controlled trial	**Sample size** N= 169 (n= 79 in the lamotrigine group and n=90 in the placebo group) **Characteristics** Age, years, mean (SD) Intervention: 9.6 (5.2) Control:10.9 (5.9) Males, n (%), p= 0.02 Intervention: 54 (68) Control: 45 (50) Moderate or severe learning disability, n (%) Intervention: 73 (92) Control: 82 (91)	**Interventions** Lamotrigine versus placebo in addition to patients' standard antiepileptic-drug regimens	**Details** A 4-week base-line period in which all participants received placebo was followed by a 4 weeks single blind baseline period. Participants were then assigned to one of four dosing regimens according to concomitant valproate use and body weight. Method of randomisation was not reported. Participants and assessors were blinded to treatment allocation.	**Results** *Primary outcomes* Reduction in seizure frequency >50% Intervention group: 26/79 Control group: 14/90 Reduction in drop attacks, median % (IQR was not reported) Intervention group: -34%, n= 75 Control group: -16%, n=90 p=0.01 Treatment cessation due to	**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 was provided to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: The intervention group had more males than the control group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effectiveness of lamotrigine in people with Lennox-Gastaut syndrome **Study dates** February 1994 - November 1995 **Source of funding** Glaxo Wellcome	**Inclusion criteria** • Those between 3 and 25 years old • >1 type of predominantly generalised seizure during the last year • Those <11 years old at the time of onset • Seizures every other day with a similar average frequency • Those with intellectual impairment or a clinical impression of intellectual deterioration **Exclusion criteria** • Those with progressive neurodegenerative disorder • Those who were receiving more than three antiepileptic drugs • Those who weighed less than 15 kg and were taking valproate		Follow-up: 16 weeks (no measure of variability was reported)	<u>adverse drug effects</u> Intervention group: 3/79 Control group: 7/90	(p=0.02) **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Nearly all, n=10 were not enrolled because of lack of compliance **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgement of bias: Some concerns** The study is judged

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					to have some concerns in at least one domain
Full citation Ng, Y. T., Conry, J. A., Drummond, R., Stolle, J., Weinberg, M. A., Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome, Neurology, 77, 1473-1481, 2011 **Ref Id** 818717 **Country/ies where the study was carried out** USA, Europe, India and Australia **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of clobazam in people with Lennox-Gastaut syndrome **Study dates** August 2007 to December 2009 **Source of funding**	**Sample size** N=238 (n=59 randomised to placebo, n=58 randomised to clobazam 0.25 mg/kg/day [low dose], n=62 randomised to clobazam 0.5 mg/kg/day [medium dose], and n=59 randomised to clobazam 1 mg/kg/day [high dose]) **Characteristics** Age, mean years (SD) Placebo group: 13 (9.2) Low dose group: 10.9 (7.2) Medium dose group: 14.1 (10.4) High dose group: 11.7 (8.5) Male, n (%) Placebo group: 38 (64.4) Low dose group: 36 (62.1) Medium dose group: 36 (58.1) High dose group: 34 (57.6) Baseline weekly seizure	**Interventions** Clobazam (low, medium and high dose) versus placebo	**Details** The study consisted of a 4-week baseline period, 3-week titration period, and a 12-week maintenance period. Approximately 50% of all patients were receiving concomitant valproic acid, valproate semisodium, or valproate sodium. Patients were assigned through central randomisation via an interactive voice response system to one of the 4 groups. Study was double-blind. Follow-up: 15 weeks (no measure of variability was reported)	**Results** *Primary outcomes* Reduction in seizure frequency >50% Placebo group: 18/57 Low dose group: 23/53 Medium dose group: 34/58 High dose group: 38/49 100% reduction in drop attacks Placebo group: 2/57 Low dose group: 4/53 Medium dose group: 7/58 High dose group: 12/49 % of patients with a change in medication dose Placebo group: 1/57 Low dose group: 4/53 Medium dose group: 9/58 High dose group:	**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, an interactive voice system was used 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: No, roughly 25% of those randomised did not have data available 3.2: Yes, analyses were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lundbeck Inc.	rate, mean (SD) Placebo group: 95.6 (168.2) Low dose group: 98.3 (198.5) Medium dose group: 58.8 (119.6) High dose group: 94.6 (152.2) **Inclusion criteria** • Those aged 2 to 60 years old • Weighing ≥12.5 kg • Onset of LGS before 11 years old **Exclusion criteria** • Not reported			15/49 % of patients with reported serious side effects Placebo group: 2/57 Low dose group: 3/53 Medium dose group: 6/58 High dose group: 5/49 Mortality Placebo group: 0/57 Low dose group: 0/53 Medium dose group: 0/58 High dose group: 0/49 Treatment cessation due to adverse drug effects Placebo group: 0/38 Low dose group: 1/36 Medium dose group: 4/36 High dose group: 5/34	intention to treat **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was analysed according to a protocol 5.2: No, eligible reported results for the outcome domain correspond to all intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Ohtsuka, Y., Yoshinaga,	N=59 (n=29 randomised	Concomitant	The study consisted of	*Primary outcomes*	Methodological limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
H., Shirasaka, Y., Takayama, R., Takano, H., Iyoda, K., Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: A randomized double-blind placebo-controlled trial in Japan, Epilepsy Research, 108, 1627-1636, 2014 **Ref Id** 1080978 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** To assess the efficacy of rufinamide as an adjunctive therapy in people with Lennox-Gastaut syndrome **Study dates** Not reported **Source of funding** Eisai Co. and a grant o the Japanese government	to rufinamide and n=30 randomised to placebo) **Characteristics** Age, years, mean (SD) Intervention: 16.0 (7.1) Control: 13.9 (6.1) Males, n (%) Intervention: 17 (60.7) Control: 19 (63.3) Time since diagnosis, mean years (SD) Intervention: 10.5 (7.1) Control: 9.3 (5.8) **Inclusion criteria** • People with Lennox-Gastaut syndrome taking between 1 and 3 anti-epileptic drugs • Those aged between 4 and 30 years old weighing > 15 kilos **Exclusion criteria** • Those who experienced <90 seizures during the 28 days prior entering the study • Those experiencing status epilepticus during the 28 days prior entering the	rufinamide versus placebo	a 4-week baseline, a 2-week titration, and a 10-week maintenance period. Eligible patients were randomised in a 1:1 ratio according to body weight. Most patients were concomitantly receiving 2 or 3 antiepileptic drugs. Follow-up: 28 days (no measure of variability was reported)	Reduction in seizure frequency >50% Intervention group: 7/28 Control group: 2/30 Reduction in tonic seizures Median reduction in intervention group= -24.2% Median reduction in the control group=-3.6%, p=0.031 Reduction in atonic seizures Median reduction in the intervention group= -63.1% Median reduction in the control group= -6.1%, p=0.221 Reduction in tonic-clonic seizures Median reduction in intervention group= -57.4% Median in control group= 2.4%, p=0.107 Reduction in tonic-clonic seizures The median percent change in the	assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 1.1: No information was provided to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: No, roughly 13% of those randomised did not have data available 3.2: Probably yes **Domain 4: Measurement of the**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	study			frequency of tonic-atonic seizures was −57.4% (n=2) in the rufinamide group and 2.4% (n=10) in the placebo group, p=0.107 % of patients with a dose reduction due to safety concerns Intervention group: 7/28 Control group: 1/30 Treatment cessation due to adverse drug effects Intervention group: 4/28 Control group: 1/30 % of patients with reported side effects Intervention group: 17/28 Control group: 5/30	**outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was analysed according to a protocol 5.2: No, eligible reported results for the outcome domain correspond to all intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias
Full citation Sachdeo, R. C., Glauser, T. A., Ritter, F., Reife, R., Lim, P., Pledger, G., A double-blind, randomized trial of topiramate in	**Sample size** N=98 (n=48 allocated to topiramate and n=50 allocated to placebo) **Characteristics**	**Interventions** Topiramate versus placebo	**Details** The trial consisted of a baseline phase followed by 4 weeks and a 11 week treatment phase.	**Results** *Primary outcomes* Reduction in major seizure frequency (drop attacks and tonic-clonic	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lennox-Gastaut syndrome, Neurology, 52, 1882-1887, 1999 **Ref Id** 1081125 Country/ies where the study was carried out USA **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy and safety of topiramate as an adjunctive treatment for Lennox-Gastaut syndrome **Study dates** Not reported **Source of funding** Not reported	Age, years, mean (SD) Intervention: 11.2 (6.2) Control: 11.2 (7.7) Males, n (%) Intervention: 25 (25) Control: 28 (58.3) **Inclusion criteria** Those aged 1 to 30 years Those with EEG showing a slow pike and wave pattern Those with seizure types such as drop attacks and atypical absence seizures Those with at least 60 seizures in the month prior joining the study **Exclusion criteria** Not reported		Randomisation was computer generated, and participants and investigators were concealed to treatment allocation. Follow-up: 11 weeks (no measure of variability was reported)	seizures) >50% Intervention group: 15/46 Control group: 4/50 Complete cessation of drop attacks Intervention group: 5/46 Control group: 0/50 Treatment cessation due to adverse drug effects Intervention group: 0/46 Control group: 0/50 % of patients with reported severe adverse side effects Intervention group: 11/46 Control group: 5/50 % of patients with dose reduction or temporary discontinuation of treatment Intervention group: 9/46 Control group: 3/50	**Domain 1: Randomisation: Low risk** 1.1: Yes, computer generated 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, nearlly all participants (no data was available for n=1) **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 5: Selection of the reported result: Low risk 5.1: Yes, data was analysed according to a protocol 5.2: No, eligible reported results for the outcome domain correspond to all intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias

