National Institute for Health and Care Excellence

Final

Epilepsies in children, young people and adults

[R] Effectiveness of antiseizure therapies for epilepsy with myoclonic-atonic seizures (Doose syndrome)

NICE guideline NG217

Evidence reviews underpinning recommendations 6.5.1 to 6.5.6 in NICE guideline

April 2022

Final

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

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

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

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Effectiveness of antiseizure therapies in the treatment of epilepsy with myoclonic-atonic seizures (Doose syndrome)

Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose syndrome)?

Introduction

Epilepsy with myoclonic-atonic seizures is an uncommon form of epilepsy that presents in childhood. Seizures involve loss of muscle tone, resulting in a sudden drop to the ground (drop attacks), these can result in serious harm to the child. This form of epilepsy has a variable prognosis over time and seizures can be difficult to control with drug therapy. The aim of this review is to determine which antiseizure therapies improve outcomes in those with childhood epilepsy with myoclonic-atonic seizures (Doose syndrome).

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Children and young people with confirmed e**pilepsy with myoclonic-atonic seizures** (Doose syndrome)
Intervention	• Clobazam • Clonazepam • Ethosuximide • Ketogenic diet • Lamotrigine • Levetiracetam • Rufinamide • Topiramate • Vagus Nerve Stimulation • Valproate • Zonisamide Intervention could be individual drug or combination
Comparison	• No treatment/placebo • Comparison between the listed intervention (individually or combination)
Outcome	**Critical**

	• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment).
	• Reduction of seizure frequency >50%
	• Reduction in drop attacks/atonic attacks
	• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)
	• Side effects, as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse effects)
	  ○ treatment cessation due to adverse events [dichotomous outcome only])
	  ○ Mortality
	
	Important
	• Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS
	• Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)

HR: hazard ratio; RR: relative risk; VABS: Vineland Adaptive Behaviour Scale

When this review was originally conducted, the name of the epilepsy syndrome used in the searches and the review was myoclonic astatic epilepsy (Doose syndrome), however the name of this epilepsy syndrome changed during guideline development to epilepsy with myoclonic-atonic seizures (Doose syndrome), and amendments to reflect this change were done as appropriate throughout this report.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1). Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

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

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

Excluded studies

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

Summary of studies included in the evidence review

No studies were identified which were applicable to this review question (and so there are no evidence tables in appendix D). No meta-analysis was undertaken for this review (and so there are no forest plots in appendix E).

Summary of the evidence

No studies were identified which were applicable to this review question (and so there are no GRADE tables in appendix F).

Quality assessment of clinical outcomes included in the evidence review

No studies were identified which were applicable to this review question and so there are no evidence profiles in appendix F.

Economic evidence

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

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

Excluded studies

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

Summary of studies included in the economic evidence review

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

Economic model

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 aim of treatment for children with epilepsy with myoclonic-atonic seizures is to minimise the impact of seizures as much as possible and the committee therefore agreed that seizure freedom, reduction in seizure frequency, and reduction in drop attacks should be prioritised as critical outcomes for this review. However, the committee acknowledged that controlling

these types of seizures can be especially difficult; and that the treatments required to do so can have challenging side effects for patients. They therefore agreed that time to withdrawal, and side effects due to treatment should also be included in the review as critical outcomes.

As epilepsy with myoclonic-atonic seizures occurs only in childhood, the committee agreed that the review should include neurodevelopmental outcomes, such as IQ and social functioning as important outcomes as it is expected that successful treatment will lead to improvements in these areas.

The quality of the evidence

No evidence was identified which was applicable to this review question, therefore the committee agreed that a research recommendation was necessary. See further details in appendix L.

Benefits and harms

No evidence was identified for this review question, therefore recommendations are based on committee experience and informal consensus agreement.

Epilepsy with myoclonic-atonic seizures (Doose syndrome) is an epilepsy syndrome which occurs in children from the age of 2 to 8 years. This type of epilepsy is rare, and accurate diagnosis is crucial; therefore, the committee recommended that a tertiary paediatric neurologist is involved in the care of children with this syndrome from the start.

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

As no evidence was identified the committee agreed, based on their experience and informal consensus, to include a range of the available antiseizure medications widely used in clinical practice in the recommendations. The committee were in agreement that sodium valproate and levetiracetam are successfully used in clinical practice as first-line treatments to treat people with generalised seizures, including epilepsy with myoclonic-atonic seizures (Doose syndrome).

