National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[H] Effectiveness of antiseizure therapies in the treatment of myoclonic seizures

NICE guideline number tbc

Evidence reviews underpinning recommendations 5.4.1-5.4.8 in the NICE guideline

November 2021

Draft for Consultation

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

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Contents

1

Evidence review for effectiveness of antiseizure therapies in the treatment of myoclonic seizures

Review question

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

Introduction

Myoclonic seizures present as brief shock-like jerks of a muscle or group of muscles. During a myoclonic seizure, a person is usually awake and able to think clearly. The jerks may be very mild, like a twitch, or they can be forceful causing an individual to fall. They may occur in isolation, but are more commonly in association with other seizure types as part of certain epilepsy syndromes. The aim of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have myoclonic seizures.

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 and adults with confirmed myoclonic seizures
Interventions	• Brivaracetam • Clobazam • Clonazepam • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Perampanel • Piracetamem • Sodium Valproate • Topiramate • Zonisamide Interventions may be monotherapy or add-on therapy
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 in 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)

	○ Treatment cessation due to adverse drug effects (dichotomous outcome only) ○ Mortality **Important** • Neuropsychological changes (IQ testing or other validated tools) • Health-related quality of life (measured using validated tools)

IQ: intelligence quotient

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 studies reporting on 9 randomised controlled trials (RCTs) were identified for inclusion in this review (Biton 2005, Kalvainen 2016, Koskiniemi 1998, Levisohn 2007, Machado 2013, Nejad 2009, Noachtar 2008, Park 2013). Kalvainen 2016 reported 2 trials in the same publication (N01187 trial and N01236 trial), referred to as Kalvainen 2016a and Kalvainen 2016b respectively hereafter.

One RCT compared add-on topiramate to placebo (Biton 2005), 2 RCTs compared add-on dose ranging brivaracetam to placebo (Kalviainen 2016a, Kalviainen 2016b), 1 RCT compared add-on dose ranging piracetam to placebo (Koskiniemi 1998), 2 RCTs compared topiramate to valproate (Levisohn 2007, Park 2013), 2 RCTs compared lamotrigine to valproate (Machado 2013, Nejad 2009), and 1 RCT compared add-on levetiracetam to placebo (Noachtar 2008).

Four of the studies assessed add-on therapy (Biton 2005, Kalvainen 2016a, Kalvainen 2016b, Koskiniemi 1998, Noachtar 2008), whereas 4 assessed monotherapy treatments. In 2 of the studies including monotherapy, patients were either newly diagnosed or other antiseizure therapies were replaced with monotherapy during the study period (Machado 2013, Park 2013). In the remaining 2 studies including monotherapy, baseline antiseizure therapies were withdrawn during the study period in order to achieve monotherapy (Levisohn 2007, Nejad 2009).

For studies including people with juvenile myoclonic epilepsy (JME), outcomes specific for those with myoclonic seizures have been reported when available, as pre-specified in the protocol (Biton 2005, Levisohn 2007). If the study did not report results for this subgroup of people, then outcomes for the whole population were reported, as long as the predominant seizure type were myoclonic seizures (Park 2013, Machado 2013, Nejad 2009).

The included studies are summarised in Table 2 to Table 7

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 7.

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

Study	Population	Intervention	Comparison	Outcomes
Biton 2005 RCT US	N=22 people with juvenile myoclonic epilepsy; n=13 with myoclonic seizures Median age: topiramate 27, placebo 34	Add-on topiramate n=5 people with myoclonic seizures Target dose: Adults: 400 mg day Children: 6 mg/kg/day	Placebo n=8 with myoclonic seizures	*Outcomes taken from the subgroup of people with myoclonic seizures* • Reduction of generalised seizure frequency >50%

RCT: randomised controlled trial

Table 3: Summary of included studies. Comparison 2, 3, 4: add-on dose ranging brivaracetam versus placebo

Study	Population	Intervention	Comparison	Outcomes
Kalviainen 2016a RCT (N01187 trial) Finland	N = 56 people with Unverricht-Lundborg disease/ progressive myoclonic epilepsy type 1 (EPM1) Mean age: BRV (50 mg/day): 39.4 (9.6) BRV (150 mg/day): 39.1 (13.3) Placebo: 39.1 (8.3)	Add-on brivaracetam (BRV) n=16 allocated to 50 mg/day BRV, n=18 allocated to 150 mg/day BRV	Placebo n=16	• Reduction in action myoclonus score • Functional disability in everyday activities • Stimulus sensitivity score • Patients with at least 1 adverse effect • Patient questionnaire score
Kalviainen 2016b RCT (N01236 trial)	N = 56 people with Unverricht-Lundborg disease/ progressive myoclonic	Add-on brivaracetam (BRV) n=20 allocated to 5 mg/day BRV, n=18 allocated to 150 mg/day BRV	Placebo n=18	• Reduction in action myoclonus score • Functional disability in everyday activities • Stimulus sensitivity score

Study	Population	Intervention	Comparison	Outcomes
Finland	epilepsy type 1 (EPM1) Mean age: BRV (5 mg/day): 35.8 (10.9) BRV (150 mg/day): 33.7 (11.4) Placebo: 34.3 (9.2)			• Patients with at least 1 adverse effect • Patient questionnaire score

BRV: brivaracetam; EPM1: progressive myoclonic epilepsy type 1; RCT: randomised controlled trial

Table 4: Summary of included studies. Comparison 5, 6, 7: add-on dose ranging piracetam versus placebo

Study	Population	Intervention	Comparison	Outcomes
Koskiniemi 1998 Crossover RCT Finland	N = 18¥ people with Unverricht-Lundborg disease *Age was not reported*	Add-on piracetam n= 12 allocated to: 9.6 g/day, 16.8 g/day, 24 g/day	Placebo n=18	• Stimulus sensitivity • Functional disability in everyday activities • Investigator's global assessment score • Patient's global assessment

RCT: randomised controlled trial
¥The number of participants included in the individual treatment arms outnumber the total number of participants included in the trial due to the crossover design of the study

Table 5. Summary of included studies. Comparison 8: topiramate versus valproate

Study	Population	Intervention	Comparison	Outcomes
Levisohn 2007 RCT US	N=28 children and adults with juvenile myoclonic epilepsy; n=23 with myoclonic seizures Age, years, median (range): topiramate 15 (9-42), valproate	Topiramate n=14 Target dose: >16 years old: 200 mg/day 12–16 years old: 3–4 mg/kg/day	Valproate n=9 Target dose: >16 years: 750 mg/day 12–16 years old: 10 mg/kg/day	*Outcomes taken from the subgroup of people with myoclonic seizures* • Reduction of myoconic seizure frequency >50%

Study	Population	Intervention	Comparison	Outcomes
	16 (12-34)			
Park 2013 RCT Republic of Korea	N=33 adults and children with juvenile myoclonic epilepsy; n=27 finished the 24-week maintenance period Age, years, median (range): topiramate: 19 (13 to 42), valproate: 17 (14 to 36)	<u>Topiramate</u> n=16; n=11 finished the 24-week maintenance period Titrated up to 100 mg day for 24 week maintenance period	<u>Valproate</u> n=17; n=16 finished the 24-week maintenance period Titrated up to 1200 mg day for 24 week maintenance period	• Number of participants who were seizure-free during the maintenance period

PGTC: primary generalised tonic clonic seizures; RCT: randomised controlled trial

Table 6. Summary of included studies. Comparison 9: lamotrigine versus valproate

Study	Population	Intervention	Comparison	Outcomes
Machado 2013 RCT Cuba	N=82 people with juvenile myoclonic epilepsy Age, years, mean (SD): Lamotrigine 26 (11), valproate 27 (13)	<u>Lamotrigine</u> n=43 Dose prescribed by treating physician.	<u>Valproate</u> n=39 Dose prescribed by treating physician.	• Time to withdrawal for any reason • Percentage of patients reported side effects • Health-related quality of life
Nejad 2009 RCT Iran	N=46 women with juvenile myoclonic epilepsy Age range: 8-30 years old	<u>Lamotrigine</u> n=23 Mean target dose was 1500-2000 mg per day	<u>Valproate</u> n=23 Mean target dose was 800 mg per day	• Mean juvenile myoclonic seizure reduction from baseline

RCT: randomised controlled trial

Table 7: Summary of included studies. Comparison 10: add-on levetiracetam versus placebo

Study	Population	Intervention	Comparison	Outcomes
Noachtar 2008 Global multi-centred RCT 14 countries across Oceania, Europe, North and Central America	N=121 adults and children with IGE and myoclonic seizures 113 had Juvenile myoclonic epilepsy and 8 had Juvenile absence epilepsy Age, years, mean (SD): levetiracetam 25 (7.4), placebo 26.8 (9.5)	<u>Levetiracetam</u> n=61 Target dose: 3,000 mg/day. 1 concomitant ASM was to be taken with the study treatment at a stable dose.	<u>Placebo</u> n=60 1 concomitant ASM was to be taken with the study treatment at a stable dose.	• Reduction of myoclonic seizure frequency >50% • Short-term seizure freedom • Serious adverse events • Treatment cessation due to adverse drug events • Health-related quality of life

ASM: antiseizure medication; IGE: idiopathic generalised epilepsy; RCT: randomised controlled trial

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

Summary of the evidence

Across all the comparisons identified in this review, the majority showed no important difference between the interventions compared (for example, add-on topiramate versus placebo, add-on brivacetam versus placebo, add-on piracetam versus placebo, and add-on topiramate versus valproate). Exceptions were add-on lamotrigine versus add-on valproate, and add-on levetiracetam versus placebo; where add-on valproate had an important benefit in terms of outcome quality of life, and add-on levetiracetam had an important benefit in terms of outcome reduction of seizure frequency >50%, short term seizure freedom and quality of life.