AED(s): anti-epileptic drug(s); EEG: electrocardiogram; IQR: interquartile range; Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation

Appendix E – Forest plots

Forest plots for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Lennox-Gastaut syndrome?

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

Comparison 2: add-on low-dose clobazam versus add-on high-dose clobazam

Figure 2: Reduction in seizure frequency >50%

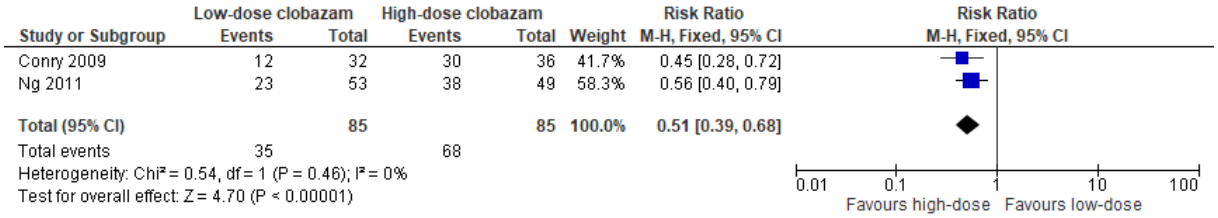


Figure 3: % of patients with reported severe side effects

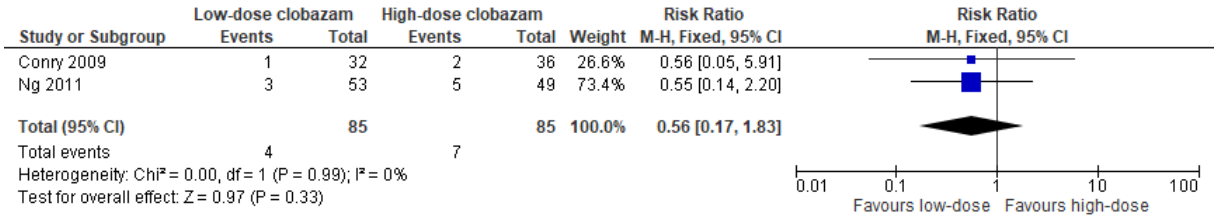
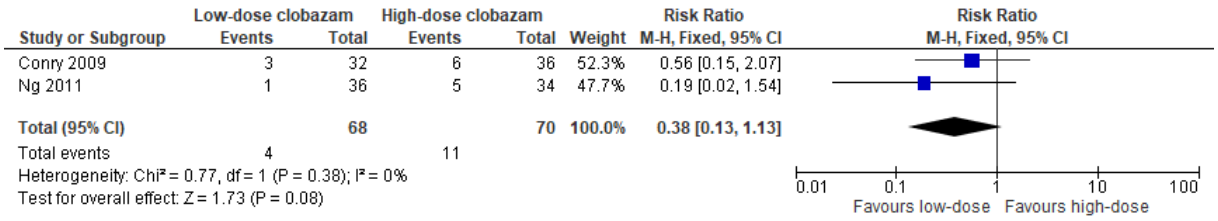


