National Institute for Health and Care Excellence

Final

Epilepsies in children, young people and adults

[I] Effectiveness of antiseizure therapies in the treatment of tonic or atonic seizures/drop attacks

NICE guideline NG217

Evidence reviews underpinning recommendations 5.5.1 to 5.5.6 in the 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

In January 2025, the section on the Committee's discussion of the evidence in this evidence review was updated following changes to recommendations that were made by a working group after Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Updates. The following MHRA updates were considered:

- guidance on the use of valproate,
- valproate use in people younger than 55 years,
- valproate use in women and girls, and
- valproate use in men.

Additionally, the working group also took into account the impact of the MHRA drug safety update concerning the use of topiramate.

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Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks?

Introduction

A drop attack may be defined as any event that may cause an individual to suddenly drop to the floor. In the context of epilepsy, these may be the result of atonic (generalised loss of tone) or tonic (sustained generalised body stiffening) seizures. These are characteristic seizures of Lennox-Gastaut syndrome, but are also seen in the context of other epilepsy syndromes and aetiologies. These seizure types are particularly relevant to quality of life as they may cause injury, through unpredictable sudden collapse to the floor (atonic seizures), or in the context of tonic seizures being thrown forward or backwards. The aim of this review is to determine which antiseizure therapies are effective in the treatment of tonic or atonic seizures/drop attacks.

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	People with confirmed epilepsy with tonic or atonic seizures/drop attacks
Intervention	The following antiseizure therapies and their combinations will be considered: • Brivaracetam • Ethosuximide • Felbamate • Ketogenic diet • Lamotrigine • Levetiracetam • Perampanel • Rufinamide • Sodium Valproate • Topiramate • Zonisamide
Comparison	• Any of the above and their combinations • No treatment/placebo
Outcomes	**Critical** • Seizure freedom (12 months data and short term, minimum 3 months with 100% freedom, of starting treatment) • Reduction of seizure frequency >50% • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)

	• Adverse effects, as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse events)
	  ○ Injuries due to drop attacks
	  ○ Treatment cessation due to adverse event (dichotomous outcome only)
	  ○ Mortality
	• Frequency of drop attacks
	
	Important
	• Health-related quality of life (validated tools only)

In order to ensure consistency with evidence report L on Lennox Gastaut syndrome, the committee agreed that it was appropriate to amend this protocol to include a number of antiseizure medications (ASMs) which they believed to be of relevance in the treatment of people with tonic or atonic seizures/drop attacks. These were:

- carbamazepine
- clobazam
- clonazepam
- gabapentin
- lacosamide
- oxcarbazepine
- pregabalin
- tiagabine
- vigabatrin

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, US, France, Greece, Italy, Poland	N= 37 infants with LGS with inadequate reponses 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 ASMs	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 drug 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) • Social functioning changes: % of patients considered to be “improved” or “very

Study	Population	Intervention	Comparison	Outcomes
				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 drug effects • Mortality
Dodson 1993 Follow-up of Felbamate study group 1993 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 seizure frequency >50% • Improvement in seizure severity • Reduction in drop attacks • Treatment cessation due to adverse drug effects • % of patients with reported serious side effects
Ohtsuka 2014 RCT Japan	N=59 people with LGS Age, years, mean (SD):	Add-on rufinamide n=29	Placebo n=30	• Reduction in seizure frequency > 50% • Reduction in tonic seizures • Reduction in atonic seizures • Reduction in tonic-clonic seizures

Study	Population	Intervention	Comparison	Outcomes
	Intervention group = 16 (7.1) Control group = 13.9 (6.1)	Maximum dose was 3200mg/day,		• % of patients with a dose reduction due to safety concerns • Treatment cessation due to adverse drug 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 of seizure frequency > 50% • Reduction in drop attacks • Treatment cessation due to adverse drug 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: add-on dose-ranging clobazam 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 to clobazam 1 mg/kg/day [high dose]	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 drug effects

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): intervention group: 11.2 (6.2) and control group: 11.2 (7.70)	Add-on topiramate n=48 Target dose was 6mg/kg/day	Placebo n=50	• Reduction of major seizure frequency (drop attacks and tonic-clonic seizures) >50% • Complete cessation of drop attacks • % of patients with reported severe side effects • Treatment cessation due to adverse drug 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 when compared with placebo; and add-on high-dose and medium-dose clobazam showed important differences when compared with low-dose clobazam. The majority of the evidence from these studies was very low to moderate quality, with most outcomes being seriously imprecise and 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: sodium valproate, clonazepam, ethosuximide, levetiracetam, zonisamide, lacosamide, carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, vigabatrin and ketogenic diet.

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.

Both papers were also included in evidence report L, as these economic analyses were relevant for both topic areas of the guideline (Benedict 2010; Verdian 2010). Data relevant to evidence report L are reported in this evidence report.

Excluded studies

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 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 number of seizures. Success was defined as a greater than 50% reduction in frequency compared to the baseline.

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 children 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 compared to TPM and LTG respectively. 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 committee agreed that seizure freedom, reduction of seizure frequency >50%, and frequency of drop attacks should be critical outcomes for this review as reducing the incidence of seizures/drop attacks is considered to be the main objective of treatment in this population.

The committee also agreed that time to withdrawal of treatment or change of medication, and adverse effects should be included as critical outcomes to ensure that data on treatment acceptability and tolerability were included.

Health-related quality of life was identified as an important outcome as tonic and atonic seizures/drop attacks can have a significant impact on a person's daily life as they can often cause injury.

The quality of the evidence

In order to ensure consistency with evidence report L on Lennox-Gastaut syndrome (because tonic and atonic seizures/drop attacks are a common feature in this syndrome), the committee agreed that it was appropriate to amend the protocol for this review to include a number of ASMs which they believe to also be of relevance in the treatment of people with tonic or atonic seizures/drop attacks. These were: carbamazepine, clobazam, clonazepam, gabapentin, lacosamide, oxcarbazepine, pregabalin, tiagabine, vigabatrin.

The review did not identify any evidence relating specifically to tonic or atonic seizures/drop attacks, except in the context of Lennox-Gastaut syndrome. However, the committee agreed that it was appropriate to use these data as the basis for their recommendations as people with Lennox-Gastaut experience tonic or atonic seizures. The committee were presented with data on 9 different comparisons relating to 5 different treatments; however, meta-analysis was only possible for 2 comparisons.

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 indicating uncertainly in the reliability of the data. Outcomes were most often downgraded due to risk of bias, with limited information provided regarding randomisation and allocation concealment. Outcomes were also downgraded due to imprecision arising as a result of small sample sizes and low event rates; which further limited confidence in the data.

Despite the lack of direct evidence from studies including population based on seizure type, the committee decided not to prioritise a research recommendation on this subject as they considered that other topics were of higher priority.

Benefits and harms

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

Tonic or atonic seizures/drop attacks cause muscle contractions that affect the whole body and cause loss of consciousness. Given the difficulties in treating tonic or atonic seizures/drop attacks, the range of syndromes of which they can feature and the impact that these can have on quality of life, the committee agreed to recommend that people who experience tonic and atonic seizures/drop attacks should be assessed by a neurologist with expertise in epilepsy with the aim of facilitating diagnosis, improving access to further investigations, and ensuring that appropriate treatment is provided. An appropriate diagnosis and timely treatment is key in preventing future seizures, which can have long-term consequences for the person, such as memory problems or severe injuries due to unpredictable sudden collapse to the floor or being thrown forwards or backwards. The involvement of a neurologist with expertise in epilepsy in the care of people with tonic or atonic seizures/drop attacks 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 strategy according to their seizure type, treatment goals and the preferences of the person and their family or carers, as appropriate. Treatment plans should be regularly reassessed, and its agreement should include a transparent explanation of the epilepsy type, severity and duration of adverse effects that the person with epilepsy may experience and how should these be managed. The person, their family and carers, should also be made aware that they should be taking the least amount of medicines as possible to be effective due to the side effects of being on numerous medications.

Tonic or atonic seizures are classified as generalised seizures. Based on the evidence reviewed in evidence report E on monotherapy for generalised tonic-clonic seizures, and given the absence of evidence of effective monotherapy treatments in this review, the committee agreed that sodium valproate was the most effective medication for treating myoclonic seizures and that this was also generally accepted across clinical practice. There was also evidence showing that add-on lamotrigine reduced seizure frequency when compared to placebo. It was noted that there is safety advice by the Medicines and Healthcare products Regulatory Agency (MHRA) on the use of valproate, valproate use by women and girls and valproate use by men has some specific safety warnings about sodium valproate. This provides specific advice and criteria for its usage. Given the the committee's decision that sodium valproate would be the most effective but that lamotrigine was also effective, it was

decided in January 2025 that they should both be options for first-line monotherapy treatment of tonic or atonic seizures. In relation to reproductive risks with sodium valproate, MHRA safety measures in women and girls able to have children and precautionary advice for boys and men were highlighted to ensure they are followed, discussed and reviewed. It was decided that if the first choice of treatment is unsuccessful the other of these options should be tried.

The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children and, as a result, recommended that lamotrigine should be used as first-line treatment in this population. There was some evidence that, when used as an add-on therapy, lamotrigine reduces seizure frequency, and the committee agreed that it was appropriate to extrapolate from this as lamotrigine is widely used in clinical practice for tonic or atonic seizures/drop attacks in women and girls able to have children and (including young girls who are likely to need treatment when they are old enough to have children). Nonetheless, the committee all agreed that in some cases, for example, if women have tried other medication and 2 specialists independently agree and document that there is no other effective and tolerated treatment, sodium valproate should be available as an option. The committee agreed that sodium valproate should only be prescribed after a full and clear discussion with the girl or woman, ensuring she understands all the potential risks and benefits. If sodium valproate is prescribed, clinicians must follow MHRA guidance, which includes enrolment in a pregnancy prevention programme, if appropriate. Precautionary advice for boys and men was also highlighted. The MHRA based the precautionary advice on 1 retrospective observational study indicating a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months before conception, compared with those born to men treated with lamotrigine or levetiracetam. Whilst it is unknown whether valproate has a causal role, it is important to make people aware of this association. Boys and men should be advised that effective contraception (condoms, plus contraception used by a female sexual partner) is recommended throughout the valproate treatment period and for 3 months after stopping valproate. Men taking valproate who are planning a family within the next year should be advised of the potential fertility risks and treatment options.