Typically, the comparisons where no difference in outcomes between interventions was found included less participants and had considerably imprecise findings, therefore they should not be taken as definitive evidence of no difference in outcomes between the interventions. There were also a number of outcomes in the protocol that were not reported by any studies, including neuropsychological changes and mortality. For the comparison of add-on levetiracetam versus placebo, the seizure related outcomes were of moderate quality, which may indicate that the true effect size is similar to the estimated effect reported by the study.

No evidence was found for clobazam, clonazepam, ketogenic diet, perampanel and zonisamide.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

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

No studies were identified which were applicable to this review question.

Economic model

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

Summary of the economic evidence

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The main treatment goal in people with myoclonic seizures is seizure freedom, therefore the committee considered this a critical outcome. As seizure freedom is not always achieved, a balance between seizure reduction and adverse effects is important, and this balance may differ between treatments. Therefore the committee also agreed to include reduction in seizure frequency, time to withdrawal of treatment, and adverse effects as critical outcomes.

People who experience myoclonic seizures as part of a specific syndrome may display negative cognitive effects over time, therefore, cognitive performance measured by intelligence quotient (IQ) and other validated tests were included as important outcomes in this review. Additionally, health related quality of life was included as an important outcome, as the impact of epilepsy has has a direct impact on daily life for people who experience myoclonic seizures which should be taken into consideration when making treatment decisions as it is hoped that greater seizure control will lead to improved quality of life.

The quality of the evidence

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

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

Benefits and harms

The committee noted that myoclonic seizures may be a feature of some severe epilepsy syndromes, such as Lennox-Gastaut syndrome or infantile spasms. Due to the high risk of developmental problems in these syndromes, rapid assessment or advice from a tertiary paediatric neurologist is required in children under 4. As this is best practice, the committee agreed that it is unlikely that this recommendation would lead to increased costs or resource use.

The committee agreed that, prior to starting antiseizure therapies 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 seizure 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.

Myoclonic 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 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. The committee discussed at length that sodium valproate has risks to women and girls who are able to have children and that it is associated with a risk of birth defects and developmental disorders. Therefore, the committee agreed that levetiracetam should be used as first-line treatment in women and girls able to have children or in those whose epilepsy is likely to continue beyond puberty. There is evidence for the efficacy of levetiracetam and prescribing this will avoid the need to change antiseizure medication at puberty. Based on this evidence, the committee agreed that levetiracetam should be offered as second-line alternative or add-on treatment if sodium valproate is unsuccessful.

Based on their expertise, the committee agreed on other medications which may be used as third-line alternative or add-on treatments if second-line alternative or add-on treatment does not achieve seizure control. Recommendations did not favour one medication over another since the choice would need to be individually tailored to take account of age, sex, symptoms, syndromes and preferences.

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

The committee agreed that, if other treatments have been unsuccessful, sodium valproate can be considered for girls and women able to have children after a full and clear discussion, with them or their families/carers, as appropriate, ensuring they understand all the important safety issues associated with this medicine. If sodium valproate is prescribed, clinicians must follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a pregnancy prevention programme, if appropriate.

In line with the BNF, the committee noted that some medications should not be used as these are known to increase the frequency of myoclonic seizures.

Despite the absence of robust evidence, the committee decided not to prioritise a research recommendation on this subject as they considered that other topics were of higher priority.

Cost effectiveness and resource use

No relevant published economic evaluations were identified and no additional economic analysis was undertaken for this topic.

The committee agreed that there was unlikely to be an impact on resource use or costs from the recommendations made as they reflect the antiseizure medications used in the treatment of myoclonic seizures that are currently used in practice. The antiseizure medications recommended first and second-line (which will make up the majority of treatment) are also indentical to the previous NICE guideline.

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 5.4.1-5.4.8.

References

Biton 2005

Biton, V., Bourgeois, B. F., Topiramate in patients with juvenile myoclonic epilepsy, Archives of Neurology, 62, 1705-1708, 2005

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Koskiniemi 1998

Koskiniemi, M., Van Vleymen, B., Hakamies, L., Lamusuo, S., Taalas, J., Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo, Journal of neurology, neurosurgery, and psychiatry, 64, 344-348, 1998

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Machado, R. A., Garcia, V. F., Astencio, A. G., Cuartas, V. B., Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial, Seizure, 22, 846-55, 2013

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Noachtar, S., Andermann, E., Meyvisch, P., Andermann, F., Gough, W. B., Schiemann-Delgado, J., Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures, Neurology, 70, 607-616, 2008

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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 myoclonic seizures?

Table 8: Review protocol for effectiveness of antiseizure therapies in treatment of myoclonic seizures

Field	Content
PROSPERO registration number	CRD42020166726
Review title	Effectiveness of antiseizure therapies for myoclonic seizures
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of myoclonic seizures?
Objective	The objective of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have myoclonic seizures. This review will determine the effectiveness of drugs given alone (monotherapy) or as add-ons (combination therapy). People with myoclonic seizures may have other seizures (such as tonic clonic seizures); and, for this review we are only looking at evidence where these have been separately reported.
Searches	**The following databases will be searched:** • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations

Field	Content
	• Embase • EMCare Searches will be restricted by: • Date: No date limit • English language studies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Epilepsy with myoclonic seizures

Population	• Inclusion: people with confirmed epilepsy with myoclonic seizures
	• Exclusion:
	  ○ Newborn babies (under 28 days) with acute symptomatic seizures
	  ○ Non-epileptic myoclonus

Intervention/Exposure/Test	The following anti-seizure therapies and their combinations will be considered: • Brivaracetam • Clobazam • Clonazepam • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Perampanel • Piracetamem • Sodium Valproate • Topiramate • Zonisamide

Field	Content
Comparator/Reference standard/Confounding factors	• 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 (for example 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 (for example including people with epilepsy with different seizure types) will be excluded, unless subgroup analysis for epilepsy with myoclonic seizures has been reported. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare 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", (*for example *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 effects) ○ treatment cessation due to adverse event [dichotomous outcome only])

Field	Content
	○ mortality
Secondary outcomes (important outcomes)	• Neuropsychological changes (IQ testing, or other validated tools) • Health-related overall quality of life (measured using 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. Titles and abstracts of the retrieved citations will be screened. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria outlined in the review protocol. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. 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. 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.

Field	Content
	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 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

Field	Content			
	baseline. If baseline SD is not available, then SD at follow up will be used. • For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. • For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity • 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 • Those with other seizure types and/or as part of other epilepsy syndrome (for example tonic-clonic seizures with myoclonous)			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	08 March 2020			
Anticipated completion date	02 June 2021			
Stage of review at time of this submission	Review stage		Started	Completed

Field	Content		
	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.		
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		

Field	Content	
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=166726	
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; myoclonic seizures	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

HR: hazard ratio; IQ: intelligence quotient; RCT: randomised controlled trial; RR: risk ratio; SD: standard deviation; SMD: standardised mean difference

Appendix B – Literature search strategies

Clinical

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

EMCare 1995 to November 27, 2019; Embase Classic+Embase 1947 to 2019 November 27; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2019 November 27, 2019
Date of last search: 27 November 2019

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	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.
2	brivaracetam/ use emczd, emcr or (brivaracetam or brivlera or nubriveo or rikelta).ti,ab.
3	clobazam/ use emczd, emcr, ppez or (chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl).ti,ab.
4	clonazepam/ use emczd, emcr, ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.
5	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
6	5 use emczd, emcr
7	diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycerides/
8	7 use ppez
9	((adequate adj3 protein*) or atkin* or keto* or kd* or (carbohydrate* adj5 (restrict* or low* or reduc*)) or (glyc?emic 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.
10	or/6,8-9
11	lamotrigine/ use emczd, emcr, 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.
12	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
13	perampanel/ use emczd, emcr or (fycompa or perampanel).ti,ab.
14	piracetam/ use emczd, emcr,ppez or (avigilen or axonyl or cerebroforte or cerebrosteril or cerebryl or cereparn or cetam or ciclofalina or cuxabrain or dinagen or durapitrop or encetrop or euvifor or gabacet or geram or geratam or memo puren or memopuren or noostan or nootron or nootrop or nootropil or nootropyl or normabrain or novocetam or oikamid or oxynium or piracebral or piracetam or piracetan or piracetrop or piramem or pirazetam or pyracetam or pyramem or pyrrolidone or sinapsan).ti,ab.
15	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.
16	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 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.
17	zonisamide/ use emczd, emcr,ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.