The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children, yet agreed that it should be offered as first line treatment as approximately two thirds of children outgrow this syndrome. In January 2025 recommendations were amended to take account of the safety advice by the Medicines and Healthcare products Regulatory Agency (MHRA) on the use of valproate, valproate use by women and girls and precautionary advice on valproate use by boys and men. This provides specific advice and criteria for its usage. However, the committee agreed that sodium valproate should only be prescribed with caution after a full and clear discussion with them or their families and carers, if appropriate, ensuring they understand all the potential risks and benefits including the potential risks to male fertility and risks to an unborn child. If sodium valproate is prescribed to women and girls able to have children, clinicians must

follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a pregnancy prevention programme, if appropriate.

If treatment is unsuccessful, the committee agreed that the ketogenic diet should be considered as second-line alternative or add-on or alternative treatment. The committee noted that it is successfully used in clinical practice in cases difficult to treat and recommended as a second-line treatment based on their expert opinion.

The committee emphasised that monotherapy should be used in the first instance. When starting alternative antiseizure medications, the dose of the new antiseizure medication should be slowly increased, whilst the existing antiseizure medication is tapered off. When starting an add-on antiseizure medication, 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 discussed that most children grow out of epilepsy with myoclonic-atonic seizures (Doose syndrome). Consequently, they agreed that, following a period of two years seizure free, withdrawal of therapy should be discussed. For those children who do not outgrow the condition, there is a significant likelihood of severe cognitive impairment.

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

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

The committee decided that a research recommendation was necessary to encourage research that would lead to better evidence for treatment (see appendix L).

Cost effectiveness and resource use

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

The committee did not make any recommendations, which changed current practice. Therefore, there will not be any impact upon resource use.

Other factors the committee took into account

In line with the MHRA, the committee emphasised that long-term treatment with sodium valproate can cause decreased bone mineral density and increased risk of osteomalacia. The committee noted that appropriate supplementation should be considered for those at risk.

Recommendations supported by this evidence review

This evidence review supports recommendations 6.5.1-6.5.6 and the research recommendation on complex epilepsy syndromes.

References

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

Appendices

Appendix A – Review protocols

Review protocol for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

Table 2: Review protocol for effectiveness of antiseizure therapies for epilepsy with epilepsy with myoclonic-atonic seizures (Doose syndrome)

Field	Content
PROSPERO registration number	CRD42019146519
Review title	Effectiveness of antiseizure therapies for epilepsy with myoclonic-atonic seizures (Doose syndrome)
Review question	What antiseizure therapies (individually or in combination) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?
Objective	The objective of this review is to determine which antiseizure therapies improve outcomes in those with childhood epilepsy with myoclonic-atonic seizures. This review will determine the effectiveness of antiseizure therapies given alone or in combination.
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by: • Date: No date limit • English language studies • Human studies

Field	Content
	• RCT and systematic review study design filter
Condition or domain being studied	Epilepsy with myoclonic-atonic seizures in children and young people
Population	Inclusion: children and young people with confirmed epilepsy with myoclonic-atonic seizures (Doose syndrome)
Intervention	• Clobazam • Clonazepam • Ethosuximide • Ketogenic diet • Lamotrigine • Levetiracetam • Rufinamide • Topiramate • Vagus Nerve Stimulation • Valproate • Zonisamide Intervention could be individual or combination
Comparator	• No treatment/placebo • Comparison between the listed intervention (individually or combination).
Types of study to be included	• Systematic Reviews of RCT • 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 children, and young people with epilepsy with myoclonic-atonic seizures and other types of epilepsy) will be excluded, unless subgroup analysis for epilepsy with myoclonic-atonic seizures has been reported. Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias

Field	Content
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% • Reduction in drop attacks/atonic attacks • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • Side effects, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ mortality ○ treatment cessation due to adverse events (dichotomous outcome only) NB: Outcomes are in line with those described in the core outcome set for epilepsy (http://www.comet-initiative.org/studies/searchresults)
Secondary outcomes (important outcomes)	• Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS (Vineland Adaptive Behaviour Scale) • Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)
Data extraction (selection and coding)	• All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. • Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. • Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.