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 it is better tolerated. The committee also 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.

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

There was also evidence which suggested that clobazam, rufinamide and topiramate are effective and the committee agreed that it was appropriate to recommend these as second-line or add-on or alternative treatments. Clobazam is not licenced for children under 6 years old in the UK, but it can be on a named-patient basis. Although there was no evidence assessing the effectiveness of clobazam, rufinamide and topiramate as monotherapy treatment, 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. In January 2025 MHRA safety advice relating to topiramate was highlighted for the use in women of childbearing potential to ensure that the conditions of the Pregnancy Prevention Programme are fulfilled because of the risks of the medication to the unborn child.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.

The review also included information relating to a small number of other ASMs, however as this evidence was generally of low quality and did not report head to head comparisons, the committee did not consider it was appropriate to recommend these. The committee noted that ketogenic diets are successfully used in clinical practice in cases which are 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 of a neurologist with expertise in epilepsy as these are calculated individually, and the person's weight and ketone levels need to be monitored.

Felbamate was considered if all other treatment options for tonic or atonic seizures/drop attacks were not successful. Felbamate is not licensed in the UK but can be obtained on a named-patient basis and requires close monitoring for haematological and hepatic adverse effects associated with this drug. For these reasons the committee felt the use of felbamate required careful consideration by a neurologist with expertise in epilepsy.

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.

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 but one study 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 5.5.1-5.5.6.

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Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011 Oct 11;77(15):1473-81.

Ohtsuka 2014

Ohtsuka Y, Yoshinaga 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. 2014 Nov 1;108(9):1627-36.

Sachdeo 1999

Sachdeo RC, Glauser TA, Ritter FO, Reife R, Lim P, Pledger G, Topiramate YL Study Group. A double-blind, randomized trial of topiramate in Lennox–Gastaut syndrome. Neurology. 1999 Jun 1;52(9):1882-.

Verdian 2010

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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 tonic or atonic seizures/drop attacks?

Table 9: Review protocol for effectiveness of antiseizure therapies in the management of tonic or atonic seizures/drop attacks

Field	Content
PROSPERO registration number	CRD42020166880
Review title	Effectiveness of antiseizure therapies for tonic or atonic seizures/drop attacks
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks? Note: The review question has been amended to include the term “drop attacks” as both tonic or atonic seizures can be described (and often are in the literature) as such.
Objective	The objective of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have tonic or atonic seizures/drop attacks. This review will determine the effectiveness of drugs given alone (monotherapy) or as add-ons (combination therapy).
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare

Field	Content
	Searches will be restricted by: • Date: No limit • English language studies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Epilepsy with tonic or atonic seizures/ drop attacks
Population	Inclusion: People with confirmed epilepsy with tonic or atonic seizures/drop attacks. Exclusion: • Newborn babies (under 28 days) with acute symptomatic seizures • People with cardiogenic drop attacks • People with syncopal drop attacks.
Intervention	The following antiseizure therapies and their combinations will be considered: • Brivaracetam • Ethosuximide • Felbamate • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Perampanel • Rufinamide • Sodium Valproate • Topiramate • Zonisamide

Field	Content
Comparator	• Any of the above and their combinations • No treatment/placebo
Types of study to be included	• Systematic review of RCTs • RCTs
Other exclusion criteria	• Studies with a mixed population (this is, including children and young people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported. • Studies with a mixed population (this is, including people with epilepsy with different seizure types) will be excluded, unless subgroup analysis for epilepsy with tonic or atonic seizures/drop attacks has been reported. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias. • Corpus callostomy
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care)

Primary outcomes (critical outcomes)	• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment).
	
	Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as "time to 12 months seizure freedom", (this is, time to event: HR or mean time) followed by "achievement of 12 months seizure freedom" (RR). Minimum follow up data of 3 months will be included.
	
	• Reduction of seizure frequency >50%
	• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)
	• Adverse effects, as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse events)
	  ○ Injuries due to drop attacks
	  ○ Treatment cessation due to adverse event (dichotomous outcome only)
	  ○ Mortality
	• Frequency of drop attacks

Field	Content
Secondary outcomes (important outcomes)	• Health-related quality of life (validated tools only) Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.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. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria. Duplicate screening will not be undertaken for this review question. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and will include: study setting; design; aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of intervention and controls; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria, once the full version has been checked, will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reasons for its exclusion. All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data synthesis Where possible pairwise 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

Field	Content
	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. Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • by age (older people (>65 years old/adults (> 25 to 65 years old)/young people (>11 to 25 years old)/ infants and children (0 to 11 years old)) • 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. Minimal important differences (MIDs): • 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.

Field	Content	
	• 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)	Stratification If data is available, results will be presented separately by: • Those with and without learning difficulties/disabilities • Part or not part of underlying epilepsy syndrome (this is, if drop attacks occur as part of another syndrome or in isolation)	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	30th April 2020	
Anticipated completion date	2nd June 2021	

Field	Content		
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	The National Guideline Alliance 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 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.		

Field	Content
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166880
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; tonic seizures; atonic seizures; drop attacks
Details of existing review of same topic by same authors	Not applicable
Additional information	Not applicable
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: The Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; HTA: Health Technology Assessment; 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; RR: risk ratio; 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 tonic or atonic seizures/drop attacks?

Clinical

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

EMCare 1995 to 2021 April 07; Embase Classic+Embase 1947 to 2021 April 07; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 April 07, 2021
Date of last search: 07 April 2021

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

#	searches
1	(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.
2	ethosuximide/ use emczd, emcr, 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.
3	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
4	3 use emczd, emcr
5	diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycerides/
6	5 use ppez
7	((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.
8	or/4,6-7
9	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.
10	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
11	topiramate/ use emczd, emcr,ppez or (epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab.
12	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.
13	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
14	cannabidiol/ use emczd, emcr,ppez or (cannabidiol or epidiolex or nabidiolex).ti,ab.

#	searches
15	brivaracetam/ use emczd, emcr
16	(brivaracetam or brivlera or nubriveo or rikelta).ti,ab.
17	or/15-16
18	felbamate/ use emczd, emcr,ppez or (felbamate or felbamyl or felbamyl or felbatol or felbatol or taloxa or taloxa).ti,ab.
19	rufinamide/ use emczd, emcr or (banzel or inovelon or rufinamid* or xilep).ti,ab.
20	perampanel/ use emczd, emcr or (fycompa or perampanel).ti,ab.
21	or/2,8-14,17-20
22	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.
23	22 use ppez
24	(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.
25	24 use ppez
26	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.
27	26 use emczd, emcr
28	or/23,25,27
29	meta-analysis/
30	meta-analysis as topic/ or systematic reviews as topic/
31	"systematic review"/
32	meta-analysis/
33	(meta analy* or metanaly* or metaanaly*).ti,ab.
34	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
35	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
36	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
37	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
38	(search* adj4 literature).ab.
39	(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.
40	cochrane.jw.
41	((pool* or combined) adj2 (data or trials or studies or results)).ab.
42	(or/29-30,33,35-41) use ppez
43	(or/31-34,36-41) use emczd, emcr
44	or/42-43
45	or/28,44
46	1 and 21 and 45
47	limit 46 to english language
48	((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.)
49	48 use emez
50	((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.)
51	50 use mesz
52	49 or 51
53	47 not 52

Database(s): Cochrane Library
Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2021; Cochrane Central Register of Controlled Trials, Issue 4 of 12, April 2021
Date of last search: 07 April 2021

#	searches
1	mesh descriptor: [seizures] explode all trees
2	(((drop or akinetic or atonic or tonic) near/2 (attack* or epileps* or seizure* or convulsion*)) or ”brief seizure” or (tonic near/3 atonic near/3 (attack* or epileps* or seizure* or convulsion*))):ti,ab,kw
3	#1 or #2
4	((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
5	((crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
6	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
7	((epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)):ti,ab,kw
8	((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 “ergenyl chrono” or “ergenyl chromosphere” 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,kw
9	((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 “ergenyl chrono” or “ergenyl chromosphere” 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,kw
10	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
11	((cannabidiol or epidiolex or nabidiolex)):ti,ab,kw
12	((brivaracetam or brivlera or nubriveo or rikelta)):ti,ab,kw
13	((felbamate or felbamyl or felbamyl or felbatol or felbatol or taloxa or taloxa)):ti,ab,kw
14	((banzel or inovelon or rufinamid* or xilep)):ti,ab,kw
15	((fycompa or perampanel)):ti,ab,kw
16	mesh descriptor: [diet, carbohydrate-restricted] this term only
17	mesh descriptor: [dietary fats] explode all trees
18	mesh descriptor: [glycemic index] explode all trees
19	mesh descriptor: [diet, ketogenic] this term only
20	mesh descriptor: [triglycerides] explode all trees
21	(((adequate near/3 protein*) or atkin* or keto* or kd or (carbohydrate* near/5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulat*)) or (“high fat*” near/5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or “low carb*” or lchf or “low glyc* index treatment*” or lgit or (“medium chain” near/ (tryglyceride* or triglyceride*)) or mct*)):ti,ab,kw
22	{or #4-#21}
23	#3 and #22

Database(s): DARE; HTA database - CRD
Date of last search: 07 April 2021

#	Searches
1	mesh descriptor seizures explode all trees
2	(((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*)))
3	#1 or #2