#	searches
18	or/2-4,10-17
19	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.
20	19 use ppez
21	(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.
22	21 use ppez
23	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.
24	23 use emczd, emcr
25	or/20,22,24
26	meta-analysis/
27	meta-analysis as topic/ or systematic reviews as topic/
28	"systematic review"/
29	meta-analysis/
30	(meta analy* or metanaly* or metaanaly*).ti,ab.
31	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
32	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
33	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
34	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
35	(search* adj4 literature).ab.
36	(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.
37	cochrane.jw.
38	((pool* or combined) adj2 (data or trials or studies or results)).ab.
39	(or/26-27,30,32-38) use ppez
40	(or/28-31,33-38) use emczd, emcr
41	or/39-40
42	or/25,41
43	1 and 18 and 42
44	43
45	limit 44 to english language
46	((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.)
47	46 use emez
48	((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.)
49	48 use mesz
50	47 or 49
51	45 not 50

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 11 of 12 November 2019; Cochrane Central Register of Controlled Trials, Issue 11 of 12, November 2019

Date of last search 27 November 2019

#	searches
1	mesh descriptor: [seizures] this term only
2	(((myoclon* near/2 (absence* or epileps* or seizure* or jerk* or “progressive familial epilep*” or spasm* or convulsion*)) or ((lafora or unverricht) near/2 disease) or “muscle jerk”)):ti,ab,kw
3	#1 or #2
4	((brivaracetam or brivlera or nubriveo or rikelta)):ti,ab,kw
5	mesh descriptor: [clobazam] this term only

#	searches
6	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab,kw
7	mesh descriptor: [clonazepam] this term only
8	((aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril)):ti,ab,kw
9	mesh descriptor: [diet, carbohydrate-restricted] this term only
10	mesh descriptor: [dietary fats] explode all trees
11	mesh descriptor: [glycemic index] this term only
12	mesh descriptor: [diet, ketogenic] this term only
13	mesh descriptor: [triglycerides] explode all trees
14	(((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
15	mesh descriptor: [lamotrigine] this term only
16	((crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
17	mesh descriptor: [levetiracetam] this term only
18	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
19	((fycompa or perampanel)):ti,ab,kw
20	mesh descriptor: [piracetam] this term only
21	((avigilen or axonyl or cerebroforte or cerebrosteril or cerebryl or cereparn or cetam or ciclofalina or cuxabrain or dinagen or durapitrop or encetrop or euvifor or gabacet or geram or geratam or "memo puren" or memopuren or noostan or nootron or nootrop or nootropil or nootropyl or normabrain or novocetam or oikamid or oxynium or piracebral or piracetam or piracetan or piracetrop or piramem or pirazetam or pyracetam or pyramem or pyrrolidone or sinapsan)):ti,ab,kw
22	mesh descriptor: [topiramate] this term only
23	((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
24	mesh descriptor: [valproic acid] this term only
25	(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 or episenta or epival cr or ergenyl or "ergenyl chrono" or "ergenyl chronosphere" or "ergenyl retard" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or "n dipropylacetic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or "sodium di n propylacetate" or "sodium 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
26	mesh descriptor: [zonisamide] this term only
27	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
28	{or #4-#27}
29	#3 and #28

Database(s): DARE; HTA database - CRD

Date of last search: 27 November 2019

#	searches
1	mesh descriptor seizures this term only
2	((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")
3	#1 or #2

Economic

Database(s): MEDLINE & Embase (Multifile) - OVID

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

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

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

#	searches
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

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

Date of last search: 31 March 2021

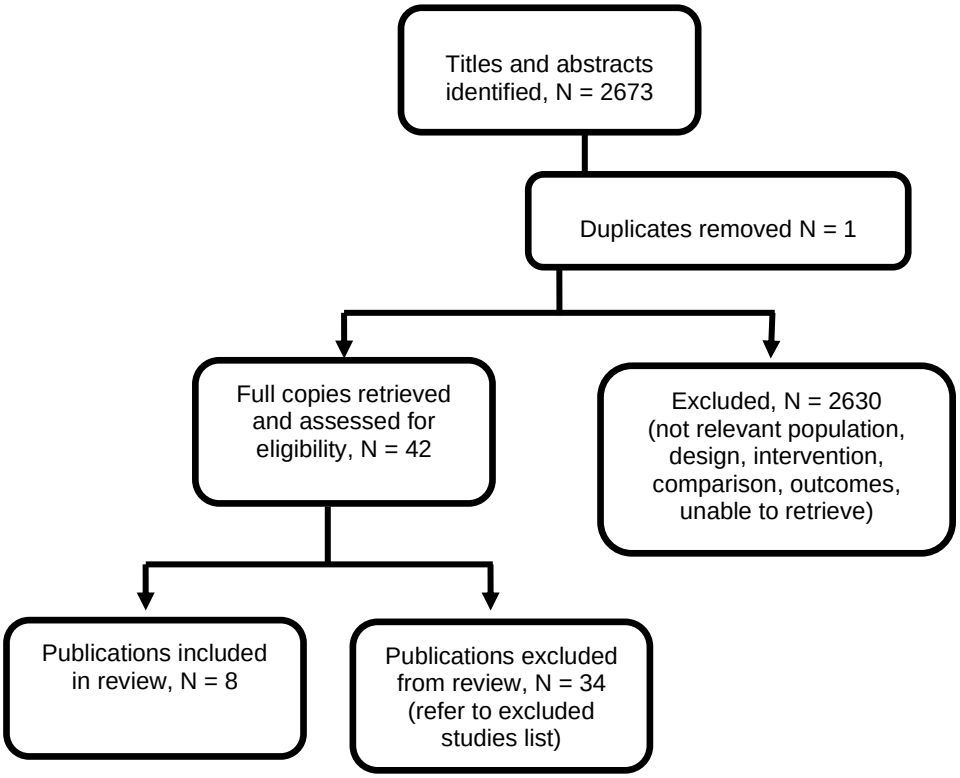
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or ("continous spike wave of slow sleep" or "infant* spasm*")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

#	searches
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or “grand mal” or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

Appendix C – Clinical evidence study selection

Clinical study selection for: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of myoclonic seizures?

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 myoclonic seizures?

Table 9: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Biton, V., Bourgeois, B. F., Topiramate in patients with juvenile myoclonic epilepsy, Archives of Neurology, 62, 1705-1708, 2005 **Ref Id** 1080000 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of	**Sample size** N=22 with juvenile myoclonic epilepsy (JME) (n=11 allocated to topiramate and n=11 allocated to placebo). Patients with myoclonic seizures accounted for n=13 (n=5 allocated to topiramate and n=8 allocated to placebo) **Characteristics** **The following characteristics are based on the total sample size (N=22)** <u>Age, years, median (range/ IQR not reported):</u> Topiramate: 27 Placebo: 34	**Interventions** Patients were randomised to topiramate or placebo. The starting dose of topiramate was 50mg/day during 4 weeks. This was then increased at 2 weeks to target doses of 400mg/day in adults or 6mg/kg/day for children. Treatment was continued for 12 weeks	**Details** Patients and parents/carers had a seizure diary, recording the occurrence of all seizures. The majority of patients (64%) were treated with 2 antiseizure therapies before topiramate was added. Follow-up: 24 weeks (maximum study duration: 34 weeks)	**Results** <u>Reduction of generalised seizure frequency >50% in those with myoclonic seizures</u> Topiramate: 3/5 Placebo: 6/8	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: High risk** 1.1: No information 1.2: No information 1.3: No information **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was open label 2.2: Yes, the study was

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topiramate as an add-on therapy compared to placebo in patients with juvenile myoclonic epilepsy **Study dates** Not reported **Source of funding** Johnson and Johnson Pharmaceutical Research and development	Female gender, n (%): 7 (64%) Topiramate: 7 (64%) Placebo: 7 (64%) Epilepsy syndrome, n (%) Primarily generalised tonic-clonic seizures, n (%) Topiramate: 11 (100) Placebo: 11 (100) Myoclonic, n (%) Topiramate: 5 (45) Placebo: 8 (73) Absence, n (%) Topiramate: 4 (36) Placebo: 5 (45) **Inclusion criteria** • Those with at least 3 primarily generalised tonic-clonic seizures during an 8 week baseline period • Presence of an EEG consistent with				open label 2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7: No information **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined 4.2: No information 4.3: Yes, open label study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	generalised epilepsy **Exclusion criteria** Not reported				4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias for all domains. **Other information** Note that only data relevant for those with myoclonic seizures has been extracted as part of the outcomes and results section

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kalviainen, R., Genton, P., Andermann, E., Andermann, F., Magaudda, A., Frucht, S. J., Schlit, A. F., Gerard, D., de la Loge, C., von Rosenstiel, P., Brivaracetam in Unverricht-Lundborg disease (EPM1): results from two randomized, double-blind, placebo-controlled studies, Epilepsia, 57, 210-221, 2016 **Ref Id** 1080603 **Country/ies where the study was carried out** Finland **Study type** Double-blind placebo-controlled RCTs. Note that 2 trials were reported within the same publication (N01187 trial and N01236 trial)	**Sample size** N01187 trial (a): N=56 (n=16 allocated to placebo, n=16 allocated to 50 mg/day BRV, n=18 allocated to 150 mg/day BRV) N01236 trial (b): N=56 (n=18 allocated to placebo, n=20 allocated to 5 mg/day BRV, n=18 allocated to 150 mg/day BRV) **Characteristics** **N01187 trial** Age, mean (SD) Placebo: 39.1 (8.3) 50 mg/day BRV: 39.4 (9.6) 150 mg/day BRV: 39.1 (13.3) Age at onset, mean (SD): Placebo: 11.4 (3.1) 50 mg/day BRV: 9.4 (2.9) 150 mg/day BRV: 11.8	**Interventions** N01187 trial: placebo, 50 mg/day BRV and 150 mg/day BRV N01236 trial: placebo, 5 mg/day BRV and 150 mg/day BRV	**Details** Using daily record cards, patients recorded type and number of seizures, adverse events, and changes in medication. The Unified Myoclonus Rating Scale (UMRS) was completed by the patients and/or caregiver at screening, randomization, and maintenance period. Section 3 of the questionnaire (sensitivity to 17 different stimuli) was evaluated using video recordings. The UMRS was used to assess the following: reduction in action myoclonus score from baseline until the last treatment, functional disability in everyday activities, stimulus sensitivity score, and patient questionnaire score. Follow-up: 14 weeks (no measure of variability was reported)	**Results** **Kalviainen 2016a: N01187 trial; ITT population** Median (range) reduction difference in action myoclonus score from baseline at last treatment visit compared to placebo 50 mg/day group: 23.3 (0.7 to 47.9), p=0.162 150 mg/day group: 9.6 (-12.0 to 37.2), p=0.596 Functional disability in everyday activities; median estimate of difference compared to placebo at last treatment visit (range: 0 [best] to 28 [worst]) 50 mg/day group: 12.3 (-10 to 36.4), p=0.247 150 mg/day group: -3.7 (-42.5 to 14.3), p=0.561	**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 1.2: Yes, people had no prior knowledge of allocation 1.3: Yes, some differences between groups at baseline. **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind 2.2: No, double blind **Domain 3: Missing outcome data: Some**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the efficacy and safety of adjunctive brivaracetam (BRV) in people with Unverricht-Lundborg disease (EPM1), also known as progressive myoclonic epilepsy type 1 **Study dates** N01187: November 2006 to October 2007 N01236: November 2006 to January 2008 **Source of funding** UCB Pharma	(6.4) Male gender, n (%): Placebo: 10 (62.5) 50 mg/day BRV: 9 (56.3) 150 mg/day BRV: 9 (50.0) **N01236 trial** Age, mean (SD) Placebo: 34.3 (9.2) 5 mg/day BRV: 35.8 (10.9) 150 mg/day BRV: 33.7 (11.4) Age at onset, mean (SD): Placebo: 8.8 (2.6) 5 mg/day BRV: 9.7 (2.8) 150 mg/day BRV: 9.7 (2.8) Male gender, n (%): Placebo: 6 (33.3) 5 mg/day BRV: 9 (45.0) 150 mg/day BRV: 9 (50.0)			Stimulus sensitivity score; median estimate of difference compared to placebo at last treatment visit (range: 0 [best] to 17 [worst]) 50 mg/day group: 25 (0 to 100), p=0.096 150 mg/day group: 2.5 (0 to 100), p=0.483 Patients with at least 1 treatment emergent adverse effect Placebo: 12/16 50 mg/day group: 12/16 150 mg/day group: 10/18 Patient questionnaire score, median estimate of difference compared to placebo at last treatment visit (range: 0 [best] to 44 [worst]) 50 mg/day group: -10 (-30.5 to 14.8),	**concerns** 3.1: No, a number of people dropped out prior to the trial ending 3.2: Probably not, no analysis methods used to correct for bias 3.3: Yes, adverse events and seizure control were often reasons for leaving the study 3.4: No, Similar numbers and reasoning in each group for leaving the study **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom 4.2: Probably no, outcomes included seizure frequency and reduction, and these are unlikely to differ between treatment arms