Field	Content			
	• A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.			
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.			
Analysis of sub-groups (stratification)	None			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	06 August 2019			
Anticipated completion date	7th April 2021			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	5a. Named contact			

Field	Content
	National Guideline Alliance 5b. Named contact e-mail epilepsies@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance (NGA) technical team
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019146519
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; Childhood; Myoclonic Atonic Seizure; epilepsy with myoclonic-atonic seizures; Doose Syndrome; Antiepileptic Drug
Details of existing review of same topic by same authors	Not Applicable

Field	Content
Additional information	Not applicable
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: Hazard ration; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; RR: relative risk; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

Clinical

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

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

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

#	searches
1	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.
2	clobazam/ use emczd, emcr or clobazam/ use ppez or (chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl).ti,ab.
3	clonazepam/ use emczd, emcr or clonazepam/ use ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.
4	ethosuximide/ use emczd, emcr or ethosuximide/ or (emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethylsuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin).ti,ab.
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 ((glycemic or glycaemic) adj5 (index or treat* or modulat*)) or (high fat* adj5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or low glyc* index treatment* or lgit or (medium chain adj (tryglyceride* or triglyceride*)) or mct*).ti,ab.
10	or/6,8,9
11	lamotrigine/ use emczd, emcr or lamotrigine/ use ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium).ti,ab.
12	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.

#	searches
13	rufinamide/ use emczd, emcr or rufinamide*.sh. or (banzel or inovelon or rufinamid* or xilep).ti,ab.
14	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.
15	vagus nerve stimulation/ use emczd, emcr or vagus nerve stimulation/ use ppez or ((vagal or vagus) adj2 (activity or stimulat*)).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 semisodium valproate or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or sodium di n propylacetate or sodium dipropyl acetate or sodium dipropylacetate or sodium n dipropylacetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.
17	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
18	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.
19	18 use ppez
20	(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.
21	20 use ppez
22	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.
23	22 use emczd, emcr
24	or/19,21,23
25	meta-analysis/
26	meta-analysis as topic/ or systematic reviews as topic/
27	"systematic review"/
28	meta-analysis/
29	(meta analy* or metanaly* or metaanaly*).ti,ab.
30	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
31	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
32	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

#	searches
33	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
34	(search* adj4 literature).ab.
35	(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.
36	cochrane.jw.
37	((pool* or combined) adj2 (data or trials or studies or results)).ab.
38	(or/25-26,29,31-37) use ppez
39	(or/27-28,30,32-37) use emczd, emcr
40	or/38-39
41	or/24,40
42	1 and 41 and or/2-4,10-17
43	limit 42 to english language
44	((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.)
45	44 use emez
46	((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.)
47	46 use mesz
48	45 or 47
49	43 not 48

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 03 of 12, March 2021; Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2021
Date of last search: 03 March 2021

#	searches
1	mesh descriptor: [epilepsies, myoclonic] explode all trees
2	((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or tonic clonic) near/2 (seizure* or spasm*)):ti,ab
3	#1 or #2
4	mesh descriptor: [clobazam] explode all trees
5	(chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl):ti,ab

#	searches
6	mesh descriptor: [clonazepam] this term only
7	(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
8	mesh descriptor: [ethosuximide] this term only
9	(emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethylsuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin):ti,ab
10	mesh descriptor: [triglycerides] explode all trees
11	mesh descriptor: [diet, ketogenic] this term only
12	mesh descriptor: [glycemic index] explode all trees
13	mesh descriptor: [dietary fats] explode all trees
14	mesh descriptor: [diet, carbohydrate-restricted] explode all trees
15	((adequate near/3 protein*) or atkin* or keto* or kd or (carbohydrate* near/5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulat*)) or (“high fat*” near/5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or “low glyc* index treatment*” or lgit or (“medium chain” near/1 (tryglyceride* or triglyceride*)) or mct*):ti,ab
16	mesh descriptor: [lamotrigine] this term only
17	(crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium):ti,ab
18	mesh descriptor: [levetiracetam] this term only
19	(elepsia or keppra or kopodex or levetiracetam* or matever or spritam):ti,ab
20	(banzel or inovelon or rufinamid* or xilep):ti,ab,kw
21	mesh descriptor: [topiramate] this term only
22	(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
23	mesh descriptor: [vagus nerve stimulation] this term only
24	((vagal or vagus) near/2 (activity or stimulat*)):ti,ab
25	mesh descriptor: [valproic acid] this term only
26	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or “di n propylacetate” or “di n propylacetate sodium” or “di n propylacetic acid” or diplexil or “dipropyl acetate” or “dipropyl acetic acid” or dipropylacetate or “dipropylacetate sodium” or “dipropylacetatic acid” or “dipropylacetic acid” or diprosin or divalproex or epilam or epilex or “epilim chrono” or “epilim chromosphere” or “epilim enteric” or epilim or episenta or “epival cr” or ergenyl or “ergenyl chrono” or “ergenyl chromosphere”" or “ergenyl retard” or ergenyl or “espa valept” or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or “myproic acid” or “n dipropylacetic acid” or orfil or orfiril or orlept or petilin or “propylisopropylacetic acid” or propymal or “semisodium valproate” or “sodium 2 propylpentanoate” or “sodium 2 propylvalerate” or “sodium di n propyl acetate” or “sodium di n propylacetate” or “sodium dipropyl acetate” or “sodium dipropylacetate” or “sodium n dipropylacetate” or stavzor or “valberg pr” or valcote or valepil or