Figure 4: Treatment cessation due to adverse medication effects



Comparison 4: add-on rufinamide versus placebo

Figure 5: Reduction in seizure frequency >50%

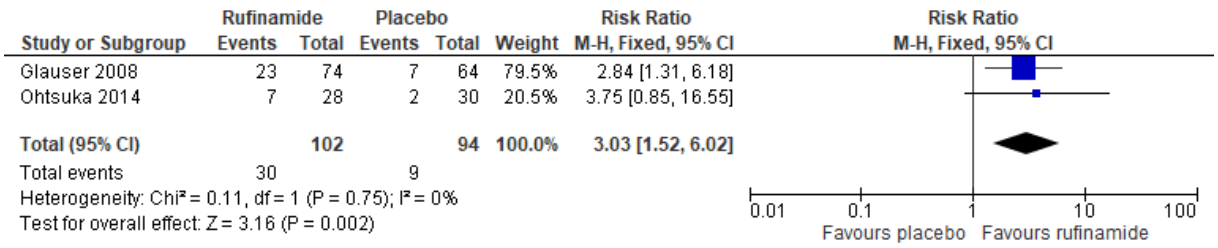


Figure 6: Treatment cessation due to adverse medication effects

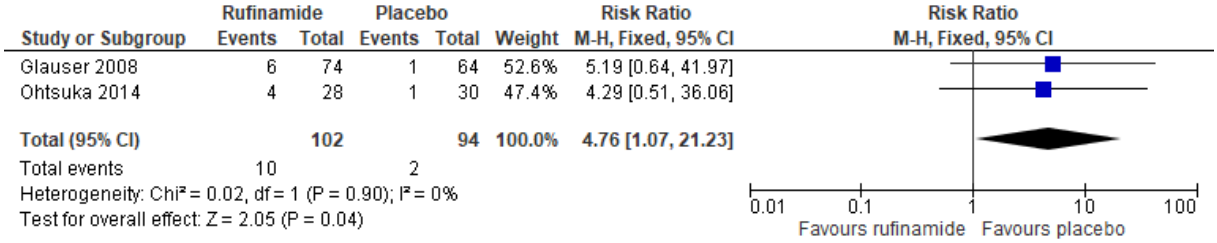
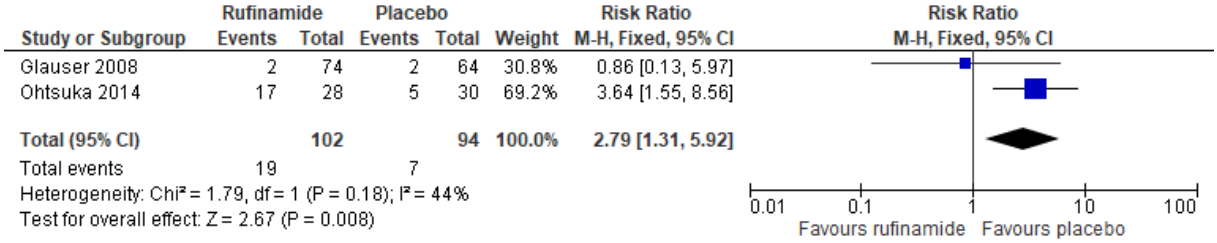


Figure 7: % of patients with reported serious side effects



Appendix F – GRADE tables

GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Lennox-Gastaut syndrome?

Table 11: Clinical evidence profile. Comparison 1: add-on rufinamide versus any other add-on antiseizure medication in paediatric patients

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Add-on any other antiepileptic medication	Relative (95% CI)	Absolute	Quality	Importance
Time to withdrawal of treatment due to adverse events or lack of seizure efficacy (paediatric patients) (median)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	12	Median time in the intervention group= 142 weeks	Median time in the control group= 28 weeks	⊕OOO VERY LOW	CRITICAL
% of patients with reported serious side effects (paediatric patients)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/25 (40%)	5/12 (41.7%)	RR 0.96 (0.42 to 2.19)	17 fewer per 1000 (from 242 fewer to 496 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse medication effects (paediatric patients)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/25 (8%)	1/12 (8.3%)	RR 0.96 (0.1 to 9.57)	3 fewer per 1000 (from 75 fewer to 714 more)	⊕OOO VERY LOW	CRITICAL
Social functioning changes: difference in total problems scores (measured with: CBCL; Better indicated by lower values) (paediatric patients)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Add-on any other antiepileptic medication	Relative (95% CI)	Absolute	Quality	Importance
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	25	12	-	MD 1.2 higher (7.6 lower to 9.99 higher)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise
3 95% CI crosses 2 MIDs (0.8 and 1.25)
4 95% CI crosses 2 MIDs (+/-0.5 x control group SD for social functioning changes=+/-6.55)

Table 12: Clinical evidence profile. Comparison 2: add-on low-dose clobazam versus add-on high-dose clobazam

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Add-on high-dose clobazam	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/85 (41.2%)	68/85 (80%)	RR 0.51 (0.39 to 0.68)	392 fewer per 1000 (from 256 fewer to 488 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mean reduction in drop attacks (Better indicated by lower values)												
1 (Conry 2009)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	36	-	MD 125 higher (55.3 to 194.7 higher)	⊕⊕OO LOW	CRITICAL
Complete reduction in drop attacks												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Add-on high-dose clobazam	Relative (95% CI)	Absolute	Quality	Importance
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	4/53 (7.5%)	12/49 (24.5%)	RR 0.31 (0.11 to 0.89)	169 fewer per 1000 (from 27 fewer to 218 fewer)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/53 (7.5%)	15/49 (30.6%)	RR 0.25 (0.09 to 0.69)	230 fewer per 1000 (from 95 fewer to 279 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with reported severe side effects												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/85 (4.7%)	7/85 (8.2%)	RR 0.56 (0.17 to 1.83)	36 fewer per 1000 (from 68 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/53 (0%)	0/49 (0%)	RD 0.00 (-0.04 to 0.04)	0 per 1000 (from 40 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse medication effects												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/68 (5.9%)	11/70 (15.7%)	RR 0.38 (0.13 to 1.13)	97 fewer per 1000 (from 137 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Social functioning changes: % of patients cosidered to be "improved" or "much improved" (patient/ carer global evaluation)												
1 (Conry 2009)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	16/29 (55.2%)	30/32 (93.8%)	RR 0.59 (0.42 to 0.83)	384 fewer per 1000 (from 159 fewer to 544 fewer)	⊕⊕OO LOW	IMPORTANT
Social functioning changes: % of patients cosidered to be "improved" or "much improved" (investigator evaluation)												
1 (Conry 2009)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/29 (44.8%)	30/32 (93.8%)	RR 0.48 (0.32 to 0.72)	488 fewer per 1000 (from 262 fewer to 637	⊕⊕⊕O MODERATE	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Add-on high-dose clobazam	Relative (95% CI)	Absolute	Quality	Importance
										fewer)		

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *95% CI crosses 1 MID (+/-0.5 x control group SD for mean reduction in drop attacks= +/- 114.5)*
[3] *95% CI crosses 1 MID (0.8)*
[4] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[5] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*

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

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on felbamate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Complete cessation of all seizures¥												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/37 (10.8%)	1/36 (2.8%)	RR 3.89 (0.46 to 33.17)	80 more per 1000 (from 15 fewer to 894 more)	⊕OOO VERY LOW	CRITICAL
Complete cessation of atonic seizures												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/28 (17.9%)	0/22 (0%)	RR 8.72 (0.51 to 149.75)	180 more per 1000 (from 20 more to 330 more)	⊕OOO VERY LOW	CRITICAL
Complete cessation of generalised tonic-clonic seizures												
1 (Felbamate study group	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	7/16 (43.8%)	1/13 (7.7%)	RR 5.69 (0.8 to	361 more per 1000	⊕⊕OO LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on felbamate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1993)									40.51)	(from 15 fewer to 1000 more)		
Mean change in frequency of all seizures¥ (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37	36	-	MD 31 lower (50 to to 11 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean change in frequency of atonic seizures (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	28	22	-	MD 37 lower (72.24 to 1.76 lower)	⊕⊕OO LOW	CRITICAL
Mean change in frequency of generalised tonic-clonic seizures (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	13	-	MD 52 lower (82.04 to 21.96 lower)	⊕⊕⊕O MODERATE	CRITICAL
Treatment cessation due to adverse medication effects												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/37 (2.7%)	1/36 (2.8%)	RR 0.97 (0.06 to 14.97)	1 fewer per 1000 (from 26 fewer to 388 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/37 (0%)	0/36 (0%)	RD 0.00 (-0.05 to 0.05)	0 per 1000 (from 50 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Global outcome variable (proxy outcome for quality of life) (Better indicated by higher values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	37	36	-	MD 0.57 higher (0.24 to 0.9 higher)	⊕⊕OO LOW	IMPORTANT