Economic

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

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

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

#	searches
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

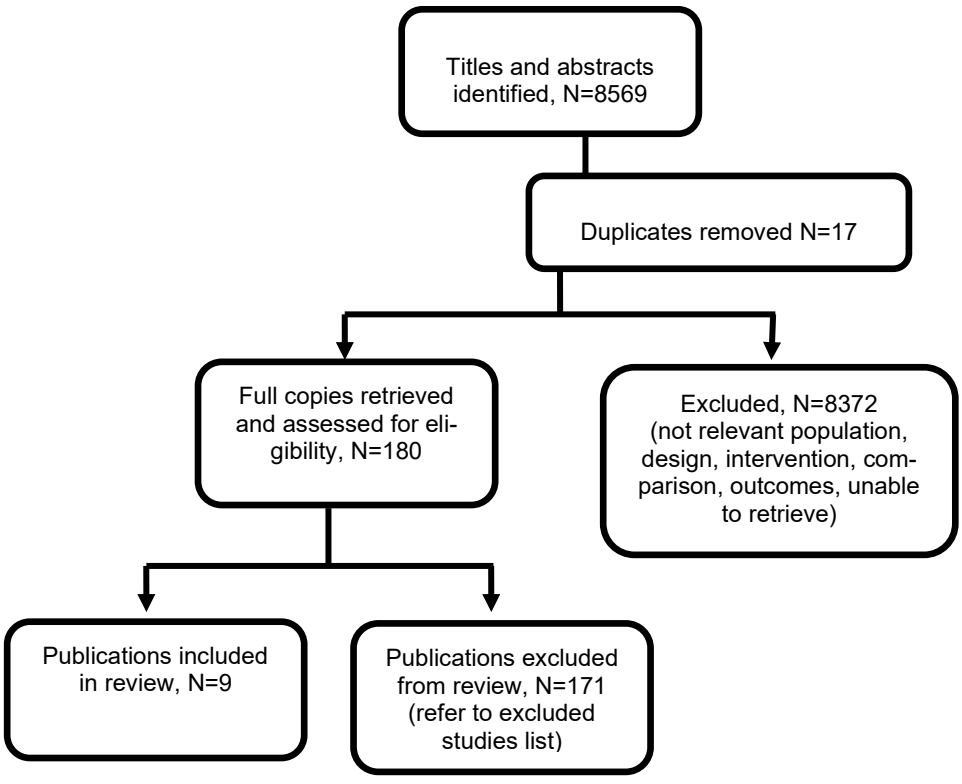
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”)
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)

#	searches
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 tonic or atonic seizures/drop attacks?

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 tonic or atonic seizures/drop attacks?

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 antiseizure medication' 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 antiseizure medication	**Details** Treatment duration: 106-weeks, including an initial 2-week titration phase and a 104-week maintenance phase After a baseline period where participants were monitored to assess whether 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 antiseizure medications. Follow-up: 110 weeks. Final follow-up visits occurred 4 weeks after the last dose of rufinamide or other add-on	**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	**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 label

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 (i.e h 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		AED at the end of the maintenance phase or after withdrawal from the study Randomisation method was not reported. Study was open label	<u>Treatment cessation due to adverse drug effects</u> Intervention group: 2/25 Control group: 1/12 *Secondary outcomes* <u>Social functioning changes: difference in total problems scores, mean difference between groups (95% CI)</u> 1.197 (-7.6 to 5.3), p =0.7083	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 risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					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** Not reported, study published in 2009	**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 antiseizure medications • At least 2 drop seizures per week	**Interventions** Low-dose clobazam (target dose of 25 mg/kg/day to a maximum of 10mg/day) or high-dose clobazam (target dose 1.0mg/kg/day to a maximum of 40mg/day)	**Details** Treatment duration: 3 week titration period followed by a 4-week maintenance period, and either an open-label extension study or, for patients not continuing into the open-label extension, a taper of up to 3 weeks. Follow-up: 11 weeks. Final visit occurred 1 week after final dose. 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"	**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: 2/36	**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 outcome data: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Ovation Pharmaceuticals.	**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			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: 30/32	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
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
Full citation Felbamate study group in Lennox-Gastaut	**Sample size** N=73 (n=37 randomised to the felbamate group	**Interventions**	**Details** Treatment duration: 14 day titration period and	**Results** *Primary outcomes*	**Limitations** Methodological limitations assessed using the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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	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 antiseizure medications 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 atypical absence seizures/ month during	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.	a 56 day maintenance period. Follow-up: 98 days. 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. Felbamate or placebo were added to the standard antiseizure medication regimen. Detailed estimate for quality of life outcome reported in Dodson 1993.	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	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 participants randomised **Domain 4: Measurement of the outcome: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	an 8 weeks prior to baseline • Those between 4 and 25 years **Exclusion criteria** • Those taking more than 2 antiseizure medications • 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 antiseizure therapy • Those with a history of drug or alcohol abuse • Those who had recently received			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</u>	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 neuropsychological tests performed, therefore it has not been reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	corticotropin, were following ketogenic diets • Those with inadequate supervision from parents/ guardians			the maintenance period Intervention group: 1/37 Control group: 1/36 Mortality during the maintenance period Intervention group: 0/37 Control group: 0/36	
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** Randomised controlled trial **Aim of the study** To assess the effectiveness of	**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) Control: 7.5 (0.1 to 34.1) **Inclusion criteria** • Those aged between 4 and 30 years	**Interventions** Rufinamide versus placebo	**Details** Treatment duration: 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). Follow-up: 84 days. 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 allocation.	**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) reduction in the intervention 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, computer generated random numbers 1.2: No information was provided regarding randomisation concealment 1.3: No baseline differences between intervention groups suggesting a randomisation problem **Domain 2: Deviations from intended** interventions: Low risk 2.1: No, double blind study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
rufinamide in people with LGS **Study dates** March 1998 and November 2000 **Source of funding** Eisai Pharmaceutical, conducted by Novartis Pharmaceutical	• 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			-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	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 **Domain 6: Overall judgment of bias: Low** risk of bias The study is judged to be at low risk of bias for all domains

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					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 **Aim of the study** To assess the effectiveness of lamotrigine in people with Lennox-Gastaut syndrome	**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) **Inclusion criteria** • Those between 3 and 25 years old • >1 type of predominantly generalised seizure during the last year	**Interventions** Lamotrigine versus placebo in addition to patients' standard antiseizure-medication regimens	**Details** Treatment duration: 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. Follow-up: 20 weeks. Method of randomisation was not reported. Participants and assessots 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 adverse drug effects Intervention group: 3/79 Control group: 7/90	**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 (p=0.02) **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates February 1994 - November 1995 **Source of funding** Glaxo Wellcome	• 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 antiseizure medications • Those who weighed less than 15 kg and were taking valproate				**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 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	**Sample size** N=238 (n=59 randomised to placebo, n=58 randomised to clobazam 0.25 mg/kg/day [low dose], n=62	**Interventions** Clobazam (low, medium and high dose) versus placebo	**Details** Treatment duration: The study consisted of a 4-week baseline period, 3-week titration period, and a 12-week	**Results** *Primary outcomes* Reduction in seizure frequency >50%	**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, 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** Lundbeck Inc.	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 rate, mean (SD) Placebo group: 95.6 (168.2) Low dose group: 98.3 (198.5) Medium dose group: 58.8 (119.6)		maintenance period. Follow-up: Not reported. 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.	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: 15/49 % of patients with reported serious side effects Placebo group: 2/57	**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 intention to treat **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	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			Low dose group: 3/53 Medium dose group: 6/58 High dose group: 5/49 <u>Mortality</u> Placebo group: 0/57 Low dose group: 0/53 Medium dose group: 0/58 High dose group: 0/49 <u>Treatment cessation due to adverse drug effects</u> Placebo group: 0/38 Low dose group: 1/36 Medium dose group: 4/36 High dose group: 5/34	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 Ohtsuka, Y., Yoshinaga, H., Shirasaka, Y., Takayama, R., Takano, H., Iyoda, K., Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: A randomized double-blind placebo-	**Sample size** N=59 (n=29 randomised to rufinamide and n=30 randomised to placebo) **Characteristics** <u>Age, years, mean (SD)</u> Intervention: 16.0 (7.1)	**Interventions** Concomitant rufinamide versus placebo	**Details** Treatment duration: The study consisted of a 4-week baseline, a 2-week titration, and a 10-week maintenance period.	**Results** *Primary outcomes* <u>Reduction in seizure frequency >50%</u> Intervention group: 7/28 Control group: 2/30	**Limitations** <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u> **Domain 1: Randomisation: Some concerns**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial in Japan, Epilepsy Research, 108, 1627-1636, 2014 **Ref Id** 1080978 **Country/ies where the study was carried out** Japan. **Study type** Randomised controlled trial. **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 from the Japanese government.	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 antiseizure medications • 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 study		Follow-up: 84 days. Eligible patients were randomised in a 1:1 ratio according to body weight. Most patients were concomitantly receiving 2 or 3 antiseizure medications.	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 frequency of tonic-atonic seizures	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 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
				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	**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 Lennox-Gastaut syndrome,	**Sample size** N=98 (n=48 allocated to topiramate and n=50 allocated to placebo) **Characteristics** Age, years, mean (SD)	**Interventions** Topiramate versus placebo	**Details** Treatment duration: 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 seizures) >50%	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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	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		Follow-up: 11 weeks. Randomisation was computer generated, and participants and investigators were concealed to treatment allocation.	Intervention group: 15/46 Control group: 4/50 <u>Complete cessation of drop attacks</u> Intervention group: 5/46 Control group: 0/50 <u>Treatment cessation due to adverse drug effects</u> Intervention group: 0/46 Control group: 0/50 <u>% of patients with reported severe adverse side effects</u> Intervention group: 11/46 Control group: 5/50 <u>% of patients with dose reduction or temporary discontinuation of treatment</u> Intervention group: 9/46 Control group: 3/50	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

ASM(s): antiseizure medication(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 tonic or atonic seizures/drop attacks?