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria • ≥16 years old • Genetically ascertained EPM1 with moderate to severe myoclonous (action myoclonus score ≥30/160 at screening) • Those who were being treated or had been treated with valproic acid and/or clonazepam, and were on a stable regimen of concomitant ASMs for at least 1 month before and during the whole study period **Exclusion criteria** • Those with hepatic impairment • Those with suicidal ideation in the prior year or a history of suicide in the previous 5 years • Those with an ongoing psychiatric condition, other than a mild, controlled disorder • Those with an acute chronic illness or a clinically significant condition			p=0.350 150 mg/day group: -5.4 (-28 to 18.2), p=0.470 **Kalviainen 2016b: N01236 trial; ITT population** Median (range) reduction difference in action myoclonus score from baseline at last treatment visit compared to placebo 5 mg/day group: -18.1 (-39.3 to 4.9), p=0.105 150 mg/day group: 0.2 (-26.1 to 25), p=0.942 Functional disability in everyday activities; median estimate of difference compared to placebo at last treatment visit (range: 0 [best] to 28 [worst]) 5 mg/day group: 0 (-33.3 to 18.8),	4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Probably yes, protocol registered 5.2: No, single measurements 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: Some concerns** The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain **Other information** Quality of life and global evaluation scale (GES) scores could not be extracted because no raw data was reported; all estimates were reported in figures

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Those receiving felbamate, phenytoin or vigabatrin • Those taking drugs with possible effects on the central nervous system or drugs that could affect the metabolism of vigabatrim were not included, unless the dose had been estable for the previous month prior assessment • Concomitant benzodiazepines were allowed, provided that the patient had been on a stable dose a month before assessment			p=0.806 150 mg/day group: 1.2 (-21.9 to 31.1), p=0.672 Stimulus sensitivity score; median estimate of difference compared to placebo at last treatment visit (range: 0 [best] to 17 [worst]) 5 mg/day group: 0 (-50.0 to 66.7), p=0.654 150 mg/day group: 0 (-25.0 to 100.0), p=0.549 Patients with at least 1 treatment emergent adverse effect Placebo: 13/18 5 mg/day group: 16/20 150 mg/day group: 15/18 Patient questionnaire score, median estimate of difference compared to placebo	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				at last treatment visit (range: 0 [best] to 44 [worst]) 5 mg/day group: 10.0 (-5.6 to 30), p=0.111 150 mg/day group: 14.3 (-1.8 to 39.4), p=0.037	
Full citation Koskiniemi, M., Van Vleymen, B., Hakamies, L., Lamusuo, S., Taalas, J., Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo, Journal of neurology, neurosurgery, and psychiatry, 64, 344-348, 1998 **Ref Id** 1100253 **Country/ies where the study was carried out**	**Sample size** N=20 were enrolled, of which n=18 were randomised; the crossover design of the study meant that each received placebo and 2 of the sequences of piracetam **Characteristics** Number of males, n (%): 12 (60) No further demographic details were provided **Inclusion criteria** • Unverricht-Lundborg disease • Onset between 6 and 15 years old	**Interventions** Study treatments were three daily dosages of piracetam: 9.6 g, 16.8 g, or 24 g and placebo.	**Details** Diagnosis was confirmed by genetic analysis. All piracetam and placebo tablets were identical in appearance, taste, and smell. Blinding was maintained by a dosage of 10 tablets twice daily to all patients during placebo and active treatment phases. The study had a crossover design; people received placebo and 2 of the 3 dose-age regimens of piracetam, each for 2 weeks for a total period of 6 weeks. There was no washout period between doses because it was previously shown that there was no carryover effect. The myoclonus rating scale was used to perform the assessments. These were performed at study entry and	**Results** Stimulus sensitivity, mean score (95% CI) (range 0 [best] to 40 [worst]) Placebo (n=18): 13.2 (7.2 to 19.1) 9.6 g/day piracetam (n=12): 13.0 (6.6 to 19.3) 16.8 g/day piracetam (n=12): 11.1 (4.8 to 17.4) 24 g/day piracetam (n=12): 9.5 (3.2 to 15.8) p-value: 0.07 Functional disability, mean score (95% CI) (range 0 [best] to	**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 1.2: Yes, people had no prior knowledge of allocation 1.3: Yes, some differences between groups at baseline. **Domain 2: Deviations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Finland **Study type** Double blind, crossover RCT **Aim of the study** To assess the effectiveness and safety of piracetam in people with progressive myoclonus epilepsy **Study dates** Not reported **Source of funding** UCB Pharma	• Stimulus sensitive myoclonus • Generalised seizures • Abnormal EEG recordings with photosensitivity and spike and wave paroxysms • On medication, with a dosage stable from at least 1 month before study entry **Exclusion criteria** • Those with mild Unverricht-Lundborg disease (sum score <3) • Pregnant or lactating women • Those of childbearing age not using adequate contraception • Those with clinically relevant abnormalities • Those enrolled in a clinical trial before 3 months of study entry • Those with another member of their family participating in the study		after 2 week treatment period by the same neurologist in the same environment and at the same time of the day. Data was reported as adjusted sum scores. Follow-up: 2 weeks per dose for a total of 6 weeks (no measure of variability was reported)	28 [worst]) Placebo (n=18): 13.3 (9.9 to 16.8) 9.6 g/day piracetam (n=12): 11.5 (7.9 to 15.1) 16.8 g/day piracetam (n=12): 11.5 (7.9 to 15.0) 24 g/day piracetam (n=12): 10.5 (7.0 to 14.1) p-value: 0.003 Investigator's global assessment, mean score (95% CI) (range 0 [best] to 4 [worst]) Placebo (n=18): 2.8 (2.3 to 3.4) 9.6 g/day piracetam (n=12): 2.5 (1.9 to 3.1) 16.8 g/day piracetam (n=12): 2.5 (1.9 to 3.1) 24 g/day piracetam (n=12): 2.2 (1.6 to 2.8)	**from intended interventions: Low risk** 2.1: No, double blind 2.2: No, double blind **Domain 3: Missing outcome data: Some concerns** 3.1: No, a number of people dropped out prior to the trial ending 3.2: Probably not, no analysis methods used to correct for bias 3.3: Yes, adverse events and seizure control were often reasons for leaving the study 3.4: No, Similar numbers and reasoning in each group for leaving the study **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				p-value: 0.002 Patient's global assessment, as measured by VAS, mean score (95% CI) (range 0 [best] to 100 [worst]) Placebo (n=18): 50.8 (41.2 to 60.4) 9.6 g/day piracetam (n=12): 45.2 (33.7 to 56.7) 16.8 g/day piracetam (n=12): 40.3 (28.8 to 51.8) 24 g/day piracetam (n=12): 34.4 (22.9 to 45.9) p-value: 0.01	whom 4.2: Probably no, outcomes included seizure frequency and reduction, and these are unlikely to differ between treatment arms 4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Probably yes, protocol registered 5.2: No, single measurements 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: Some concerns** The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain **Other information** SDs were calculated from confidence intervals by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the NGA team
Full citation Levisohn, P. M., Holland, K. D., Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison, Epilepsy & Behavior, 10, 547-52, 2007 **Ref Id** 1080743 **Country/ies where the study was carried out** US **Study type** Open label RCT **Aim of the study** To evaluate clinical response when these topiramate and valproate are titrated to optimal effect in adolescents/adults with juvenile myoclonic	**Sample size** N=28 with juvenile myoclonic epilepsy (JME) (n=19 allocated to topiramate and n=9 allocated to valproate). Patients with myoclonic seizures accounted for n=23 (n=14 allocated to topiramate and n=9 allocated to valproate) **Characteristics** **The following characteristics are based on the total sample size (N=28)** Age, years, median (range) Topiramate: 15 (9-42), Valproate: 16 (12-34) Gender, female (%) Topiramate: 13 (68%), Valproate: 4 (44%)	**Interventions** A 14-week titration phase was followed by a 12-week maintenance phase. Topiramate target dosage was 3–4 mg/kg/day (maximum, 9 mg/kg/day) for people 12–16 years of age and 200 mg/day (maximum, 600 mg/day) for patients >16 years of age. Valproate target dosages were 10 mg/kg/day in patients 12–16 years of age and 750 mg/day in those >16 years (overall maximum, 60 mg/kg/day).	**Details** Seizure counts were captured with seizure diaries maintained by patients and were reviewed at each study visit. Questionnaires were used to assess drug-related systemic toxicity and neurotoxicity. The questionnaires were completed at each post-baseline visit (4, 8, 14, and 26 weeks). Follow-up: 26 weeks (no measure of variability was reported)	**Results** People with over 50% reduction in myoclonic seizure frequency Topiramate: 12/14 Valproate: 9/9	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Yes, computer generated 1.2: Yes, people had no prior knowledge of allocation 1.3: Yes, some differences between groups at baseline. Topiramate group had higher percentage of women, PGTCS seizures, and people not on baseline ASMs. Valproate group had a higher weight and percentage of people with myoclonic seizures. **Domain 2: Deviations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
epilepsy **Study dates** Unclear **Source of funding** Not stated	**Inclusion criteria** • 12–65 years old • >/=25 kg • Confirmed diagnosis of juvenile myoclonic epilepsy • People who had active epilepsy in the form of myoclonus or >/=1 PGTCS in the 3 months before study entry. • Topiramate or valproate could be initiated as monotherapy or as an adjunct to another ASM (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy. • Females of childbearing potential had to be premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception. **Exclusion criteria** • Previous discontinuation of topiramate or				**from intended interventions: Some concerns** 2.1: Yes, open label 2.2: Yes, open label 2.3. Probably no, no indication the context affected recruitment or engagement 2.4 NA 2.5. NA 2.6 ITT used 2.7 NA **Domain 3: Missing outcome data: Some concerns** 3.1: No, a number of people dropped out prior to the trial ending 3.2: Probably not, no analysis methods used to correct for bias 3.3: Yes, adverse events and seizure control were often reasons for leaving the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	valproate due to an adverse event • Abnormal cranial CT or MRI scan • Dementia or mental retardation • Progressive myoclonic epilepsy • Clinically unstable medical conditions • History of nephrolithiasis • SGPT levels greater than two times the upper limit of the normal range • Co-therapy with a carbonic anhydrase inhibitor or barbiturate ASM • Use of an experimental medication or device within 30 days of study entry.				3.4: No, Similar numbers and reasoning in each group for leaving the study **Domain 4: Measurement of the outcome: Some concerns** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, outcomes standardised though there was no blinding 4.3: Yes, open label study 4.4: No, the outcomes appear to be objective **Domain 5: Selection of the reported result: Some concerns** 5.1: Probably no, the study authors do not make reference to any study protocol 5.2: No, single measurements 5.3: No, analysis details