¥All seizures: atonic, tonic, generalised tonic-clonic, atypical absence, and complex partial
1 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)
3 95% CI crosses 1 MID (1.25)
4 Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)
5 95% CI crosses 1 MID (+/- 0.5 x SD in the control group for mean change in frequency of atonic seizures= +/- 6.5, for global outcome variable= +/-0.3425)

Table 14: Clinical evidence profile. Comparison 4: add-on rufinamide versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/102 (29.4%)	9/94 (9.6%)	RR 3.03 (1.52 to 6.02)	194 more per 1000 (from 50 more to 481 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Improvement in seizure severity												
1 (Glauser 2008)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/73 (53.4%)	19/62 (30.6%)	RR 1.74 (1.13 to 2.68)	227 more per 1000 (from 40 more to 515 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Reduction in drop-attacks (median)												
1 (Glauser 2008)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	73	60	Median (range) reduction in the interventio n group -42.5 (-100.0 to 1190.8)	Median (range) reduction in the control group 1.4 (-100 to -709.6), p<0.0001	⊕⊕OO LOW	CRITICAL
Reduction in tonic seizures (median)												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28	28	Median reduction in interventio n group= -24.2%	Median reduction in the control group= -3.6%, p=0.031	⊕⊕OO LOW	CRITICAL
Reduction in atonic seizures (median)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10	12	Median reduction in the interventio n group= -63.1%	Median reduction in the control group= -6.1%, p=0.221	⊕⊕OO LOW	CRITICAL
Reduction in tonic-clonic seizures (median)												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2	10	Median reduction in interventio n group= -57.4%	Median in control group= 2.4%, p=0.107	⊕⊕OO LOW	CRITICAL
% of patients with a dose reduction due to safety concerns												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	7/28 (25%)	1/30 (3.3%)	RR 7.5 (0.98 to 57.16)	217 more per 1000 (from 1 fewer to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment cessation due to adverse medication effects												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/102 (9.8%)	2/94 (2.1%)	RR 4.76 (1.07 to 21.23)	80 more per 1000 (from 1 more to 430 more)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with reported serious side effects												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/102 (18.6%)	7/94 (7.4%)	RR 2.79 (1.31 to 5.92)	133 more per 1000 (from 23 more to 366 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] *Evidence downgraded by 2 as ranges are subjectively very wide*
[2] *Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise*
[3] *The evidence was downgraded by 1 as the 95% CI crosses 1 MID (1.25)*

Table 15: Clinical evidence profile. Comparison 5: add-on lamotrigine versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on lamotrigine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Motte 1997)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/79 (32.9%)	14/90 (15.6%)	RR 2.12 (1.19 to 3.76)	174 more per 1000 (from 30 more to 429 more)	⊕⊕⊕O MODERATE	CRITICAL
Reduction in drop attacks												
1 (Motte 1997)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	75	90	Median reduction in intervention group= -34%	Median reduction in control group= -16% p=0.01	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse medication effects												
1 (Motte 1997)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/79 (3.8%)	7/90 (7.8%)	RR 0.49 (0.13 to 1.82)	40 fewer per 1000 (from 68 fewer to 64 more)	⊕OOO VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise*
[3] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 16: Clinical evidence profile. Comparison 6: add-on low-dose clobazam versus placebo

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Placebo	Relative (95% CI)	Absolute		
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23/53 (43.4%)	18/57 (31.6%)	RR 1.37 (0.84 to 2.24)	117 more per 1000 (from 51 fewer to 392 more)	⊕⊕⊕O MODERATE	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/53 (7.5%)	2/57 (3.5%)	RR 2.15 (0.41 to 11.26)	40 more per 1000 (from 21 fewer to 360 more)	⊕⊕OO LOW	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/53 (7.5%)	1/57 (1.8%)	RR 4.3 (0.5 to 37.27)	58 more per 1000 (from 9 fewer to 636 more)	⊕⊕OO LOW	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/53 (5.7%)	2/57 (3.5%)	RR 1.61 (0.28 to 9.28)	21 more per 1000 (from 25 fewer to 291 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/53 (0%)	0/57 (0%)	RD 0.00 (-0.03 to 0.03)	0 per 1000 (from 30 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse medication effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/36 (2.8%)	0/38 (0%)	RR 3.16 (0.13 to 75.2)	30 more per 1000 (from 40 fewer to 100 more)	⊕⊕OO LOW	CRITICAL

[1] *95% CI crosses 1 MID (1.25)*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[3] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*

Table 17: Clinical evidence profile. Comparison 7: add-on medium-dose clobazam versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on medium-dose clobazam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/58 (58.6%)	18/57 (31.6%)	RR 1.86 (1.2 to 2.88)	272 more per 1000 (from 63 more to 594 more)	⊕⊕⊕O MODERATE	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/58 (12.1%)	2/57 (3.5%)	RR 3.44 (0.75 to 15.86)	86 more per 1000 (from 9 fewer to 521 more)	⊕⊕OO LOW	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/58 (15.5%)	1/57 (1.8%)	RR 8.84 (1.16 to 67.57)	138 more per 1000 (from 3 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/58 (10.3%)	2/57 (3.5%)	RR 2.95 (0.62 to 14)	68 more per 1000 (from 13 fewer to 456 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/58 (0%)	0/57 (0%)	RD 0.00 (-0.03 to 0.03)	0 per 1000 (from 30 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse medication effects												
1 (Ng 2011)1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/36 (11.1%)	0/38 (0%)	RR 9.49 (0.53 to 170.17)	110 more per 1000 (from 0 to 220 more)	⊕⊕OO LOW	CRITICAL

[1] *95% CI crosses 1 MID (1.25)*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*

[3] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*

Table 18: Clinical evidence profile. Comparison 8: add-on high-dose clobazam versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on high-dose clobazam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/49 (77.6%)	18/57 (31.6%)	RR 2.46 (1.63 to 3.7)	461 more per 1000 (from 199 more to 853 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/49 (24.5%)	2/57 (3.5%)	RR 6.98 (1.64 to 29.68)	210 more per 1000 (from 22 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/49 (30.6%)	1/57 (1.8%)	RR 17.45 (2.39 to 127.38)	289 more per 1000 (from 24 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/49 (10.2%)	2/57 (3.5%)	RR 2.91 (0.59 to 14.33)	67 more per 1000 (from 14 fewer to 468 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/49 (0%)	0/57 (0%)	RD 0.00 (-0.04 to 0.04)	0 per 1000 (from 40 fewer to 40 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on high-dose clobazam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Treatment cessation due to adverse medication effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/34 (14.7%)	0/38 (0%)	RR 12.26 (0.7 to 213.79)	150 more per 1000 (from 20 more to 270 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[2] *Absolute effect range crosses 2 absolute MIDs (10 more and 10 fewer per 1000)*