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%

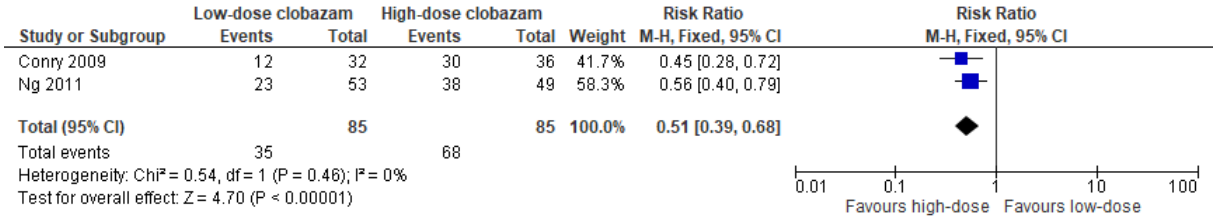


Figure 3: % of patients with reported severe side effects

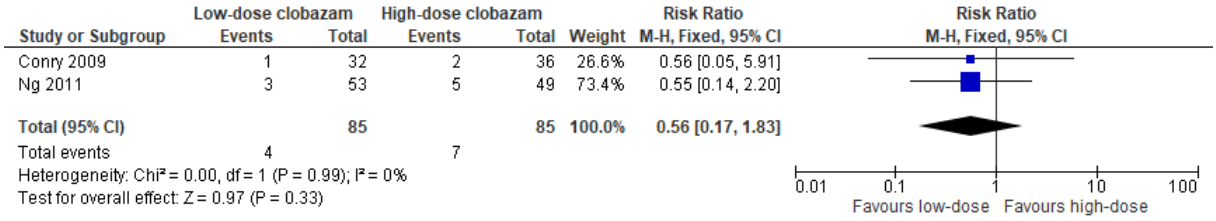
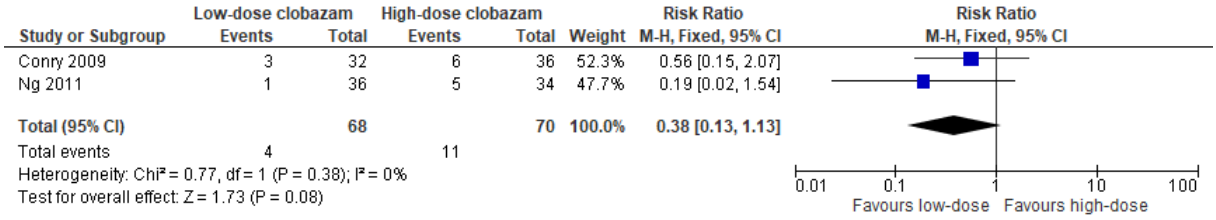


Figure 4: Treatment cessation due to adverse drug effects



Comparison 4: add-on rufinamide versus placebo

Figure 5: Reduction in seizure frequency >50%

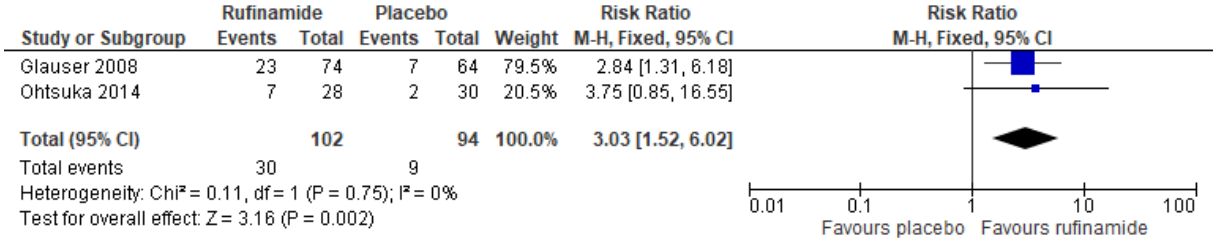


Figure 6: Treatment cessation due to adverse drug effects

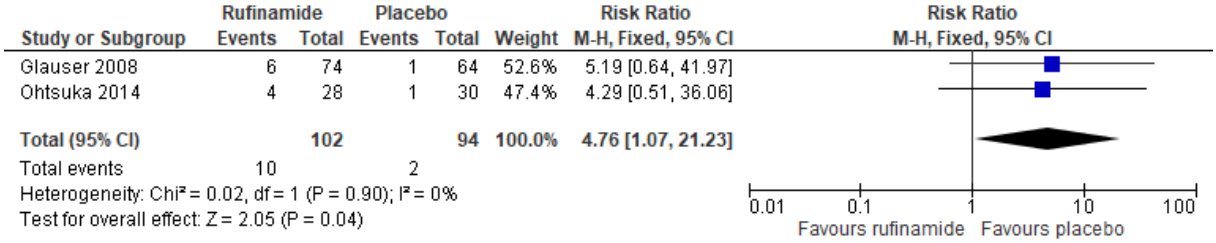


Figure 7: % of patients with reported serious side effects

Appendix F – GRADE tables

GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks?

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	Any other add-on antiseizure 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 drug 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)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	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% 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		Quality	Importance
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		
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												
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												

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	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 drug 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 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

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 1993)	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 40.51)	361 more per 1000 (from 15 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
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 drug 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												

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
1 (Felbamate study group 1993)	RCT	serious[1]	no serious in-consistency	no serious in-directness	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 in-consistency	no serious in-directness	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 in-consistency	no serious in-directness	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												

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 (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 intervention 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 intervention group= -24.2%	Median reduction in the control group= -3.6%, p=0.031	⊕⊕OO LOW	CRITICAL
Reduction in atonic seizures (median)												
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 intervention 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 intervention group=	Median in control group= 2.4%, p=0.107	⊕⊕OO LOW	CRITICAL

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
									-57.4%			
% 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 drug 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							No of patients		Effect			
No 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 drug 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			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-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	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 drug 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 drug 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							No 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
Treatment cessation due to adverse drug 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	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No 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
										more to 270 more)		

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
% 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 drug effects												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute		
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 tonic or atonic seizures/drop attacks?

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 tonic or atonic seizures/drop attacks?

Table 20: Economic evidence tables

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 **Source of cost data:**	**<u>Drop Attack Analysis</u>** **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 **<u>Total Seizures Analysis</u>** **Total Costs (95% CI not reported)** • LTG: £37,064 • TPM: £38,557 • RUF: £38,828	**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
		Resource use was estimated through telephone interviews with 5 UK doctors specialising in paediatric epilepsy. Unit drug 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.	• 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 accompanying clinical evidence review was used to estimate treatment	**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 RUF (95% CI)** • Vs LTG: £3,209 (-£1,392-£4,935) • Vs TPM: £1,632 (-£189-£3,523) **Incremental QALYs for RUF (95% CI)** • Vs LTG: 0.021 (0.081-0.120) • Vs TPM: 0.079 (0.039-0.179) **ICER for RUF (cost per QALY)** • Vs LTG: £154,831	**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 **Applicability:** Directly Applicable

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		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 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	**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 medications; 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 tonic or atonic seizures/drop attacks?

Table 21: Economic evidence profile

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 limitations1	Partially applicable2	**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

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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 limitations3	Directly applicable4	**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 £30k threshold Vs TPM 65% VS LTG 15%

ASM: antiseizure medications; 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

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Appendix J – Economic analysis

Economic evidence analysis for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks?

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 tonic or atonic seizures/drop attacks?

Clinical studies

Table 22: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Arnold, S., Badalamenti, V., Diaz, A., Gasalla, T., McShea, C., Whitesides, J., Fakhoury, T., Conversion to brivaracetam monotherapy for the treatment of patients with focal seizures: Two double-blind, randomized, multicenter, historical control, Phase III studies, Epilepsy Research, 141, 73-82, 2018	Does not report on atonic/tonic/drop group specifically - sample were people with focal seizures, focal epilepsy or epileptic syndrome group
Arroyo, S., Dodson, W. E., Privitera, M. D., Glauser, T. A., Naritoku, D. K., Dlugos, D. J., Wang, S., Schwabe, S. K., Twyman, R. E., Randomized dose-controlled study of topiramate as first-line therapy in epilepsy, Acta Neurologica Scandinavica, 112, 214-222, 2005	Does not report on atonic/tonic/drop group specifically - only reports on generalised onset tonic-clonic and partial onset seizure groups
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	Unplanned post hoc analysis
Balagura, G., Riva, A., Marchese, F., Verrotti, A., Striano, P., Adjunctive rufinamide in children with lennox-gastaut syndrome: A literature review, Neuropsychiatric Disease and Treatment, 16, 369-379, 2020	Does not report on atonic/tonic/drop group specifically except in the context of Lennox-Gastaut syndrome. All randomised studies included in this paper have been included in review 3.11
Baulac, M., Leon, T., O'Brien, T. J., Whalen, E., Barrett, J., A comparison of pregabalin, lamotrigine, and placebo as adjunctive therapy in patients with refractory partial-onset seizures, Epilepsy Research, 91, 10-9, 2010	Does not report on atonic/tonic/drop group specifically - focuses on partial seizure group only
Benbadis, S., Klein, P., Schiemann, J., Diaz, A., Elmoufti, S., Whitesides, J., Efficacy, safety, and tolerability of brivaracetam with concomitant lamotrigine or concomitant topiramate in pooled Phase III randomized, double-blind trials: A post-hoc analysis, Epilepsy & Behavior, 80, 129-134, 2018	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures
Ben-Menachem, E., Clinical efficacy of topiramate as add-on therapy in refractory partial epilepsy: The European experience, Epilepsia, 38, S28-S30, 1997	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary GTC seizures
Ben-Menachem, E., Mameniskiene, R., Quarato, P. P., Klein, P., Gamage, J., Schiemann, J., Johnson, M. E., Whitesides, J., McDonough, B., Eckhardt, K., Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies, Neurology, 87, 314-23, 2016	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary GTC seizures.