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Full citation Machado, R. A., García, V. F., Astencio, A. G., Cuartas, V. B., Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial, Seizure, 22, 846-855, 2013 **Ref Id** 1080800 **Country/ies where the study was carried out** Cuba **Study type** Open label RCT	**Sample size** N=82 Lamotrigine n=43, valproate n=39 Eight people randomized to valproate regimen and 2 patients randomized to the lamotrigine group were not treated, and were excluded because they did not pick up their medication. Analysed numbers: lamotrigine n=41, valproate n=31 **Characteristics** Age, years, mean (SD)	**Interventions** Although the prescribed drug was determined by randomization, drug dose was that prescribed by the physicians in their everyday practice. The initial maintenance dose, and any subsequent increment or decrement was decided by the epileptologists, but the rate of titration was aided by guidelines. People on carbamazepine or phenytoin were instructed to drop the doses out slowly during the following 3 weeks and afterwards,	**Details** The primary end points of the study were: • time from randomization to treatment withdrawal • time from randomization to seizure remission. • frequency of clinically important adverse events and side-effects emerging after randomization • quality of life outcomes Follow-up: 24 months (Authors attempted to follow all patients for at least 2 years, but those who did not return to the outpatient clinic were included until the date of their last follow-up). No measure of variability was	**Results** ITT analysis used. Median (range) time to withdrawal for any reason Lamotrigine 11 (3 to 20) Valproate 12 (3 to 20) Percentage of patients with reported side effects Lamotrigine 7 of 41, valproate 11 of 31 Difference in QOLIE-31 from start of study to end of study (mean ± 2.5 SD) Lamotrigine 7.3, valproate 12.3: no	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: No information 1.2: No information 1.3: No, groups similar at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes, open label study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the efficacy and tolerability of lamotrigine in adult patients with juvenile myoclonic epilepsy **Study dates** 2008 to 2010 **Source of funding** It was stated that no funding was received from pharmaceutical companies for this study	Lamotrigine 26 (11), valproate 27 (13) Gender, female (%) Lamotrigine 26 (63%), valproate 21 (67%) Prior treatment 63 of 82 people had been treated with carbamazepine. 2 people had received phenytoin. 17 people had never received any medication before. **Inclusion criteria** • Juvenile myoclonic epilepsy **Exclusion criteria** Not reported	they should enter the study. Lamotrigine Highest guideline dose was 300mg per day and could be reached after 25 weeks. Valproate Highest dose was 3000mg per day and this could be reached after 9 weeks	reported	measure of variance provided	2.2: Yes, open label study 2.3: No, none reported 2.4: NA 2.5: NA 2.6: ITT used 2.7: NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Some concerns** 4.1: Probably no, median change often used and this can obscure the more extreme results 4.2: Probably no, outcomes appear well defined 4.3: Yes, open label study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					4.4: Yes, there were subjective outcomes 4.5: Possibly not, no reason to think it would **Domain 5: Selection of the reported result: Some concerns** 5.1: No mention of a study protocol 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result. **Other information** All patients presented with juvenile myoclonic epilepsy (JME). The predominant seizure type were myoclonic jerks.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nejad, S. E. M., Nikpour, M. R. A., Rahim, F., Naghibi, S. N., Bahrammi, M. A., A randomized open-label comparison of lamotrigine and valproate in patients with juvenile myoclonic epilepsy, International Journal of Pharmacology, 5, 313-318, 2009 **Ref Id** 1080944 **Country/ies where the study was carried out** Iran **Study type** Randomised open label trial **Aim of the study** To assess the effectiveness of lamotrigine compared with valproate in	**Sample size** N=46 women (n=23 randomised to lamotrigine and n=23 randomised to valproate) **Characteristics** Age, years, mean (SD), n (%): age 8-30 years Female gender, n (%): 46 (100%) Epilepsy syndrome, n (%) Juvenile myoclonic epilepsy, n (%) 46 (100%) Tonic-clonic seizures, n (%) 43 (93.48%) Myoclonic absences, n (%) 5 (11%) **Inclusion criteria**	**Interventions** Lamotrigine was started at the dose of 500 mg day and was progressively increased to a mean dose of 1500-2000 mg day in a time course of 8 weeks. The target maintenance dose for valproate was 800 mg day after starting valproate at the dose of 200 mg/12 h. The mean dose was reached within 4 weeks. Patients were clinically observed every 3 months.	**Details** The basis for comparison was defined as the myoclonic seizure frequency in the 6 months prior to the commencement of treatment. We classified patients post-treatment into three categories: those achieving seizure freedoms, those achieving between 50 and 99% reduction in seizures and those with worsening. We observed the reduction of massive or focal epileptic myoclonus and other generalized seizures (for example absence, tonic-clonic). Follow-up: 28 weeks (no measure of variability was reported)	**Results** **Mean seizure reduction from baseline** *Juvenile myoclonic* Mean seizure frequency at baseline (SD) Valproate: 5.10 (1.51), n=23 Lamotrigine: 4.77 (1.63), n=23 Mean seizure frequency at follow-up (SD) Valproate: 0.60 (1.31), n=23 Lamotrigine: 0.86 (1.69), n=23	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: High risk** 1.1: No information 1.2: No information 1.3: No information **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7: No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients with juvenile myoclonic epilepsy **Study dates** 2007 to 2008 **Source of funding** Not reported	Women with juvenile myoclonic epilepsy **Exclusion criteria** Not reported				**Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined 4.2: No information 4.3: Yes, open label study 4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias for all domains. **Other information** Note that only data relevant for those with myoclonic seizures has been extracted as part of the outcomes and results section.
Full citation Noachtar, S., Andermann, E., Meyvisch, P., Andermann, F., Gough, W. B., Schiemann-Delgado, J., Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures, Neurology, 70, 607-616, 2008 **Ref Id**	**Sample size** N=121 Levetiracetam n=61, placebo n=60 113 had Juvenile myoclonic epilepsy and 8 had Juvenile absence epilepsy **Characteristics** Age, years, mean (SD)	**Interventions** Following an 8-week, single-blind, prospective, placebo baseline period, patients were randomly assigned to receive levetiracetam or placebo. Levetiracetam 4 week titration per Following an 8-week, single-blind, prospective, placebo	**Details** Daily record cards used by people or their families to record seizures. Follow-up: 16 weeks (no measure of variability was reported)	**Results** Reduction of myoclonic seizure frequency >50% Levetiracetam 35 of 60, placebo 14 of 60 Short term seizure freedom during 16-week treatment period Levetiracetam 8 of 61, placebo 0of 60 Serious adverse events	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: some concerns** 1.1: Yes, central randomization centre 1.2: Yes, central