Table 19: Clinical evidence profile. Comparison 9: 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 in major seizure frequency (drop attacks and tonic-clonic seizures) >50%												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/46 (32.6%)	4/50 (8%)	RR 4.08 (1.46 to 11.39)	246 more per 1000 (from 37 more to 831 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete cessation of drop attacks												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/46 (10.9%)	0/50 (0%)	RR 11.94 (0.68 to 210.06)	110 more per 1000 (from 10 more to 200 more)	⊕⊕OO LOW	CRITICAL

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
% of patients with reported severe side effects												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/46 (23.9%)	5/50 (10%)	RR 2.39 (0.90 to 6.36)	139 more per 1000 (from 10 fewer to 290 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment cessation due to adverse medication effects												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/46 (0%)	0/50 (0%)	RD 0.00 (-0.04 to 0.04)	0 per 1000 (from 40 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
% of patients with dose reduction or temporary discontinuation of treatment												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	9/46 (19.6%)	3/50 (6%)	RR 3.26 (0.94 to 11.31)	136 more per 1000 (from 4 fewer to 619 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[2] *The evidence was downgraded by 1 as the 95% CI crosses 1 MID (1.25)*
[3] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*

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 Lennox-Gastaut syndrome?

A global search of economic evidence was undertaken for all review questions in 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 Lennox-Gastaut syndrome?

Table 20: Economic evidence tables for antiseizure therapies in the treatment of seizures in people with Lennox-Gastaut syndrome

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Benedict 2010 **Country:** United Kingdom **Type of economic analysis:** Cost Effectiveness Analysis **Source of funding:** Eisai Ltd	**Interventions in detail:** Rufinamide (RUF) Lamotrogine (LTG) Topirimate (TPM) Standard therapy (ST)	**Population characteristics:** Not reported but as the base-line and effectiveness data are based on 3 studies identified in the accompanying clinical evidence review (Glauser 2008, Motte 1997, Sachdeo 1999). The studies had a mean age of 14, 10 and 11 years respectively. **Modelling approach:** Individual patient simulation model **Source of base-line and effectiveness data:** Baseline seizure frequency and 'drop attacks' was taken from Glauser 2008 discussed in detail in the accompanying clinical evidence review. Effectiveness data for Rufinamide was taken from patient level data Glauser 2008. Motte 1997 and Sachdeo 1999 were used to inform effectiveness for LTG, TPM and ST	**Drop Attack Analysis** **Total Costs (95% CI not reported)** • LTG: £50,975 • TPM: £50,728 • RUF: £50,985 • ST: £51,437 **Mean reduction in drop attacks (95% CI not reported)** • LTG: 26.3% • TPM: 27.4% • RUF: 30.4% • ST: 24.2% **ICER for TPM (cost per 1% reduction in drop attacks):** • Vs LTG: Dominated • Vs RUF: £62 • Vs ST: Dominated **Total Seizures Analysis** **Total Costs (95% CI not reported)** • LTG: £37,064 • TPM: £38,557	**Perspective:** • UK NHS & PSS **Currency:** • UK pound sterling (£) **Cost year:** • 2006/7 **Time horizon:** • 3 years (5 years investigated in sensitivity analysis) **Discounting:** • 3.5% costs per annum • 0% outcomes per annum **Applicability:** Partially Applicable-results not reported in quality adjusted life years. **Limitations:** Potentially serious limitations **Other comments:**

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		Source of cost data: Resource use was estimated through telephone interviews with 5 UK doctors specialising in paediatric epilepsy. Unit medication costs were taken from the BNF 2007. Other medical cost and adverse event costs were estimated from PSSRU 2006 costs and NHS reference costs 2005/6. **Source of QoL data:** Utility values were not applied in the model.	• RUF: £38,828 • ST: £38,366 **Mean reduction in seizures (95% CI not reported)** • LTG: 25.8% • TPM: 25.1% • RUF: 27.0% • ST: 22.1% **ICER for LTG (cost per 1% reduction in seizures):** • Vs TPM: Dominated • Vs RUF: £2151 • Vs ST: Dominated	Unclear why different analyses result in different total costs.
Author & year: Verdian 2010 **Country:** United Kingdom **Type of economic analysis:** Cost Utility Analysis **Source of funding:** Eisai Ltd	**Interventions in detail:** Rufinamide (RUF) Lamotrogine (LTG) Topirimate (TPM)	**Population characteristics:** Not reported but as the base-line and effectiveness data are based on 3 studies identified in the accompanying clinical evidence review (Glauser 2008, Motte 1997, Sachdeo 1999). The studies had a mean age of 14, 10 and 11 years respectively. **Modelling approach:** Markov Model **Source of base-line and effectiveness data:** An indirect treatment comparison of 3 studies (Glauser 2008, Motte 1997, Sachdeo 1999) included in the	**Total Costs (95% CI)** • LTG: £21,783 (£17,309-£26,887) • TPM: £23,360 (£18,972-£28,927) • RUF: £24,992 (£20,928-£29,910) **QALYs (95% CI)** • LTG: 1.42 (1.27-1.57) • TPM: 1.36 (1.21-1.53) • RUF: 1.44 (1.30-1.59) **Incremental Costs for RFU (95% CI)** • Vs LTG: £3,209 (-£1,392-£4,935) • Vs TPM: £1,632 (-£189-£3,523) **Incremental QALYs for RFU (95% CI)** • Vs LTG: 0.021 (0.081-0.120) • Vs TPM: 0.079 (0.039-0.179) **ICER for RFU (cost per QALY)**	**Perspective:** • UK NHS & PSS **Currency:** • UK pound sterling (£) **Cost year:** • 2006/7 **Time horizon:** • 3 years (5 years investigated in sensitivity analysis) **Discounting:** • 3.5% costs per annum • 3.5% outcomes per annum

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		accompanying clinical evidence review was used to estimate treatment effectiveness and proportion of treatment limiting adverse events. **Source of cost data:** Resource use was estimated based on a survey of doctors specialising in paediatric epileptology. Drug and other medical cost and adverse event costs were estimated from PSSRU 2007 costs and NHS reference costs 2006/7 **Source of QoL data:** Health state utilities were elicited from 119 members of the UK general population using time trade-off methodology. These estimated utility values were not reported in the published paper.	• Vs LTG: £154,831 • Vs TPM: £20,538 **Deterministic sensitivity analysis:** Results were most sensitive to transition probabilities between health states associated with the ASMs. Changes to other parameters, discounting rate and time horizon resulted in comparable results. **Probabilistic sensitivity analysis:** *Probability RUF cost effective at £20,000 per QALY threshold compared to:* • TPM: 52% • LTG: 8% *Probability RUF cost effective at £30,000 per QALY threshold compared to:* • TPM: 65% • LTG: 15% No probabilistic sensitivity analysis presented which compared all three interventions simultaneously	**Applicability:** Directly Applicable **Limitations:** Potentially serious limitations. There is a lack of transparency around a number of key parameters including utilities and effectiveness. The study is also funded by the manufacturer of Rufinamide. **Other comments:** LGS is considered an orphan disease by the European Medicines Agency. NICE typically relax their threshold of £20,000 at which new technologies are recommended when considering drugs for such conditions.