Study	Reason for exclusion
Beran, R. G., Berkovic, S. F., Dunagan, F. M., Vajda, F. J. E., Danta, G., Black, A. B., Mackenzie, R., Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy, Epilepsia, 39, 1329-1333, 1998	Does not report on atonic/tonic/drop group specifically - sample were people with generalised epilepsy as manifested by seizure patterns of absences, myoclonus, or tonic- clonic seizures or a combination of these
Berkovic, S. F., Knowlton, R. C., Leroy, R. F., Schiemann, J., Falter, U., Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy, Neurology, 69, 1751-1760, 2007	Does not report on atonic/tonic/drop group specifically - only reports on people with idiopathic generalized epilepsies group. NB Some of the sample are described at baseline as epxerienc-ing tonic seizures
Besag, F. M. C., Wallace, S. J., Dulac, O., Alving, J., Spencer, S. C., Hosking, G., Lamotrigine for the treatment of epilepsy in childhood, Journal of Pediatrics, 127, 991-997, 1995	Trials on which analysis is based were not randomised/comparative
Beydoun, A., Sackellares, J. C., Shu, V., Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: A double-blind, concentration-response design clinical trial, Neurology, 48, 182-188, 1997	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
Biton, V., Di Memmo, J., Shukla, R., Lee, Y. Y., Poverennova, I., Demchenko, V., Saiers, J., Adams, B., Hammer, A., Vuong, A., Messenheimer, J., Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study, Epilepsy and Behavior, 19, 352-358, 2010	Does not report on atonic/tonic/drop group specifically - sample were people with primary GTC
Biton, V., Krauss, G., Vasquez-Santana, B., Bibbiani, F., Mann, A., Perdomo, C., Narurkar, M., A randomized, double-blind, placebo-controlled, parallel-group study of rufinamide as adjunctive therapy for refractory partial-onset seizures, Epilepsia, 52, 234-42, 2011	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures. with/without secondary generalisation
Biton, V., Montouris, G. D., Ritter, F., Riviello, J. J., Reife, R., Lim, P., Pledger, G., A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures, Neurology, 52, 1330-1337, 1999	Does not report on atonic/tonic/drop group specifically - sample were people with primary GTC (at baseline atonic/tonic seizures and drop attacks were recorded)
Biton, V., Sackellares, J. C., Vuong, A., Hammer, A. E., Barrett, P. S., Messenheimer, J. A., Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures, Neurology, 65, 1737-1743, 2005	Does not report on atonic/tonic/drop group specifically - sample were people with primary GTC
Biton, V., Shneker, B. F., Naritoku, D., Hammer, A. E., Vuong, A., Caldwell, P. T., Messenheimer, J. A., Long-term tolerability and safety of lamotrigine extended-release: Pooled analysis of three clinical trials, Clinical Drug Investigation, 33, 359-364, 2013	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures and primary GTC
Bonnett, L. J., Smith, C. T., Donegan, S., Marson, A. G., Treatment outcome after failure of a first antiepileptic drug, Neurology, 83, 552-560, 2014	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without SG, GTC, absence, myoclonic, absence or myoclonic with TC, TC
Bonnett, L. J., Smith, C. T., Smith, D., Williamson, P. R., Chadwick, D., Marson, A. G., Time to 12-month remission and treatment failure for	Does not report on atonic/tonic/drop group specifically - sample were people with GTC, absence, myoclonic or absence seizures

Study	Reason for exclusion
generalised and unclassified epilepsy, Journal of Neurology, Neurosurgery and Psychiatry, 85, 603-610, 2014	
Bonnett, Lj, Powell, Ga, Tudur, Smith C, Marson, Ag, Breakthrough seizures-Further analysis of the Standard versus New Antiepileptic Drugs (SANAD) study, Plos one, 12, e0190035, 2017	Does not report on atonic/tonic/drop group specifically - sample were people with partial with/without secondary generalisation, absence, myoclonic or absence seizures with tonic- clonic seizures
Brandl, U., Kurlemann, G., Neubauer, B., Rettig, K., Schauble, B., Schreiner, A., Seizure and cognitive outcomes in children and adolescents with epilepsy treated with topiramate, Neuropediatrics, 41, 113-20, 2010	Not comparative
Bresnahan, R., Panebianco, M., Marson, A. G., Lamotrigine add-on therapy for drug-resistant generalised tonic-clonic seizures, Cochrane Database of Systematic Reviews, 2020 (7) (no pagination), 2020	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome
Briant, R. H., Foote, S. E., Wallis, W. E., Sodium valproate (Epilim) in epilepsy: a trial, New Zealand Medical Journal, 88, 479-82, 1978	Does not report on atonic/tonic/drop group specifically
Brigo, F., Igwe, S. C., Bragazzi, N. L., Lattanzi, S., Clonazepam monotherapy for treating people with newly diagnosed epilepsy, Cochrane Database of Systematic Reviews, 2019	Does not report data on participants who experience atonic or tonic/drop seizures/attacks
Brodie, M. J., Whitesides, J., Schiemann, J., D'Souza, J., Johnson, M. E., Tolerability, safety, and efficacy of adjunctive brivaracetam for focal seizures in older patients: A pooled analysis from three phase III studies, Epilepsy Research, 127, 114-118, 2016	Does not report on atonic/tonic/drop group specifically - sample were people with focal seizures with/without secondary generalisation
Chandra, B., First seizure in adults: to treat or not to treat, Clinical Neurology & Neurosurgery, 94 Suppl, S61-3, 1992	Does not report on atonic/tonic/drop group specifically - sample were people with tonic-clonic and partial seizures
Christensen, J., Andreasen, F., Poulsen, J. H., Dam, M., Randomized, concentration-controlled trial of topiramate in refractory focal epilepsy, Neurology, 61, 1210-8, 2003	Does not report on atonic/tonic/drop group specifically - focuses on simple partial seizures and complex partial seizures, with or without secondary generalization groups
Chung, S. S., Hogan, R. E., Blatt, I., Lawson, P. B., Nguyen, H., Clark, A. M., Anders, B., Halvorsen, M. B., Prevail Ole Study Group, Long-term safety and sustained efficacy of USL255 (topiramate extended-release capsules) in patients with refractory partial-onset seizures, Epilepsy & Behavior, 59, 13-20, 2016	Not comparative
Coppola, G., Caliendo, G., Veggiotti, P., Romeo, A., Tortorella, G., De Marco, P., Pascotto, A., Topiramate as add-on drug in children, adolescents and young adults with Lennox-Gastaut syndrome: an Italian multicentric study, Epilepsy Research, 51, 147-53, 2002	Not comparative
Coppola, G., Capovilla, G., Montagnini, A., Romeo, A., Spano, M., Tortorella, G., Veggiotti, P., Viri, M., Pascotto, A., Topiramate as add-on drug in severe myoclonic epilepsy in infancy: an	Not comparative

Study	Reason for exclusion
Italian multicenter open trial, Epilepsy Research, 49, 45-8, 2002	
Crawford, P., Chadwick, D., A comparative study of progabide, valproate, and placebo as add-on therapy in patients with refractory epilepsy, Journal of Neurology Neurosurgery and Psychiatry, 49, 1251-1257, 1986	Does not report on atonic/tonic/drop group specifically - sample were people with severe, partial or generalised
Cross, J. H., Epilepsy (generalised seizures), BMJ clinical evidence, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without, generalised, progressive myoclonic
Cross, J. H., Auvin, S., Patten, A., Giorgi, L., Safety and tolerability of zonisamide in paediatric patients with epilepsy, European Journal of Paediatric Neurology, 18, 747-758, 2014	Does not report on atonic/tonic/drop group specifically - sample were people with generalised epilepsy
Dodson, W. E., Kamin, M., Kraut, L., Olson, W. H., Wu, S. C., Topiramate titration to response: analysis of individualized therapy study (TRAITS), Annals of Pharmacotherapy, 37, 615-20, 2003	Not comparative
Dooley, M., Plosker, G. L., Levetiracetam. A review of its adjunctive use in the management of partial onset seizures, Drugs, 60, 871-93, 2000	Narrative overview. References checked
Dozieres-Puyravel, B., Auvin, S., An evidence-based review on the use of perampanel for the treatment of focal-onset seizures in pediatric patients, Neuropsychiatric Disease and Treatment, 15, 2789-2798, 2019	Does not report on atonic/tonic/drop group specifically - only reports on focal onset seizure group
Duron, R. M., Medina, M. T., Martinez-Juarez, I. E., Bailey, J. N., Perez-Gosiengfiao, K. T., Ramos-Ramirez, R., Lopez-Ruiz, M., Alonso, M. E., Ortega, R. H. C., Pascual-Castroviejo, I., Machado-Salas, J., Mija, L., Delgado-Escueta, A. V., Seizures of idiopathic generalized epilepsies, Epilepsia, 46, 34-47, 2005	Narrative overview. References checked
Fang, Y., Wu, X., Xu, L., Tang, X., Wang, J., Zhu, G., Hong, Z., Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types, Journal of Clinical Neuroscience, 21, 55-62, 2014	Does not report on atonic/tonic/drop group specifically - sample were people with partial and generalised seizures
Faught, E., Sachdeo, R. C., Remler, M. P., Chayasirisobhon, S., Iragui-Madoz, V. J., Ramsay, R. E., Sutula, T. P., Kanner, A., Harner, R. N., Kuzniecky, R., Kramer, L. D., Kamin, M., Rosenberg, A., Felbamate monotherapy for partial-onset seizures: An active-control trial, Neurology, 43, 688-692, 1993	Does not report on atonic/tonic/drop group specifically - focuses on partial-onset seizures with or without secondarily generalized seizures
Freeman,J.M., The ketogenic diet: additional information from a crossover study, Journal of Child Neurology, 24, 509-512, 2009	Not randomised
French, J. A., Costantini, C., Brodsky, A., von Rosenstiel, P., N. Study Group, Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial, Neurology, 75, 519-25, 2010	Does not report on atonic/tonic/drop group specifically - focuses on patients with POS (secondarily generalised/not secondarily generalised