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1080960 **Country/ies where the study was carried out** 14 countries (Australia, New Zealand, Europe, and North and Central America) **Study type** Multi-centre RCT **Aim of the study** To assess the efficacy, safety, and tolerability of levetiracetam as adjunctive therapy for people with myoclonic seizures that were not fully controlled despite treatment with an ASM. **Study dates** From 2001 to 2004 **Source of funding** This study was funded	Levetiracetam 25 (7.4), placebo 26.8 (9.5) <u>Female gender, n (%)</u> Levetiracetam 39 (63.9%), placebo 38 (63.3%) <u>Epilepsy syndrome, n (%)</u> Juvenile myoclonic epilepsy: Levetiracetam 54 (88.5%), placebo 59 (98.3%) Juvenile absence epilepsy: Levetiracetam 7 (11.5%), placebo 1 (1.7%) <u>Concomitant ASM, n (%)</u> Valproic acid: levetiracetam 37 (61%), placebo 33 (55%) Lamotrigine levetiracetam 15 (25%), placebo 17 (28%) Other: levetiracetam 15 (14%), placebo 17 (17%) **Inclusion criteria** • 12 to 65 years old • a diagnosis of IGE with myoclonic seizures • receiving a stable dose of one ASM for at least 4	baseline period, patients were randomly assigned to receive levetiracetam or placebo. Levetiracetam 4 week titration period where dose was incresaed to 3,000 mg/day. This was continued for 12 weeks. 1 concomitant ASM was to be taken with the study treatment at a stable dose. People were discontinued from the study if they withdrew consent for any reason or for lack of efficacy or safety reasons, as judged by the investigator. Placebo: Followed same pattern as intervention group with placebo. iod where dose was incresaed to 3,000 mg/day. This was continued for 12 weeks. 1 concomitant ASM was to be taken		Levetiracetam 4 of 61, placebo 1 o <u>Treatment cessation due to adverse drug effects</u> Levetiracetam 3 of 61, placebo 1 of 60 <u>Improvement in overall HRQoL via QoLIE-31-P</u> Levetiracetam 88.3%, placebo 60.4%. No measure of variance provided.	randomisation centre ensured concealment 1.3: Yes, more people with juvenile absence epilepsy in the levetiracetam group **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study 2.3: NA 2.4: NA 2.5: NA 2.6: ITT used 2.7: NA **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
by UCB Pharma SA, Braine-l'Alleud, Belgium.	weeks before study entry • females of childbearing potential were eligible if they used a medically accepted contraceptive method. **Exclusion criteria** • nonepileptic seizures within the previous year • signs suggestive of a progressive brain lesion • history of partial-onset seizures • status epilepticus within the previous 3 months • previous or current treatment with levetiracetam • current use of vigabatrin or tiagabine • current use of felbamate with less than 18 months exposure	with the study treatment at a stable dose. People were discontinued from the study if they withdrew consent for any reason or for lack of efficacy or safety reasons, as judged by the investigator. Placebo: Followed same pattern as intervention group with placebo.			3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably yes, outcomes have been well defined 4.2: Probably no, assessors were blinded and outcomes standardised 4.3: No, double blind study 4.4: NA **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, study protocol agreed before recruitment 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
Full citation Park, K. M., Kim, S. H., Nho, S. K., Shin, K. J., Park, J., Ha, S. Y., Kim, S. E., A randomized open-label observational study to compare the efficacy and tolerability between topiramate and valproate in juvenile myoclonic epilepsy, Journal of Clinical Neuroscience, 20, 1079-1082, 2013 **Ref Id** 1081001 **Country/ies where the study was carried out** Republic of Korea **Study type**	**Sample size** N=33 (n=16 allocated to topiramate and n=17 allocated to valproate) **Characteristics** <u>Age, years, median (range)</u> Topiramate: 19 (13 to 42), valproate: 17 (range 14 to 36) <u>Sex (male:female)</u> Topiramate: 1:1, valproate: 1:1.1 <u>Epilepsy syndrome, n (%)</u> *Absence seizure* Topiramate: 5 (31) Valproate: 8 (47)	**Interventions** Patients medication was titrated for 8 weeks, followed by a 24-week maintenance phase. Valproate was titrated up to 1200 mg/day and topiramate up to 100 mg/day. The dose of valproate was titrated up to 300mg/day for 2 weeks, and the dose of topiramate was increased 25mg/day for 2 weeks.	**Details** Patients were randomised with a computer program in a 1:1 ratio to topiramate or valproate. Patients were withdrawn from the study in they continued to present with seizures after researching the maximal dose. Patients were requested to record seizure frequency in a diary, which was reviewed at each visit. Because counting myoclonic seizures can be difficult, the number of days without myoclonic seizures was counted. Follow-up: 24 weeks (no measure of variability was reported)	**Results** <u>Number of participants who were seizure-free during the 24-week maintenance period</u> Topiramate:7/11 Valproate: 9/16	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Low risk** 1.1: Yes, computerised randomisation 1.2: No information 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: High risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To assess the efficacy of valproate as compared to topiramate in patients with juvenile myoclonic epilepsy **Study dates** July 2006 to August 2008 **Source of funding** Study partially supported by a grant from Janssen Pharmaceuticals, Korea	*Generalised tonic clonic seizure* Topiramate: 14 (88) Valproate: 14 (82) *Absence seizure + generalised tonic clonic seizure* Topiramate: 4 (25) Valproate:5 (29) **Inclusion criteria** • A history of myoclonic seizures was compulsory for the diagnosis of juvenile myoclonic epilepsy, but those with a history of tonic-clonic seizures or absence seizures were also included • Those with newly or previously diagnosed juvenile myoclonic epilepsy with a history, poor response or adverse events to other antiseizure medications **Exclusion criteria**				2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: No information 2.4: No information 2.5: NA 2.6: No information 2.7: No information **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants randomised 3.2: NA 3.3: NA 3.4: NA **Domain 4: Measurement of the outcome: High risk** 4.1: Probably yes, outcomes have been well defined

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Those who had previously taken topiramate or valproate • Those with absence of myoclonic seizures • Significantly abnormal cranial CT scans or MRI • Presence of a progressive neurological condition • History of nephrolithiasis • Abnormal liver enzymes test • Pregnancy				4.2: No information 4.3: Yes, open label study 4.4: No information 4.5: No information **Domain 5: Selection of the reported result: High risk** 5.1: No information 5.2: No, outcomes standardised 5.3: No, analysis details in the methods section **Domain 6: Overall judgment of bias: High risk of bias** The study is judged to be at high risk of bias for all domains. **Other information** A history of myoclonic seizures was compulsory for the diagnosis of juvenile myoclonic epilepsy, but those with a history of tonic-clonic seizures or absence seizures were also

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					included

ASM: Anti-seizure medication; IGE: Idiopathic generalised epilepsy; GTC: Generalised tonic clonic seizures; PGTC: Primary generalised tonic clonic seizures; RCT: Randomised controlled trial; TEAEs: Treatment emergent adverse event; VAL: Valproate.

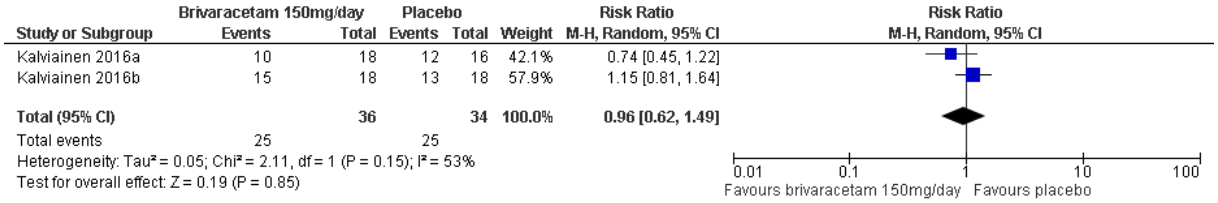
Appendix E – Forest plots

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

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 4: add-on brivaracetam (150mg/day) versus placebo

Figure 2: Patients with at least 1 adverse effect



Appendix F – GRADE tables

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

Table 10: Clinical evidence profile. Comparison 1: add-on topiramate versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction of generalised seizure frequency >50%												
1 (Biton 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/5 (60%)	6/8 (75%)	RR 0.8 (0.35 to 1.82)	150 fewer per 1000 (from 488 fewer to 615 more)	⊕OOO VERY LOW	CRITICAL

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

Table 11: Clinical evidence profile. Comparison 2: add-on brivaracetam (5mg/day) versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on brivaracetam (5mg/day)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in action myoclonous score : difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on brivaracetam (5mg/day)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	18	-	Median (range) difference: -18.1 (-39.3 to 4.9), p=0.1	⊕OOO VERY LOW	CRITICAL
Functional disability in everyday activities: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	18	-	Median (range) difference: 0 (-33.3 to 18.8), p=0.8	⊕OOO VERY LOW	CRITICAL
Stimulus sensitivity score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	18	-	Median (range) difference: 0 (-50.0 to 66.7), p=0.6	⊕OOO VERY LOW	CRITICAL
Patients with at least 1 adverse effect												
1 (Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/20 (80%)	13/18 (72.2%)	RR 1.11 (0.77 to 1.59)	79 more per 1000 (from 166 fewer to 426 more)	⊕OOO VERY LOW	CRITICAL
Patient questionnaire score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	18	-	Median (range) difference: 10.0 (-5.6 to 30), p=0.1	⊕OOO VERY LOW	IMPORTANT