ASM: antiseizure medication; BNF: British National Formulary; CEA: cost effectiveness analysis; CI: confidence interval; CUA: cost utility analysis; ICER: incremental cost effectiveness ratio;LGS; Lennox-Gastaut Syndrome LTG: lamotrigine; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality adjusted life year; QoL: quality of life. RUF: rufinamide; ST: standard therapy TPM: topiramate; 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 Lennox-Gastaut syndrome?

Table 21: Economic evidence profile

Table 22: <Insert Table Title here>

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Author & year: Benedict 2010 **Country:** United Kingdom **Interventions:** Rufinamide (RUF) Lamotrogine (LTG) Topirimate (TPM) Standard therapy(ST) **Population:** People with Lennox-Gastaut syndrome	Potentially serious limitationsa	Partially applicableb	**Type of economic analysis:** CEA **Time horizon:** 3 years **Primary measure of outcome:** Cost per 1% increase in successfully treated patient	Drop attack analysis vs ST TPM: -£709 LTG: -£462 RUF: -£452 Total seizures analysis vs ST TPM: £191 LTG: -£1,302 RUF: £462	**Drop attack analysis vs ST** (% reduction) TPM: 3.2% LTG: 2.1% RUF: 6.2% **Total seizures analysis vs ST** (% reduction) TPM: 3.0% LTG: 3.7% RUF: 4.9%	**ICER for TPM (cost per 1% reduction in drop attacks):** Vs LTG: Dominated Vs RUF: £62 Vs ST: Dominated **ICER for LTG (cost per 1% reduction in seizures):** Vs TPM: Dominated Vs RUF: £2151 Vs ST: Dominated	**Deterministic sensitivity analyses**: Results were robust to various sensitivity analyses **PSA:** *Willingness to pay for 1% reduction in drop attacks and total seizures for 80% probability RUF prefered option:* Drop attack: £250 Total seizures: £900

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Author & year: Verdian 2010 **Country:** United Kingdom **Interventions:** Rufinamide (RUF) Lamotrogine (LTG) Topirimate (TPM) **Population:** Children with Lennox-Gastaut syndrome	Potentially serious limitationsc	Directly applicabled	**Type of economic analysis:** CUA **Time horizon:** 3 years **Primary measure of outcome:** Cost per QALY	**Incremental costs for RUF Vs** TPM: £1,632 LTG: £3,209	**Incremental QALYS for RUF Vs** TPM: 0.079 LTG: 0.021	**Cost per additional QALY** RUF vs TPM: £20,538 RUF vs LTG: £154,831	**Deterministic sensitivity analyses:** Results were most sensitive to transition probabilities between health states associated with the ASMs. Changes to other parameters, discounting rate and time horizon resulted in comparable results. **PSA:** Probability RUF cost effective at £20k threshold Vs TPM 52% VS LTG 8% Probability RUF cost effective at

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
							£30k threshold Vs TPM 65% VS LTG 15%

ASM: antiseizure medication; CEA: cost effectiveness analysis CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; LTG: lamotrigine; QALY: quality adjusted life year; RUF: rufinamide; ST: standard therapy TPM: topiramate; VS: versus

1

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 Lennox-Gastaut syndrome?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Lennox-Gastaut syndrome?

Clinical studies

Table 23: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Al-Banji, M. H., Zahr, D. K., Jan, M. M., Lennox-gastaut syndrome: Management update, Neurosciences, 20, 207-212, 2015	Narrative review, references checked for inclusion
Arzimanoglou, A., Ferreira, J. A., Satlin, A., Mendes, S., Williams, B., Critchley, D., Schuck, E., Hussein, Z., Kumar, D., Dhadda, S., et al.,, Safety and pharmacokinetic profile of rufinamide in pediatric patients aged less than 4 years with Lennox-Gastaut syndrome: an interim analysis from a multicenter, randomized, active-controlled, open-label study, European journal of paediatric neurology: EJPN, 20, 393â□□402, 2016	No relevant outcomes were reported
Arzimanoglou, A., French, J., Blume, W. T., Cross, J. H., Ernst, J. P., Feucht, M., Genton, P., Guerrini, R., Kluger, G., Pellock, J. M., Perucca, E., Wheless, J. W., Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology, The Lancet Neurology, 8, 82-93, 2009	Narrative review; references checked for inclusion
Auvin, S., Williams, B., McMurray, R., Kumar, D., Perdomo, C., Malhotra, M., Novel seizure outcomes in patients with Lennox-Gastaut syndrome: Post hoc analysis of seizure-free days in rufinamide Study 303, Epilepsia Open, 4, 275-280, 2019	Post-hoc analysis of Arzimanoglou 2019
Borrelli, S., El Tahry, R., Therapeutic approach to Lennox-Gastaut syndrome: a systematic review, Acta Neurologica Belgica, 119, 315-324, 2019	Systematic review; insufficient data to allow extraction
Caraballo, R. H., Flesler, S., Reyes Valenzuela, G., Fortini, S., Chacon, S., Ross, L., Noli, D., Sulthiame add-on therapy in children with Lennox-Gastaut syndrome: A study of 44 patients, Seizure, 62, 55-58, 2018	Not a randomised trial
Caraballo, R. H., Fortini, S., Fresler, S., Armeno, M., Ariela, A., Cresta, A., Mestre, G., Escobal, N., Ketogenic diet in patients with Lennox-Gastaut syndrome, Seizure, 23, 751-5, 2014	Not a randomised trial
Carmant, L., Whiting, S., Lennox-Gastaut syndrome: An update on treatment, Canadian Journal of Neurological Sciences, 39, 702-711, 2012	Narrative review; references checked for inclusion
Chung, S. S., Gidal, B. E., Lemming, O. M., Karnik-Henry, M., Hackler, E., Tolbert, D., Tworek, D. M., Sayeed, S., Combination AED treatment with clobazam in patients with lennox-gastaut syndrome: post hoc analyses of the contain study, Neurology, 90, 2018	Conference abstract
Conry, J. A., Ng, Y. T., Kernitsky, L., Mitchell, W. G., Veidemanis, R., Drummond, R., Isojarvi, J., Lee, D., Paolicchi, J. M., Stable dosages of clobazam for Lennox-Gastaut syndrome are associated with sustained drop-seizure and total-seizure improvements over 3 years, Epilepsia, 55, 558â□□567, 2014	Open-label extension study; all participants received clobazam and no comparison group was included