Study	Reason for exclusion
French, J. A., Gil-Nagel, A., Malerba, S., Kramer, L., Kumar, D., Bagiella, E., Time to prerandomization monthly seizure count in perampanel trials, Neurology, 84, 2014-2020, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
French, J. A., Gil-Nagel, A., Malerba, S., Kramer, L., Kumar, D., Bagiella, E., Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint, Neurology, 84, 2014-20, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
French, J. A., Krauss, G. L., Biton, V., Squillacote, D., Yang, H., Laurenza, A., Kumar, D., Rogawski, M. A., Adjunctive perampanel for refractory partial-onset seizures: Randomized phase III study 304, Neurology, 79, 589-596, 2012	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
French, J. A., Krauss, G. L., Wechsler, R. T., Wang, X. F., Diventura, B., Brandt, C., Trinka, E., O'Brien, T. J., Laurenza, A., Patten, A., Bibbiani, F., Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy, Neurology, 85, 950-957, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with primary GTC and IGE. At baseline some participants are reported as having experienced atonic and tonic seizures but there are no results presented which relate specifically to these groups
French, Ja, Krauss, Gl, Wechsler, Rt, Wang, Xf, DiVentura, B, Brandt, C, Trinka, E, O'Brien, Tj, Laurenza, A, Patten, A, et al.,, Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial, Neurology, 85, 950â□□957, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with primary GTC and IGE. At baseline some participants are reported as having experienced atonic and tonic seizures but there are no results presented which relate specifically to these groups
Garnett, W. R., Optimizing antiepileptic drug therapy in the elderly, Annals of Pharmacotherapy, 39, 1852-1860, 2005	Narrative overview. References checked
Giorgi, L., Gomez, G., O'Neill, F., Hammer, A. E., Risner, M., The tolerability of lamotrigine in elderly patients with epilepsy, Drugs & Aging, 18, 621-30, 2001	Does not report on atonic/tonic/drop group specifically - focuses mainly on patients with complex partial seizures and primary generalised seizures. Included non randomised trials
Giri, V. P., Giri, O. P., Khan, F. A., Kumar, N., Kumar, A., Haque, A., Valproic acid versus lamotrigine as first-line monotherapy in newly diagnosed idiopathic generalized tonic -Clonic seizures in adults - A randomized controlled trial, Journal of Clinical and Diagnostic Research, 10, FC01-FC04, 2016	Does not report on atonic/tonic/drop group specifically - focuses on people with idiopathic generalized tonic-clonic seizures
Glauser, A. T., Dlugos, J. D., Dodson, E. W., Grinspan, A., Wang, S., Wu, S. C., Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents, Journal of Child Neurology, 22, 693-699, 2007	Does not report on atonic/tonic/drop group specifically - focuses on people with partial or generalised onset seizures
Glauser, T, Laurenza, A, Yang, H, Williams, B, Ma, T, Fain, R, Efficacy and tolerability of adjunct perampanel based on number of antiepileptic drugs at baseline and baseline predictors of efficacy: a phase III post-hoc analysis, Epilepsy research, 119, 34â□□40, 2016	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
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 (excluded from L-G review)

Study	Reason for exclusion
Gram, L., Bentsen, K. D., Valproate: an updated review, Acta Neurologica Scandinavica, 72, 129-39, 1985	Not empirical/narrative overview
Hancock, E., Cross, H., Treatment of Lennox-Gastaut syndrome, Cochrane database of systematic reviews (Online), CD003277, 2003	Review - references checked
Hellings, J. A., Barth, F. X., Logan, M., Cook-Wiens, G., Osorio, I., Reed, R. C., Overnight versus progressive conversion of multiple daily-dose divalproex to once-daily divalproex extended release: Which strategy is better tolerated by adults with intellectual disabilities?, Journal of Clinical Psychopharmacology, 29, 492-495, 2009	Data on epilepsy/seizure type are not presented
Hemery, C., Ryvlin, P., Rheims, S., Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: A meta-analysis, Epilepsia, 55, 1789-1799, 2014	Does not report on atonic/tonic/drop group specifically - sample were people with focal seizures with/without secondary generalisation
Henriksen, O., Johannessen, S. I., Clinical and pharmacokinetic observations on sodium valproate - a 5-year follow-up study in 100 children with epilepsy, Acta Neurologica Scandinavica, 65, 504-23, 1982	Not comparative
Hogan, R. E., Blatt, I., Lawson, B., Nagaraddi, V., Fakhoury, T. A., Anders, B., Clark, A. M., Laine, D., Halvorsen, M. B., Chung, S. S., Efficacy of once-daily extended-release topiramate (USL255): a subgroup analysis based on the level of treatment resistance, Epilepsy & Behavior, 41, 136-9, 2014	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures
Hoy, S. M., Topiramate Extended Release: A Review in Epilepsy, CNS Drugs, 30, 559-566, 2016	Narrative review. References checked
Hoy, S. M., Brivaracetam: A Review in Partial-Onset (Focal) Seizures in Patients with Epilepsy, CNS Drugs, 30, 761-772, 2016	Narrative overview. References checked
Ieiri, I., Hirata, K., Higuchi, S., Kojima, K., Ikeda, M., Yamada, H., Aoyama, T., Pharmacoepidemiological study on adverse reactions of antiepileptic drugs, Chemical & Pharmaceutical Bulletin, 40, 1280-8, 1992	Not comparative
Kaminow, L., Schimschock, J. R., Hammer, A. E., Vuong, A., Lamotrigine monotherapy compared with carbamazepine, phenytoin, or valproate monotherapy in patients with epilepsy, Epilepsy & Behavior, 4, 659-66, 2003	Does not report on atonic/tonic/drop group specifically - people with any type of seizure were eligible
Kerr, M. P., Baker, G. A., Brodie, M. J., A randomized, double-blind, placebo-controlled trial of topiramate in adults with epilepsy and intellectual disability: Impact on seizures, severity, and quality of life, Epilepsy and Behavior, 7, 472-480, 2005	Does not report on atonic/tonic/drop group specifically – included people with GTC, partial seizures only, partial seizures with generalisation, 'other'
Khan, N., Shah, D., Tongbram, V., Verdian, L., Hawkins, N., The efficacy and tolerability of perampanel and other recently approved anti-epileptic drugs for the treatment of refractory partial	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset with/without secondary generalisation

Study	Reason for exclusion
onset seizure: A systematic review and Bayesian network meta-analysis, Current Medical Research and Opinion, 29, 1001-1013, 2013	
Klein, P., Johnson, M. E., Schiemann, J., Whitesides, J., Time to onset of sustained >=50% responder status in patients with focal (partial-onset) seizures in three phase III studies of adjunctive brivaracetam treatment, Epilepsia, 58, e21-e25, 2017	Does not report on atonic/tonic/drop group specifically - sample were people with focal seizures
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 overview. References checked
Ko, D., Yang, H., Williams, B., Xing, D., Laurenza, A., Perampanel in the treatment of partial seizures: Time to onset and duration of most common adverse events from pooled Phase III and extension studies, Epilepsy and Behavior, 48, 45-52, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures
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 which reports data from observational studies (excluded from L-G review)
Krauss, G. L., Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society, Neurology, 64, 172-4; author reply 172-4, 2005	Letter/commentary
Krauss, G. L., Perucca, E., Kwan, P., Ben-Menachem, E., Wang, X. F., Shih, J. J., Patten, A., Yang, H., Williams, B., Laurenza, A., Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: Study 307, Epilepsia, 59, 866-876, 2018	Not comparative
Krauss, G., Wechsler, R., Bibbiani, F., Patten, A., Williams, B., Yang, H., Gidal, B., Hussein, Z., Relationship between perampanel exposure, seizure outcomes and treatment-emergent adverse events (TEAEs) in patients with primary generalized tonic-clonic seizures (PGTCS): A randomized, double-blind (DB) phase III study, Neurology, 86, 2016	Conference abstract
Kwan, P., Mintzer, S., Laurenza, A., Patten, A., Cartwright, K., Evaluation of perampanel as monotherapy for focal seizures: Experience from open-label extension studies, Epilepsy and Behavior Case Reports, 9, 1-5, 2018	Does not report on atonic/tonic/drop group specifically - sample were people with focal with/without secondary generalisation and primary GTC
Lee, S. K., Lee, S. A., Kim, D. W., Loesch, C., Pelgrims, B., Osakabe, T., Lee, B., N. study group, A randomized, open-label, multicenter	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome

Study	Reason for exclusion
comparative trial of levetiracetam and topiramate as adjunctive treatment for patients with focal epilepsy in Korea, Epilepsy & Behavior, 97, 67-74, 2019	
Leppik, I. E., Yang, H., Williams, B., Zhou, S., Fain, R., Patten, A., Bibbiani, F., Laurenza, A., Analysis of falls in patients with epilepsy enrolled in the perampanel phase III randomized double-blind studies, Epilepsia, 58, 51-59, 2017	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
Leppik, I., Morrell, M., Godfroid, P., Arrigo, C., Seizure-free days observed in randomized placebo-controlled add-on trials with levetiracetam in partial epilepsy, Epilepsia, 44, 1350-2, 2003	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures
Machado, V. H., Palmini, A., Bastos, F. A., Rotert, R., Long-term control of epileptic drop attacks with the combination of valproate, lamotrigine, and a benzodiazepine: a 'proof of concept,' open label study, Epilepsia, 52, 1303-10, 2011	Not comparative
Maguire, M., Marson, A. G., Ramaratnam, S., Epilepsy (generalised), Clinical Evidence, 20, 20, 2012	Does not report on atonic/tonic/drop group specifically - sample were people with generalised epilepsy (tonic clonic type)
Maguire, M., Marson, A. G., Ramaratnam, S., Epilepsy (generalised), BMJ clinical evidence, 2010	Does not report on atonic/tonic/drop group specifically - sample were people with generalised epilepsies, partial onset, primary GTC
Malhotra, M., Ngo, L. Y., Patten, A., Salah, A., Efficacy and safety of adjunctive perampanel in south korean patients with partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS): Post hoc analysis of phase ii and III double-blind and open-label extension (OLEX) studies, Neurology. Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN, 94, 2020	Conference abstract
Manitpisitkul, P., Shalayda, K., Todd, M., Wang, S. S., Ness, S., Ford, L., Pharmacokinetics and safety of adjunctive topiramate in infants (1-24 months) with refractory partial-onset seizures: A randomized, multicenter, open-label phase 1 study, Epilepsia, 54, 156-164, 2013	Does not report on atonic/tonic/drop group specifically – focused on infants with simple or complex partial onset seizures, with or without secondary generalization – but did include infants with tonic seizures although data on these children are not reported separately
Marson, A. G., Maguire, M., Ramaratnam, S., Epilepsy, BMJ clinical evidence, 2009	Does not report on atonic/tonic/drop group specifically - sample were people with generalised (tonic clonic type
McCormack, P. L., Rufinamide: a pharmacoeconomic profile of its use as adjunctive therapy in Lennox-Gastaut syndrome, Pharmacoeconomics, 30, 247-56, 2012	Cost-effectiveness/utility analysis only. Clinical results not included
McDonald, T. J. W., Henry-Barron, B. J., Felton, E. A., Gutierrez, E. G., Barnett, J., Fisher, R., Lwin, M., Jan, A., Vizthum, D., Kossoff, E. H., Cervenka, M. C., Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial, Seizure, 60, 132-138, 2018	Does not report on atonic/tonic/drop group specifically - sample were people with focal and generalised epilepsies
McMurray, R., Striano, P., Treatment of Adults with Lennox-Gastaut Syndrome: Further	Post-hoc analysis including a subgroup of adult patients (not pre-planned). Default NGA