#	searches
	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
27	mesh descriptor: [zonisamide] this term only
28	(excegran or excemid or zonegran or zonisamid*):ti,ab
29	{or #4-#28}
30	#3 and #29

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

#	searches
1	mesh descriptor epilepsies, myoclonic this term only
2	((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*))
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.

#	searches
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD
Date of last search: 31 March 2021

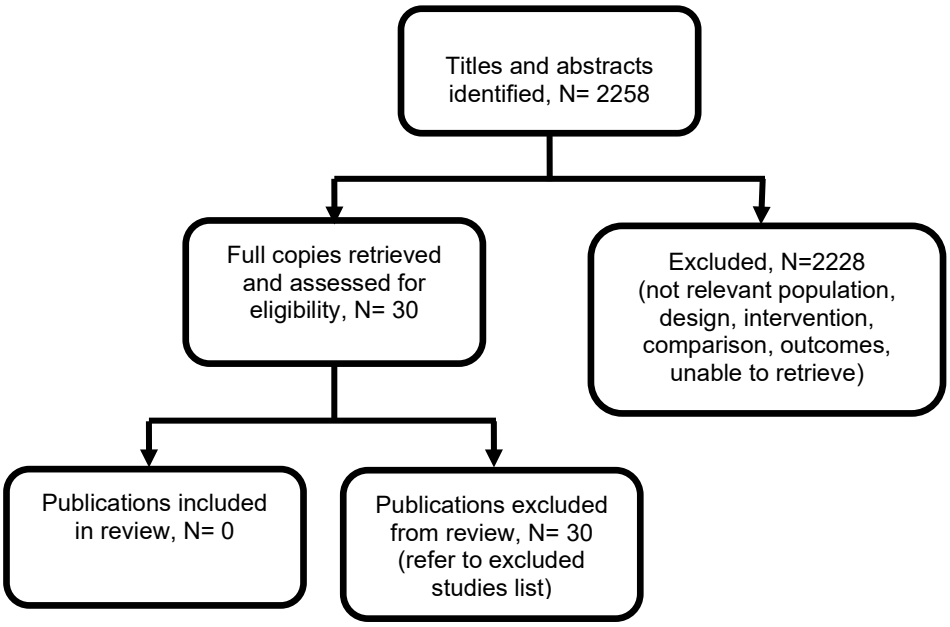
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”)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

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

Appendix C – Clinical evidence study selection

Study selection for: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

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

Appendix E – Forest plots

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

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – GRADE tables

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

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

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 epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

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 epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

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 epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

No economic 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 epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