Study	Reason for Exclusion
Coppola, G., Grosso, S., Franzoni, E., Veggiotti, P., Zamponi, N., Parisi, P., Spalice, A., Habetswallner, F., Fels, A., Capovilla, G., Verrotti, A., Mangano, S., Balestri, A., Curatolo, P., Pascotto, A., Rufinamide in children and adults with Lennox-Gastaut syndrome: first Italian multicenter experience, Seizure, 19, 587-91, 2010	Not a randomised trial
Cramer, J. A., Sapin, C., Francois, C., Indirect comparison of clobazam and other therapies for Lennox-Gastaut syndrome, Acta Neurologica Scandinavica, 128, 91-9, 2013	No relevant outcomes were reported. This study performed indirect comparisons and, due to differences in how outcomes were reported across studies, only a Cohen's *d* effect size was calculated and reported. Studies included in this paper had already been included in the evidence review
Donaldson, J. A., Glauser, T. A., Olberding, L. S., Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut syndrome), Epilepsia, 38, 68-73, 1997	Not a randomised trial
Duchowny, M., Gilman, J., Messenheimer, J., Womble, G., Risner, M., Ayala, R., Konkol, R., Campbell, R., Crumrine, P. K., Cruse, R. P., Delgado, M., Fountain, N., Enlow, T., Fakhoury, T. A., Casadonte, J., Frank, L. M., Graf, W., Griebel, M. L., Griesemer, D. A., Wannamaker, B., Olson, D. M., Silverstein, F., Hurst, D., Jackson, A., Laxer, K. D., Bluestone, D., Maria, B., Lassiter, A., Levisohn, P. M., Libenson, M., Mitchell, W., Montouris, G., Murphy, J., Oommen, K. J., Park, Y. D., Parks, B. R., Snodgrass, S., Pellock, J. M., Ramsay, E., Ritter, F. J., Schimschock, J. R., Khan, A., Shuman, R., Tennison, M., Cheng, R. D., Turk, W., Wise, M. S., Bebin, E., Gonzalez, A., Ruiz, M., Gonzalez, R. C., Llamosa, G., Saiers, J., Long-term tolerability and efficacy of lamotrigine in pediatic patients with epilepsy, Journal of Child Neurology, 17, 278-285, 2002	Open label study; all participants received lamotrigine and no comparison group was included
Eriksson, A. S., Nergårdh, A., Hoppu, K., The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study, Epilepsia, 39, 495â□□501, 1998	Treatment effects were not reported by treatment arm for the Lennox-Gastaut subgroup of children
Freeman,J.M., Vining,E.P., Kossoff,E.H., Pyzik,P.L., Ye,X., Goodman,S.N., A blinded, crossover study of the efficacy of the ketogenic diet, Epilepsia, 50, 322-325, 2009	Treatment effects were not reported by treatment arm
Glauser, T. A., Levisohn, P. M., Ritter, F., Sachdeo, R. C., Topiramate in Lennox-Gastaut syndrome: Open-label treatment of patients completing a randomized controlled trial, Epilepsia, 41, S86-S90, 2000	Open-label extension study; all participants received topiramate and no comparison group was included
Glauser, T. A., Sachdeo, R. C., Ritter, F. J., Reife, R., Lim, P., A double-blind trial of topiramate in Lennox-Gastaut syndrome (LGS), Epilepsia, 38 Suppl 3, 131, 1997	Conference abstract
Glauser, T., Kluger, G., Krauss, G., Arroyo, S., Effects of rufinamide on the frequency of different seizure types in patients with Lennox-Gastaut syndrome: a long-term study, Epilepsia, 48 Suppl 7, 156, 2007	Conference abstract
Glauser, T., Kluger, G., Sachdeo, R., Krauss, G., Perdomo, C., Arroyo, S., Open-label extension study of the efficacy and safety of rufinamide adjunctive therapy in patients with Lennox-Gastaut syndrome, Epilepsia, 46 Suppl 6, 408, 2005	Conference abstract
Glauser, T., Kluger, G., Sachedo, R., Krauss, G., Perdomo, C., Arroyo, S., Efficacy and safety of rufinamide adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS): a multicenter, randomized, double-blind, placebo-controlled, parallel trial, Neurology, 64, 1826, 2005	Conference abstract

Study	Reason for Exclusion
Guerreiro, M. M., Manreza, M. L., Scotoni, A. E., Silva, E. A., Guerreiro, C. A., Souza, E. A., Ferreira, V. B., Reed, U. C., Diament, A., Trefiglio, R., Chiu, H. C., Bacaltchuk, J., A pilot study of topiramate in children with Lennox-Gastaut syndrome, Arquivos de Neuro-Psiquiatria, 57, 167-75, 1999	Not a randomised trial
Isojarvi, J., Gidal, B. E., Chung, S., Wechsler, R. T., Optimizing clobazam treatment in patients with Lennoxâ□“Gastaut syndrome, Epilepsy & Behavior, 78, 149â□□154, 2018	Post-hoc analysis of Conry 2009 and Ng 2011
Isojarvi, J., Lee, D., Peng, G., Sperling, M. R., Clobazam-treated patients with Lennox-Gastaut syndrome experienced fewer seizure-related injuries than placebo patients during trial OV-1012, Epilepsia, 57, e113-e116, 2016	Post-hoc analysis of Ng 2011
Jensen, P. K., Felbamate in the treatment of Lennox-Gastaut syndrome, Epilepsia, 35, S54-S57, 1994	Conference abstract
Kim, S. H., Eun, S. H., Kang, H. C., Kwon, E. J., Byeon, J. H., Lee, Y. M., Lee, J. S., Eun, B. L., Kim, H. D., Rufinamide as an adjuvant treatment in children with Lennox-Gastaut syndrome, Seizure, 21, 288-91, 2012	Not a randomised trial
Kluger, G., Bauer, B., Role of rufinamide in the management of Lennox-Gastaut syndrome (childhood epileptic encephalopathy), Neuropsychiatric Disease and Treatment, 3, 3-11, 2007	Narrative review; references checked for inclusion
Kluger, G., Glauser, T., Sachdeo, R., Krauss, G., Perdomo, C., Arroyo, S., Short-term and long-term efficacy and safety of rufinamide as adjunctive therapy in patients with inadequately controlled Lennox-Gastaut syndrome, Epilepsia, 47 Suppl 3, 139, 2006	Conference abstract
Kluger,G., Glauser,T., Krauss,G., Seeruthun,R., Perdomo,C., Arroyo,S., Adjunctive rufinamide in Lennox-Gastaut syndrome: A long-term, open-label extension study, Acta Neurologica Scandinavica, 122, 202-208, 2010	Open-label extension study; all participants received rufinamide and no comparison group was included
Kothare, S., Kluger, G., Sachdeo, R., Williams, B., Olhaye, O., Perdomo, C., Bibbiani, F., Dosing considerations for rufinamide in patients with Lennox-Gastaut syndrome: Phase III trial results and real-world clinical data, Seizure, 47, 25-33, 2017	Systematic review; observational studies were also included
Krauss, G. L., Glauser, T., Kluger, G., Arroyo, S., Long-term safety of rufinamide in patients with Lennox-Gastaut syndrome, Epilepsia, 48 Suppl 6, 359, 2007	Conference abstract
Montouris, G. D., Wheless, J. W., Glauser, T. A., The efficacy and tolerability of pharmacologic treatment options for Lennox-Gastaut syndrome, Epilepsia, 55 Suppl 4, 10-20, 2014	Systematic review; observational studies were also included
Mullens, L., Gallagher, J., Improved neurological function accompanies effective control of the Lennox-Gastaut syndrome with Lamictal: results of a multinational, placebo-controlled trial, Epilepsia, 37 Suppl 5, 163, Abstract no: 6.47, 1996	Conference abstract
Ng, Y. T., Conry, J., Mitchell, W. G., Buchhalter, J., Isojarvi, J., Lee, D., Drummond, R., Chung, S., Clobazam is equally safe and efficacious for seizures associated with Lennox-Gastaut syndrome across different age groups: Post hoc analyses of short- and long-term clinical trial results, Epilepsy and Behavior, 46, 221-226, 2015	Post-hoc analysis of Conry 2009 and Ng 2011
Ng, Y. T., Conry, J., Paolicchi, J., Kernitsky, L., Mitchell, W., Drummond, R., Isojarvi, J., Lee, D., Owen, R., Long-term safety and efficacy of clobazam for Lennox-Gastaut syndrome: interim results of an	Open-label extension study; all participants received clobazam and no comparison group was included