Study	Reason for exclusion
Analysis of Efficacy and Safety/Tolerability of Rufinamide, Neurology and Therapy, 5, 35-43, 2016	approach is not to include unplanned post-hoc analyses
Messenheimer,J.A., Giorgi,L., Risner,M.E., The tolerability of lamotrigine in children, Drug Safety, 22, 303-312, 2000	Narrative overview. References checked
Milovanovic, J. R., Jankovic, S. M., Pejcic, A., Milosavljevic, M., Opancina, V., Radonjic, V., Protrka, Z., Kostic, M., Evaluation of brivaracetam: a new drug to treat epilepsy, Expert Opinion on Pharmacotherapy, 18, 1381-1389, 2017	Narrative overview. References checked
Mintzer, S., French, J., Williams, B., Patten, A., Laurenza, A., Extrapolation of Adjunctive Efficacy and Safety Data from Phase III Partial Epilepsy Trials to Evaluate Perampanel as Monotherapy, Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN, 90, 2018	Conference abstract
Montouris, G., Yang, H., Williams, B., Zhou, S., Laurenza, A., Fain, R., Efficacy and safety of perampanel in patients with drug-resistant partial seizures after conversion from double-blind placebo to open-label perampanel, Epilepsy Research, 114, 131-40, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures
Moseley, B., Diaz, A., Elmoufti, S., Whitesides, J., Efficacy of adjunctive brivaracetam in patients with secondarily generalized tonic-clonic seizures at baseline: Pooled results from long-term follow-up studies, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Moseley, Bd, Sperling, Mr, Asadi-Pooya, Aa, Diaz, A, Elmouft, S, Schiemann, J, Whitesides, J, Efficacy, safety, and tolerability of adjunctive brivaracetam for secondarily generalized tonic-clonic seizures: pooled results from three Phase III studies, Epilepsy research, 127, 179â□□185, 2016	Does not report on atonic/tonic/drop group specifically - sample were people with focal seizures/SGTC
Mullens, E. L., Clinical experience with lamotrigine monotherapy in adults with newly diagnosed epilepsy: A review of published randomised clinical trials, Clinical Drug Investigation, 16, 125-133, 1998	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation and primary GTC
Nct,, A Double-blind, Placebo-controlled Study of Levetiracetam in Epilepsy Patients With Generalized Tonic-clonic Seizures (Except Partial Seizures Evolving to Secondarily Generalized Seizures), Https://clinicaltrials.gov/show/nct01228747, 2010	Trial record (GTC population)
Nevitt, S. J., Sudell, M., Tudur Smith, C., Marson, A. G., Topiramate versus carbamazepine monotherapy for epilepsy: an individual participant data review, Cochrane Database of Systematic Reviews, 2019	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome
Nevitt, S. J., Sudell, M., Weston, J., Tudur Smith, C., Marson, A. G., Antiepileptic drug monotherapy for epilepsy: A network meta-	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures (simple partial, complex partial or

Study	Reason for exclusion
analysis of individual participant data, Cochrane Database of Systematic Reviews, 2017 (6) (no pagination), 2017	secondary generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus)
Nishida, T., Lee, S. K., Inoue, Y., Saeki, K., Ishikawa, K., Kaneko, S., Adjunctive perampanel in partial-onset seizures: asia-Pacific, randomized phase III study, Acta Neurologica Scandinavica, 137, 392â□□399, 2018	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures
Nishida, T., Lee, S. K., Wu, T., Tiamkao, S., Dash, A., Efficacy and safety of perampanel in generalized and focal to bilateral tonic-clonic seizures: A comparative study of Asian and non-Asian populations, Epilepsia, 60, 47-59, 2019	Does not report on atonic/tonic/drop group specifically - only reports on focal to bilateral tonic-clonic and generalised tonic-clonic seizure groups
Nolan, S. J., Sudell, M., Weston, J., Tudur Smith, C., Marson, A. G., Antiepileptic drug monotherapy for epilepsy: A network meta-analysis, Cochrane Database of Systematic Reviews, 2014 (12) (no pagination), 2014	Protocol for a review on partial onset and generalised onset TC seizures
Novotny, E., Renfroe, B., Yardi, N., Nordli, D., Ness, S., Wang, S., Weber, T., Kurland, C. L., Yuen, E., Eerdekens, M., Venkatraman, L., Nye, J. S., Ford, L., Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures, Neurology, 74, 714-20, 2010	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
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 (excluded from L-G review)
Olsson, P., Reimers, A., Kallen, K., Quality of life after switching to generic levetiracetam - A prospective comparative study, Epilepsy and Behavior, 96, 169-174, 2019	Not randomised
Ormrod, D., McClellan, K., Topiramate: A review of its use in childhood epilepsy, Paediatric Drugs, 3, 293-319, 2001	Narrative overview. References checked
Pålhagen, S, Canger, R, Henriksen, O, van, Parys Ja, Rivière, Me, Karolchyk, Ma, Rufinamide: a double-blind, placebo-controlled proof of principle trial in patients with epilepsy, Epilepsy research, 43, 115â□□124, 2001	Does not report on atonic/tonic/drop group specifically - sample were people with partial or primary generalised epilepsy
Pellock, J., Carman, W., Thyagarajan, V., Daniels, T., Morris, D., D'Cruz, O., Determining antiepileptic drug efficacy in pediatric patients: Results from a systematic review of clinical trials in adults compared to children, Neurology. Conference: 64th American Academy of Neurology Annual Meeting. New Orleans, LA United States. Conference Publication:, 78, 2012	Conference abstract
Pohlmann-Eden, B., Marson, A. G., Noack-Rink, M., Ramirez, F., Tofighy, A., Werhahn, K. J., Wild, I., Trinka, E., Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized,	Mixed population. No indication that sample included people with atonic/tonic seizures or drop attacks

Study	Reason for exclusion
unblinded KOMET study, BMC Neurology, 16, 149, 2016	
Ramsay, R. E., DeToledo, J., Tonic-clonic seizures: A systematic review of antiepilepsy drug efficacy and safety, Clinical Therapeutics, 19, 433-446, 1997	Does not report on atonic/tonic/drop group specifically - sample were people with GTC seizures
Ramsay, R. E., Uthman, B., Pryor, F. M., Rowan, A. J., Bainbridge, J., Spitz, M., Sirven, J. I., Frederick, T. E., Topiramate in older patients with partial-onset seizures: a pilot double-blind, dose-comparison study, Epilepsia, 49, 1180-5, 2008	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures
Rektor, I., Krauss, G. L., Inoue, Y., Kaneko, S., Williams, B., Patten, A., Bibbiani, F., Laurenza, A., Wechsler, R. T., Assessment of the long-term efficacy and safety of adjunctive perampanel: Pooled analyses of four open-label extension studies, Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN, 88, 2017	Conference abstract
Rektor, I., Krauss, G. L., Inoue, Y., Kaneko, S., Williams, B., Patten, A., Malhotra, M., Laurenza, A., Wechsler, R. T., Assessment of the long-term efficacy and safety of adjunctive perampanel in tonic-clonic seizures: Analysis of four open-label extension studies, Epilepsia, 61, 1491-1502, 2020	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome
Richens, A., Yuen, A. W., Overview of the clinical efficacy of lamotrigine, Epilepsia, 32 Suppl 2, S13-16, 1991	Narrative overview. References checked
Rosenfeld, W. E., Benbadis, S., Edrich, P., Tassinari, C. A., Hirsch, E., Levetiracetam as add-on therapy for idiopathic generalized epilepsy syndromes with onset during adolescence: Analysis of two randomized, double-blind, placebo-controlled studies, Epilepsy Research, 85, 72-80, 2009	Does not report on atonic/tonic/drop group specifically - sample were people with idiopathic generalized epilepsy syndromes (JAE, JME or GTC on awakening)
Rosenfeld, W., Conry, J., Lagae, L., Rozentals, G., Yang, H., Fain, R., Williams, B., Kumar, D., Zhu, J., Laurenza, A., Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a combined extension study, European Journal of Paediatric Neurology, 19, 435-45, 2015	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures
Rugg-Gunn, F., Adverse effects and safety profile of perampanel: a review of pooled data, Epilepsia, 55 Suppl 1, 13-5, 2014	Narrative overview. References checked
Sachdeo, R. C., Reife, R. A., Lim, P., Pledger, G., Topiramate monotherapy for partial onset seizures, Epilepsia, 38, 294-300, 1997	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures
Sachdeo, R., Kramer, L. D., Rosenberg, A., Sachdeo, S., Felbamate monotherapy: Controlled trial in patients with partial onset seizures, Annals of Neurology, 32, 386-392, 1992	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures

Study	Reason for exclusion
Sander, J. W. A. S., Patsalos, P. N., Oxley, J. R., Hamilton, M. J., Yuen, W. C., A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy, Epilepsy Research, 6, 221-226, 1990	Does not report on atonic/tonic/drop group specifically - sample were people with partial and secondary generalised and generalised seizures
Siegel, H., Kelley, K., Stertz, B., Reeves-Tyer, P., Flamini, R., Malow, B., Gaillard, W. D., Ko, D., Theodore, W. H., The efficacy of felbamate as add-on therapy to valproic acid in the Lennox-Gastaut syndrome, Epilepsy Research, 34, 91-97, 1999	Not randomised
Slater, J., Chung, S., Huynh, L., Duh, M. S., Gorin, B., McMicken, C., Ziemann, A., Isojarvi, J., Efficacy of antiepileptic drugs in the adjunctive treatment of refractory partial-onset seizures: Meta-analysis of pivotal trials, Epilepsy Research, 143, 120-129, 2018	Does not report on atonic/tonic/drop group specifically - samples were people with partial onset seizures
Smith, C. T., Marson, A. G., Chadwick, D. W., Williamson, P. R., Multiple treatment comparisons in epilepsy monotherapy trials, Trials, 8 (no pagination), 2007	Does not report on atonic/tonic/drop group specifically - sample were people with partial and generalised onset seizures
Smith, D., Baker, G., Davies, G., Dewey, M., Chadwick, D. W., Outcomes of add-on treatment with lamotrigine in partial epilepsy, Epilepsia, 34, 312-322, 1993	Does not report on atonic/tonic/drop group specifically - sample were people with partial epilepsy with/without secondary generalised seizures
Steinhoff, B. J., Adjunctive perampanel for partial-onset seizures, Acta Neurologica Scandinavica, 137, 376-377, 2018	Editorial
Tallian, K. B., Nahata, M. C., Tsao, C. Y., Role of the ketogenic diet in children with intractable seizures, Annals of Pharmacotherapy, 32, 349-61, 1998	Narrative overview. References checked
Thibault, M., Blume, W. T., Saint-Hilaire, J. M., Zakhari, R., Sommerville, K. W., Divalproex extended-release versus the original divalproex tablet: results of a randomized, crossover study of well-controlled epileptic patients with primary generalized seizures, Epilepsy Research, 50, 243â□□249, 2002	Does not report on atonic/tonic/drop group specifically - sample were people with generalised epilepsy. Included people who experienced tonic seizures but results are not reported separately
Tian, X., Yuan, M., Zhou, Q., Wang, X., The efficacy and safety of brivaracetam at different doses for partial-onset epilepsy: a meta-analysis of placebo-controlled studies, Expert Opinion on Pharmacotherapy, 16, 1755-67, 2015	Does not report on atonic/tonic/drop group specifically. Sample comprised of people with partial onset seizures
Tjia-Leong, E., Leong, K., Marson, A., Lamotrigine add-on for refractory generalized tonic-clonic seizures, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	Protocol for a review on GTC
Tjia-Leong, E., Leong, K., Marson, A. G., Lamotrigine adjunctive therapy for refractory generalized tonic-clonic seizures, Cochrane database of systematic reviews (Online), 12, CD007783, 2010	Does not report on atonic/tonic/drop group specifically - sample were people with with primary generalized epilepsy (this is, experiencing myoclonic epilepsy, generalized epilepsy with tonic clonic seizures on awakening and other idiopathic seizures). Studies involving participants with absence epilepsy and Lennox Gastaut syndrome were excluded

Study	Reason for exclusion
Tomson, T., Hirsch, L. J., Friedman, D., Bester, N., Hammer, A., Irizarry, M., Ishihara, L., Krishen, A., Spaulding, T., Wamil, A., Leadbetter, R., Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials, Epilepsia, 54, 135-140, 2013	Includes partial and generalised seizures. Results for generalised seizures are reported separately and authors state that this includes tonic seizures
Trinka, E., Tsong, W., Toupin, S., Patten, A., Wilson, K., Isojarvi, J., James, D., A systematic review and indirect treatment comparison of perampanel versus brivaracetam as adjunctive therapy in patients with focal-onset seizures with or without secondary generalization, Epilepsy Research, 166 (no pagination), 2020	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome
Tsai, J. J., Ikeda, A., Hong, S. B., Likasitwattanakul, S., Dash, A., Efficacy, safety, and tolerability of perampanel in Asian and non-Asian patients with epilepsy, Epilepsia, 60, 37-46, 2019	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome
Vadney, V. J., Kraushaar, K. W., Effects of switching from Depakene to generic valproic acid on individuals with mental retardation, Mental Retardation, 35, 468-72, 1997	Type of epilepsy/seizures not reported. States only that participants had seizure disorders
Vadney, V., Ricketts, R. W., Cole, R. W., Effects on individuals with mental retardation of changing Depakote to Depakene, Mental Retardation, 32, 341-6, 1994	Not comparative
Verrotti, A., Loiacono, G., Ballone, E., Mattei, P. A., Chiarelli, F., Curatolo, P., Efficacy of rufinamide in drug-resistant epilepsy: A meta-analysis, Pediatric Neurology, 44, 347-349, 2011	Does not report on atonic/tonic/drop group specifically - appears to only focus on L-G. Relevant study (Glauser, 2008) is included in L-G review
Villanueva, V., Majid, O., Nabangchang, C., Yang, H., Laurenza, A., Ferry, J., Hussein, Z., Pharmacokinetics, exposure-cognition, and exposure-efficacy relationships of perampanel in adolescents with inadequately controlled partial-onset seizures, Epilepsy research, 127, 126-134, 2016	Does not report on atonic/tonic/drop group specifically - sample were people with partial onset seizures with/without secondary generalised
Vining, E. P., Botsford, E., Freeman, J. M., Valproate sodium in refractory seizures: a study of efficacy, American Journal of Diseases of Children, 133, 274-6, 1979	Does not report on atonic/tonic/drop group specifically
Vossler, D. G., Zonisamide as adjunctive therapy for adults with partial- onset epileptic seizures: An efficacy and safety review, Clinical Medicine Insights: Therapeutics, 2, 331-339, 2010	Narrative overview. References checked
Wang, Y., Zhou, D., Wang, B., Kirchner, A., Hopp, P., Kerling, F., Pauli, E., Stefan, H., Clinical effects of topiramate against secondarily generalized tonic-clonic seizures, Epilepsy Research, 49, 121-130, 2002	Does not report on tonic/atonic/drop population specifically (focuses on people with partial seizures and SGTC) but does report on improvements in 'tonic signs' Comparison is low vs high dose
Wechsler, R. T., Leroy, R., Van Cott, A., Hammer, A. E., Vuong, A., Huffman, R., Van-Landingham, K., Messenheimer, J. A., Lamotrigine extended-release as adjunctive therapy with optional conversion to monotherapy in older adults with epilepsy, Epilepsy Research, 108, 1128-36, 2014	Not comparative

Study	Reason for exclusion
Wheless, J. W., Use of topiramate in childhood generalized seizure disorders, Journal of Child Neurology, 15, S7-S13, 2000	Narrative overview
Wheless, J. W., Levetiracetam in the treatment of childhood epilepsy, Neuropsychiatric Disease and Treatment, 3, 409-421, 2007	Narrative overview. References checked
Wisniewski, C. S., Rufinamide: A new antiepileptic medication for the treatment of seizures associated with Lennox-Gastaut syndrome, Annals of Pharmacotherapy, 44, 658-667, 2010	Narrative overview. References checked
Wu, L., Yagi, K., Hong, Z., Liao, W., Wang, X., Zhou, D., Inoue, Y., Ohtsuka, Y., Sasagawa, M., Terada, K., Du, X., Muramoto, Y., Sano, T., Adjunctive levetiracetam in the treatment of Chinese and Japanese adults with generalized tonic-clonic seizures: A double-blind, randomized, placebo-controlled trial, Epilepsia Open, 3, 474-484, 2018	Does not report on atonic/tonic/drop group specifically - only reports on generalised tonic-clonic seizure group. Although at baseline some patients reported that they had experienced atonic/tonic seizures
Xiao, Z., Li, J. M., Wang, X. F., Xiao, F., Xi, Z. Q., Lv, Y., Sun, H. B., Efficacy and safety of levetiracetam (3,000 mg/Day) as an adjunctive therapy in Chinese patients with refractory partial seizures, European Neurology, 61, 233-9, 2009	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures with/without secondary generalisation
Xu, Z., Zhao, H., Chen, Z., The efficacy and safety of rufinamide in drug-resistant epilepsy: A meta-analysis of double-blind, randomized, placebo controlled trials, Epilepsy Research, 120, 104-110, 2016	Only reports on atonic/tonic/drop group as part of the Lennox-Gastuat population. Not reported as a subgroup. The relevant study (Glauser, 2008) has been included in the NGA Lennox-Gastaut review
Zaccara, G., Giovannelli, F., Cincotta, M., Verrotti, A., Grillo, E., The adverse event profile of perampanel: meta-analysis of randomized controlled trials, European Journal of Neurology, 20, 1204-11, 2013	Does not report on atonic/tonic/drop group specifically - sample were people with partial epilepsy or Parkinsons disease
Zhang, L., Huang, J., Zhuang, J. H., Huang, L. Q., Zhao, Z. X., Topiramate as an adjunctive treatment for refractory partial epilepsy in the elderly, Journal of International Medical Research, 39, 408-15, 2011	Does not report on atonic/tonic/drop group specifically - sample were people with partial epilepsy
Zhang, Y., Xu, J., Zhang, K., Yang, W., Li, B., The Anticonvulsant Effects of Ketogenic Diet on Epileptic Seizures and Potential Mechanisms, Current Neuropharmacology, 16, 66-70, 2018	Narrative overview
Zhao, T., Feng, X., Liu, J., Gao, J., Zhou, C., Evaluate the Efficacy and Safety of Anti-Epileptic Medications for Partial Seizures of Epilepsy: A Network Meta-Analysis, Journal of Cellular Biochemistry, 118, 2850-2864, 2017	Does not report on atonic/tonic/drop group specifically - sample were people with partial seizures
Zhou S, Zhan Q, Wu X; Effect of levetiracetam on cognitive function and clonic seizure frequency in children with epilepsy, Current Molecular Medicine, 2019	Does not include participants who experience drop or tonic/atonic seizures and does not report on these as an outcome

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 tonic or atonic seizures/drop attacks?

No research recommendations were made for this review question.