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*

1 *2 Evidence downgraded by 2 as ranges are subjectively very wide*
2 *3 95% CI crosses 2 MIDs (0.8 and 1.25)*

3

4 **Table 12: Clinical evidence profile. Comparison 3: add-on brivaracetam (50mg/day) versus placebo**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brivaracetam (50mg/day)	Placebo	Relative (95% CI)	Absolute		
Reduction in action myoclonous score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016a)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	16	-	Median (range) difference: 23.3 (0.7 to 47.9), p=0.1	⊕OOO VERY LOW	CRITICAL
Functional disability in everyday activities: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016a)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	16	-	Median (range) difference:12 .3 (-10 to 36.4), p=0.2	⊕OOO VERY LOW	CRITICAL
Stimulus sensitivity score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016a)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	16	-	Median (range) difference: 25 (0 to 100), p=0.09	⊕OOO VERY LOW	CRITICAL
Patients with at least 1 adverse effect: difference from baseline to last treatment visit compared to placebo												
1 (Kalviainen 2016a)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/16 (75%)	12/16 (75%)	RR 1 (0.67 to 1.49)	0 fewer per 1000 (from 247 fewer to 368 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brivaracetam (50mg/day)	Placebo	Relative (95% CI)	Absolute		
Patient questionnaire score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												
1 (Kalviainen 2016a)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	16	-	Median (range) difference: -10 (-30.5 to 14.8), p=0.3	⊕OOO VERY LOW	CRITICAL

1 *[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *[2] Evidence downgraded by 2 as ranges are subjectively very wide*
3 *[3] 95% CI crosses 2 MIDs (0.8 and 1.25)*

4

5 **Table 13: Clinical evidence profile. Comparison 4: add-on brivaracetam (150mg/day) versus placebo**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brivaracetam (150mg/day)	Placebo	Relative (95% CI)	Absolute		
Reduction in action myoclonous score: difference from baseline to last treatment visit compared to placebo (median) (Bettwe indicated by lower values)												
2 (Kalviainen 2016a,	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18	16	-	Median (range) difference:9.6 (-12.0 to 37.2), p=0.5	⊕OOO VERY LOW	CRITICAL
Kalviainen 2016b)							18	18		Median (range) difference: 0.2 (-26.1 to 25), p=0.9		

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brivaracetam (150mg/day)	Placebo	Relative (95% CI)	Absolute		
Functional disability in everyday activities: difference from baseline to last treatment visit compared to placebo (median) (Bettwe indicated by lower values)												
2 (Kalviainen 2016a,	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18	16	-	Median (range) difference: 3.7 (-42.5 to 14.3), p=0.5	⊕OOO VERY LOW	CRITICAL
Kalviainen 2016b)							18	18		Median (range) difference: 1.2 (-21.9 to 31.1), p=0.6		
Stimulus sensitivity score: difference from baseline to last treatment visit compared to placebo (median) (Bettwe indicated by lower values)												
2 (Kalviainen 2016a, Kalviainen 2016b)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18	16	-	Median (range) difference: 2.5 (0 to 100), p=0.4	⊕OOO VERY LOW	CRITICAL
							18	18		Median (range) difference: 0 (-25.0 to 100.0), p=0.5		
Patients with at least 1 adverse effect												
2 (Kalviainen 2016a, Kalviainen 2016b)	RCT	serious[1]	serious[4]	no serious indirectness	very serious[3]	none	25/36 (69.4%)	25/34 (73.5%)	RR 0.96 (0.62 to 1.49)	37 fewer per 1000 (from 213 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL
Patient questionnaire score: difference from baseline to last treatment visit compared to placebo (median) (Better indicated by lower values)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brivaracetam (150mg/day)	Placebo	Relative (95% CI)	Absolute		
2 (Kalviainen 2016a,	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18	16	-	Median (range) difference: -5.4 (-28 to 18.2), p=0.4	⊕OOO VERY LOW	CRITICAL
Kalviainen 2016b)							18	18		Median (range) difference: 14.3 (-1.8 to 39.4), p=0.03		

1 [1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *Evidence downgraded by 2 as ranges are subjectively very wide*
3 [3] *95% CI crosses 2 MIDs (0.8 and 1.25)*
4 [4] *I^2>50%*

5 **Table 14: Clinical evidence profile. Comparison 5: add-on piracetam (9.6g/day) versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piracetam (9.6 g/day)	placebo	Relative (95% CI)	Absolute		
Stimulus sensitivity score (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12	18	-	MD 0.2 lower (8.05 lower to 7.65 higher)	⊕OOO VERY LOW	CRITICAL
Functional disability in everyday activities (Better indicated by lower values)												

Quality assessment							No of patients		Effect			Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piracetam (9.6 g/day)	placebo	Relative (95% CI)	Absolute	Quality	
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	18	-	MD 1.8 lower (6.32 lower to 2.72 higher)	⊕⊕OO LOW	IMPORTANT
Investigator's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	18	-	MD 0.3 lower (1.04 lower to 0.44 higher)	⊕⊕OO LOW	IMPORTANT
Patient's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	18	-	MD 5.7 lower (19.27 lower to 7.87 higher)	⊕⊕OO LOW	IMPORTANT

1 [1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *95% CI crosses 2 MIDs (+/-0.5 x control group SD for stimulus sensitivity=+/-5.98)*
3 [3] *95% CI crosses 1 MID (+/-0.5 x control group SD for functional disability=+/-3.45; for investigator's global assessment=+/-0.55; for patient's global assessment=+/-9.65)*

4 **Table 15: Clinical evidence profile. Comparison 6: add-on piracetam (16.8g/day) versus placebo**

Quality assessment							No of patients		Effect			Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piracetam (16.8g/day)	Placebo	Relative (95% CI)	Absolute	Quality	
Stimulus sensitivity score (Better indicated by lower values)												

Quality assessment							No of patients		Effect			Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piracetam (16.8g/day)	Placebo	Relative (95% CI)	Absolute	Quality	
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 2.1 lower (9.97 lower to 5.77 higher)	⊕⊕OO LOW	CRITICAL
Functional disability in everyday activities (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 1.8 lower (6.32 lower to 2.72 higher)	⊕⊕OO LOW	IMPORTANT
Investigator's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 0.3 lower (1.04 lower to 0.44 higher)	⊕⊕OO LOW	IMPORTANT
Patient's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 10.5 lower (24.04 lower to 3.04 higher)	⊕⊕OO LOW	IMPORTANT

1 [1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *95% CI crosses 1 MID (+/-0.5 x control group SD for stimulus sensitivity=+/-5.98; for functional disability=+/-3.45; for investigator's global assessment=+/-0.55; for patient's global*
3 *assessment=+/-9.65)*

4

Table 16: Clinical evidence profile. Comparison 7: add-on piracetam (24g/day) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piracetam (24g/day)	Placebo	Relative (95% CI)	Absolute		
Stimulus sensitivity score (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 3.7 lower (11.57 lower to 4.17 higher)	⊕⊕OO LOW	IMPORTANT
Functional disability in everyday activities (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 2.8 lower (7.29 lower to 1.69 higher)	⊕⊕OO LOW	IMPORTANT
Investigator's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 0.6 lower (1.34 lower to 0.14 higher)	⊕⊕OO LOW	IMPORTANT
Patient's global assessment (Better indicated by lower values)												
1 (Koskiniemi 1998)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	18	-	MD 16.4 lower (29.94 to 2.86 lower)	⊕⊕OO LOW	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 stimulus sensitivity=+/-5.98; for functional disability=+/-3.45; for investigator's global assessment=+/-0.55; for patient's global assessment=+/-9.65)

Table 17: Clinical evidence profile. Comparison 8: topiramate versus valproate

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Valproate	Relative (95% CI)	Absolute		
Reduction of myoclonic seizure frequency >50%												
1 (Levisohn 2007)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/14 (85.7%)	9/9 (100%)	RR 0.88 (0.67 to 1.15)	120 fewer per 1000 (from 330 fewer to 150 more)	⊕OOO VERY LOW	CRITICAL
Number of participants who were seizure free during the 24 week maintenance period												
1 (Park 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/11 (63.6%)	9/16 (56.3%)	RR 1.13 (0.61 to 2.11)	73 more per 1000 (from 219 fewer to 624 more)	⊕OOO VERY LOW	CRITICAL

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

4 **Table 18: Clinical evidence profile. Comparison 9: lamotrigine versus valproate**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Valproate	Relative (95% CI)	Absolute	Quality	Importance
Mean seizure reduction from baseline (juvenile myoclonic) (Better indicated by lower values)												
1 (Nejad 2009)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	23	-	MD 0.6 lower (1.85 lower to 0.65 higher)	⊕OOO VERY LOW	CRITICAL
Time to withdrawal for any reason (median)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Valproate	Relative (95% CI)	Absolute		
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	41	31	-	Median (range) in lamotrigine: 11 (3-20), valproate: 12 (3-20)	⊕OOO VERY LOW	CRITICAL
Percentage of patients with reported side effects												
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	7/41 (17.1%)	11/31 (35.5%)	RR 0.48 (0.21 to 1.10)	185 fewer (from 280 fewer to 35 more)	⊕OOO VERY LOW	CRITICAL
Mean QOLIE-31 change score from baseline to end of the study (Better indicated by higher values)												
1 (Machado 2013)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	31	-	MD 5 lower (6.17 to 3.83 lower)	⊕⊕OO LOW	IMPORTANT

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

Table 19: Clinical evidence profile. Comparison 10: add-on levetiracetam versus placebo

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Placebo	Relative (95% CI)	Absolute		
Reduction of myoclonic seizure frequency >50%												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/61 (58.3%)	14/60 (23.3%)	RR 2.48 (1.48 to 4.08)	345 more per 1000 (from 112 more to 719 more)	⊕⊕⊕O MODERATE	CRITICAL
Short-term seizure freedom during the 16 week treatment period												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/61 (13.3%)	0/60 (0%)	POR 8.22 (1.97 to 34.29)	13 more per 1000 (from 4 more to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/61 (6.7%)	1/60 (1.7%)	RR 3.93 (0.45 to 34.19)	49 more per 1000 (from 9 fewer to 553 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug events												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/61 (5%)	1/60 (1.7%)	RR 2.95 (0.32 to 27.58)	33 more per 1000 (from 11 fewer to 443 more)	⊕OOO VERY LOW	CRITICAL
Patients global evaluation scores improved on QOLIE-31-P scale												
1 (Noachtar 2008)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	52/61 (86.7%)	36/60 (60%)	RR 1.42 (1.13 to 1.79)	252 more per 1000 (from 78 more to 474 more)	⊕⊕OO LOW	IMPORTANT

[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)*

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 myoclonic seizures?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of myoclonic seizures?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of myoclonic seizures?