Study	Reason for Exclusion
open-label extension study, Epilepsy & Behavior, 25, 687â□□694, 2012	
Ohtsuka, Y., Yoshinaga, H., Shirasaka, Y., Takayama, R., Takano, H., Iyoda, K., Long-term safety and seizure outcome in Japanese patients with Lennox-Gastaut syndrome receiving adjunctive rufinamide therapy: An open-label study following a randomized clinical trial, Epilepsy Research, 121, 1-7, 2016	Open-label extension study; all participants received rufinamide and no comparison group was included
Oletsky, H., Kelley, K., Stertz, B., Reeves-Tyer, P., Flamini, R., Malow, B., Theodore, W., Nag,, D,, Garg,, et al.,, The efficacy of felbamate as add-on therapy to valproic acid in the Lennox-Gastaut syndrome (LGS), Epilepsia, 37 Suppl 5, 155, Abstract no: 6.13, 1996	Conference abstract
Paolicchi, J. M., Ross, G., Lee, D., Drummond, R., Isojarvi, J., Clobazam and Aggression-Related Adverse Events in Pediatric Patients with Lennox-Gastaut Syndrome, Pediatric Neurology, 53, 338-342, 2015	Post-hoc study for Ng 2011
Purcarin, G., Ng, Y. T., Experience in the use of clobazam in the treatment of Lennox-Gastaut syndrome, Therapeutic Advances in Neurological Disorders, 7, 169-176, 2014	Narrative review; references checked for inclusion
Sachdeo, S., Sachdeo, R. C., Kugler, S., An open label evaluation of topiramate in Lennox-Gastaut syndrome, Epilepsia, 37 Suppl 5, 112, 1996	Conference abstract
Stafstrom, C. E., Update on the management of Lennox-Gastaut syndrome with a focus on rufinamide, Neuropsychiatric Disease and Treatment, 5, 547-551, 2009	Narrative review; references checked for inclusion
Tolbert, D., Harris, S. I., Bekersky, I., Lee, D., Isojarvi, J., Withdrawal-related adverse events from clinical trials of clobazam in Lennox-Gastaut syndrome, Epilepsy and Behavior, 37, 11-15, 2014	No relevant outcomes reported
Trevathan, E., Motte, J., Arvidsson, J., Manasco, P., Mullens, L., Safety and tolerability of adjunctive Lamictal® for the treatment of the Lennox-Gastaut syndrome: results of a multinational, double-blind, placebo-controlled trial, Epilepsia, 37 Suppl 5, 202, 1996	Conference abstract
Trevathan, E., Mullens, E. L., Manasco, P., Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome, New England Journal of Medicine, 339, 851-2, 1998	Conference abstract
Vajda, F. J., Bladin, P. F., Parsons, B. J., Clinical experience with clobazam: a new 1,5 benzodiazepine in the treatment of refractory epilepsy, Clinical and experimental neurology, 21, 177-182, 1985	Sample included patients who did not have Lennox-Gastaut syndrome and results are not reported separately
Vassella, F., Rüdeberg, A., Da Silva, V., Pavlincova, E., Double-blind study on the anti-convulsive effect of phenobarbital and valproate in the Lennox syndrome, Schweizerische medizinische wochenschrift, 108, 713â□□716, 1978	Study in German
You, S. J., Kang, H. C., Kim, H. D., Lee, H. S., Ko, T. S., Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience, Brain & Development, 30, 287-90, 2008	Not a randomised trial

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 Lennox-Gastaut syndrome?

Research question

What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?

Why this is important

There is paucity of evidence from RCTs to support evidence-based treatment decisions in complex epilepsy syndromes when first-line therapy is not successful or not tolerated. These complex epilepsy syndromes are considerered developmental and epileptic encephalopathies due to the negative effects on cognition and behaviour. Seizures are frequently drug-resistant and, in some cases, these syndromes can have long-lasting effects on cognition. Research is needed to identify the safety and effectiveness of second-line antiseizure therapies in Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy (Doose syndrome).

Table 24: Research recommendation rationale

Research question	**What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?**
Why is this needed	
Importance to 'patients' or the population	To generate evidence to inform which treatments or combinations of treatments are most likely to result in the significant reduction of seizures and/or achieve the best balance between reducing the frequency of seizures and better outcomes for patients when first-line therapy is unsuccessful or not tolerated
Relevance to NICE guidance	This recommendation is to enable better guidance for the treatment of complex epilepsy syndrome
Relevance to the NHS	Evidence in this area would lead to optimisation of medicines usage in the holistic approach to treating people with complex epilepsy syndromes
National priorities	Complex epilepsy syndromes are a difficult to control form of epilepsy. Ongoing seizures result in risk of mortality and morbidity and injury
Current evidence base	Current evidence base to support treatment decisions when first-line therapy is not successful or not tolerated is limited
Equality	N/A
Feasibility	N/A

Research question	**What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?**
Other comments	Dravet syndrome and Lennox-Gastaut syndrome can present in adults and children. Doose syndrome and infantile spasms can extend into adulthood, so studies should not only be limited to children

N/A: not applicable

Table 25: Research recommendation modified PICO table

Criterion	Explanation
Population	People with complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome])
Intervention	• Antiseizure medications • Dietary treatments • Novel treatments • Surgical therapies
Comparator	• Placebo • No treatment • Combinations of above

Outcomes	Important outcomes:
	• Reduction in seizure frequency >50%
	• Ongoing seizures
	
	Tolerability:
	• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures, intolerable side effects, behavioural changes)
	• Adverse events, as assessed by:
	  ○ % of patients with reported side effects (as defined by trialists)
	  ○ Treatment cessation due to adverse medication effects
	
	Other outcomes:
	• Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)
	• Overall quality of life (reported by caregiver/the individual with epilepsy and as measured with a validated scale)

Study design	Multicentre/UK wide RCT

Criterion	Explanation
Timeframe	12 months
Additional information	Consider a concomitant qualitative research methodology that explores people with complex epilepsy syndromes and carers' views and experiences of the treatment approaches.

RCT: randomised controlled trial