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

Appendix J – Economic analysis

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

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 myoclonic seizures?

Clinical studies

Table 20: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Auvin, S., Treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy, Neuropsychiatric Disease and Treatment, 3, 729-734, 2007	Narrative review. References checked for inclusion
Auvin, S., Treatment of juvenile myoclonic epilepsy, CNS Neuroscience & Therapeutics, 14, 227-33, 2008	Narrative review. References checked for inclusion
Beydoun, A., D'Souza, J., Treatment of idiopathic generalized epilepsy - A review of the evidence, Expert Opinion on Pharmacotherapy, 13, 1283-1298, 2012	Narrative review. References checked for inclusion
Brigo, F., Igwe, S. C., Bragazzi, N. L., Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy, Cochrane Database of Systematic Reviews, 2017	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Brigo, F., Storti, M., Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy, Cochrane Database of Systematic Reviews, CD010483, 2013	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Chiron, C., Marchand, M. C., Tran, A., Rey, E., D'Athis, P., Vincent, J., Dulac, O., Pons, G., Stiripentol in severe myoclonic epilepsy in infancy: A randomised placebo-controlled syndrome-dedicated trial, Lancet, 356, 1638-1642, 2000	Study included in Dravet syndrome review
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 Italian multicenter open trial, Epilepsy Research, 49, 45-8, 2002	Observational study
Euctr, D. E., A double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in myoclonic seizures associated with idiopathic generalised epilepsy, Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2007-003556-10-de, 2007	Trial protocol. No published study reults
Euctr, E. S., Double-blind, placebo controlled cross-over study to assess the efficacy of Levetiracetam in paediatric and childhood non-epileptic myoclonus Estudio cruzado, aleatorizado, doble ciego controlado con placebo, para evaluar la eficacia del Levetiracetam en el tratamiento del mioclonus no epiléctico en pacientes pediátricos y adolescentes, Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2005-002042-19-es, 2005	Trial protocol. No published study reults

Study	Reason for Exclusion
Euctr, H. U., Open label Extension Study Following Double-blind, Randomized, Placebo-controlled, Multicentre Study to Assess Efficacy and Safety of Adjunctive Zonisamide in Myoclonic Seizures associated with Idiopathic Generalized Epilepsy, Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2007-006696-36-hu, 2008	Trial protocol. No published study reults
Euctr, I. T., A multicentre randomized controlled trial comparing topiramate, stiripentol and clobazam at the maximal tolerated dosage, as adjunctive therapy to valproate and clobazam in paediatric patients with dravet`s syndrome (SMEI), and auxiliary pharmacogenetic study, Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2007-002198-30-it, 2012	Trial protocol. No published study reults
Gordon, N., Review: juvenile myoclonic epilepsy, Child: Care, Health & Development, 20, 71-6, 1994	Narrative review. References checked for inclusion
Kassai, B., Chiron, C., Augier, S., Cucherat, M., Rey, E., Gueyffier, F., Guerrini, R., Vincent, J., Dulac, O., Pons, G., Severe myoclonic epilepsy in infancy: A systematic review and a meta-analysis of individual patient data, Epilepsia, 49, 343-348, 2008	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Koepp, M. J., Thomas, R. H., Wandschneider, B., Berkovic, S. F., Schmidt, D., Concepts and controversies of juvenile myoclonic epilepsy: Still an enigmatic epilepsy, Expert Review of Neurotherapeutics, 14, 819-831, 2014	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Koskiniemi, M., Hyyppa, M., Sainio, K., Transient effect of L-tryptophan in progressive myoclonus epilepsy without Lafora bodies: Clinical and electrophysiological study, Epilepsia, 21, 351-357, 1980	Observational study
Kyllerman, M., Ben-Menachem, E., Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients, Epilepsy Research, 29, 109-14, 1998	Observational study
Levisohn, P. M., Holland, K. D., Hulihan, J. F., Fisher, A. C., Topiramate versus valproate in patients with juvenile myoclonic epilepsy, Epilepsia, 44 Suppl 9, 267â€• 268, 2003	Conference abstract
Liu, J., Wang, L. N., Wang, Y. P., Topiramate monotherapy for juvenile myoclonic epilepsy, The Cochrane database of systematic reviews, 12, CD010008, 2015	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Liu, J., Wang, L. N., Wang, Y. P., Topiramate for juvenile myoclonic epilepsy, Cochrane Database of Systematic Reviews, 2019 (1) (no pagination), 2019	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Michelucci, R., Pasini, E., Riguzzi, P., Andermann, E., Kalviainen, R., Genton, P., Myoclonus and seizures in progressive myoclonus epilepsies: pharmacology and therapeutic trials, Epileptic Disorders, 18, S145-S153, 2016	Narrative review. References checked for inclusion
Mikkelsen, B., Birket-Smith, E., Bradt, S., Holm, P., Bparm, null, Lung, M., Thorn, I., Vestermark, S., Olsen, P. Z., Clonazepam in the treatment of epilepsy. A controlled clinical trial in simple absences, bilateral massive epileptic myoclonus, and atonic seizures, Archives of Neurology, 33,	Observational study

Study	Reason for Exclusion
322â€• 325, 1976	
Nolan, S. J., Marson, A. G., Pulman, J., Tudur Smith, C., Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures, The Cochrane database of systematic reviews, 8, CD001769, 2013	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Nolan, S. J., Marson, A. G., Weston, J., Tudur Smith, C., Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review, Cochrane Database of Systematic Reviews, 4, CD001769, 2016	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Plosker, G. L., Stiripentol: In severe myoclonic epilepsy of infancy (Dravet syndrome), CNS Drugs, 26, 993-1001, 2012	Narrative review. References checked for inclusion
Striano, P., Belcastro, V., Update on pharmacotherapy of myoclonic seizures, Expert Opinion on Pharmacotherapy, 18, 187â€• 193, 2017	Narrative review. References checked for inclusion
Striano, P., Belcastro, V., Treating myoclonic epilepsy in children: State-of-the-art, Expert Opinion on Pharmacotherapy, 14, 1355-1361, 2013	Narrative review. References checked for inclusion
Striano, P., Coppola, A., Pezzella, M., Ciampa, C., Specchio, N., Ragona, F., Mancardi, M. M., Gennaro, E., Beccaria, F., Capovilla, G., Rasmini, P., Besana, D., Coppola, G. G., Elia, M., Granata, T., Vecchi, M., Vigevano, F., Viri, M., Gaggero, R., Striano, S., Zara, F., An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy, Neurology, 69, 250-254, 2007	Observational study
Striano, P., Sofia, V., Capovilla, G., Rubboli, G., Di Bonaventura, C., Coppola, A., Vitale, G., Fontanillas, L., Giallonardo, A. T., Biondi, R., Romeo, A., Viri, M., Zara, F., Striano, S., A pilot trial of levetiracetam in eyelid myoclonia with absences (Jeavons syndrome), Epilepsia, 49, 425-430, 2008	Observational study
Sundqvist, A., Nilsson, B. Y., Tomson, T., Valproate monotherapy in juvenile myoclonic epilepsy: dose-related effects on electroencephalographic and other neurophysiologic tests, Therapeutic Drug Monitoring, 21, 91-6, 1999	Observational study
Thanh, T. N., Chiron, C., Dellatolas, G., Rey, E., Pons, G., Vincent, J., Dulac, O., Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome), Archives de Pediatrie, 9, 1120â€• 1127, 2002	Observational study
Trevathan, E., Kerls, S. P., Hammer, A. E., Vuong, A., Messenheimer, J. A., Lamotrigine for juvenile myoclonic epilepsy: analysis of data from a randomized controlled clinical trial, Epilepsia, 46 Suppl 8, 219, 2005	Conference abstract
van den Ende, T., Sharifi, S., van der Salm, S. M. A., van Rootselaar, A. F., Familial Cortical Myoclonic Tremor and Epilepsy, an Enigmatic Disorder: From Phenotypes to Pathophysiology	Narrative review. References checked for inclusion

Study	Reason for Exclusion
and Genetics. A Systematic Review, Tremor and Other Hyperkinetic Movements, 8, 503, 2018	
Wallace, S. J., Myoclonus and epilepsy in childhood: a review of treatment with valproate, ethosuximide, lamotrigine and zonisamide, Epilepsy Research, 29, 147-54, 1998	Narrative review. References checked for inclusion
Zareba, G., Zonisamide: review of its use in epilepsy therapy, Drugs of Today, 41, 589-97, 2005	Full text unavailable from the British Library. Last checked 29/03/21

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 myoclonic seizures?

No research recommendations were made for this review question.