Clinical studies

Table 3: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Aysun, S., Renda, Y., The effect of clonazepam on myoclonic seizures in infancy and childhood, Turkish Journal of Pediatrics, 20, 91-9, 1978	Study design does not meet the inclusion criteria. A prospective cohort study
Beran, R. G., Berkovic, S. F., Dunagan, F. M., Vajda, F. J., Danta, G., Black, A. B., Mackenzie, R., Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy, Epilepsia, 39, 1329-1333, 1998	RCT of refractory generalised epilepsy. No sub-group report for epilepsy with myoclonic-atonic seizures. No relevant data
Cao, J., Lin, X. X., Ma, X. M., Liu, H., The efficacy and safety of lamotrigine for absence seizures in children and adolescents: A systematic review and meta-analysis, Journal of Clinical Neuroscience, 71, 199-204, 2020	Sample did not include patients with Doose syndrome
Chi, Ctr Iir, Ketogenic diet therapy for rare epilepsy syndromes, multicenter randomly controlled clinical trial, Http://www.who.int/trialsearch/trial2.aspx? Trialid=chictr-iir-16008342, 2016	Trial registration
Coppola, Giangennaro, Update on rufinamide in childhood epilepsy, Neuropsychiatric disease and treatment, 7, 399-407, 2011	Narrative review
Ctri,, A clinical trial to study the effects of two drugs, levetiracetam and valproate in patients with refractory status epilepticus, Http://www.who.int/trialsearch/trial2.aspx? Trialid=ctri/2013/11/004178, 2013	Trial registration
Elia, M., Klepper, J., Leiendecker, B., Hartmann, H., Ketogenic diets in the treatment of epilepsy, Current Pharmaceutical Design, 23, 5691-5701, 2017	Narrative review. References checked for inclusion, 2 additional relevant references found (Neal 2008; Sharma 2013)
Ferlazzo, E., Trenite, D. K., Haan, G. J., Felix Nitschke, F., Ahonen, S., Gasparini, S., Minassian, B. A., Update on Pharmacological Treatment of Progressive Myoclonus Epilepsies, Current Pharmaceutical Design, 23, 5662-5666, 2017	Literature review
Fitton, A., Goa, K. L., Lamotrigine. An update of its pharmacology and therapeutic use in epilepsy, Drugs, 50, 691-713, 1995	Commentary

Study	Reason for Exclusion
Kanner, Andres M., Ashman, Eric, Gloss, David, Harden, Cynthia, Bourgeois, Blaise, Bautista, Jocelyn F., Abou-Khalil, Bassel, Burakgazi-Dalkilic, Evren, Park, Esmeralda Llanas, Stern, John, Hirtz, Deborah, Nespeca, Mark, Gidal, Barry, Faught, Edward, French, Jacqueline, Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, Epilepsy Currents, 18, 260-268, 2018	Does not include data on epilepsy with myoclonic-atonic seizures or patients with Doose syndrome
Lambrechts, D. A. J. E., de Kinderen, R. J. A., Vles, J. S. H., de Louw, A. J. A., Aldenkamp, A. P., Majoie, H. J. M., A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta Neurologica Scandinavica, 135, 231-239, 2017	RCT on refractory childhood epilepsies. No subgroup analysis for Doose syndrome reported. No relevant data
Liguori, Sara, Is topiramate effective and tolerated in young people with juvenile myoclonic epilepsy? A Cochrane Review summary with commentary, Developmental Medicine and Child Neurology, 62, 895-896, 2020	Summary only
Maheshwari, N., Question 1: Efficacy of the ketogenic diet in difficult childhood epilepsies, Archives of Disease in Childhood, 95, 560-562, 2010	Literature review. References checked, 1 additional relevant study found (Neal 2009)
Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., Cramp, C., Cockerell, O. C., Cooper, P. N., Doughty, J., et al.,, The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial, Lancet (london, england), 369, 1016â□□1026, 2007	RCT on generalised and unclassified epilepsy in children. No relevant data for epilepsy with myoclonic-atonic seizures reported
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, 322â□□325, 1976	Study design does not meet inclusion criteria - non-randomised controlled crossover trial
Nct,, Levetiracetam as add-on Treatment of Myoclonic Jerks in Adolescents + Adults, Https://clinicaltrials.gov/show/nct00150774, 2005	RCT. No relevant data for epilepsy with myoclonic-atonic seizures reported
Neal, A randomised of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy, Epilepsia, 50, 1109-1117, 2009	Subgroup analysis for epilepsy with myoclonic-atonic seizures not reported. No relevant data
Neal, The Ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial, Lancet, 7, 500-506, 2008	RCT on childhood epileptic syndromes including 8 patients with epilepsy with myoclonic-atonic seizures. Subgroup analysis for epilepsy with myoclonic-atonic seizures not reported. No relevant data

Study	Reason for Exclusion
Nevitt, S. J., Sudell, M., Weston, J., Tudur Smith, C., Marson, A. G., Antiepileptic drug monotherapy for epilepsy: A network meta-analysis of individual participant data, Cochrane Database of Systematic Reviews, 2017 (6) (no pagination), 2017	Network meta-analysis. No relevant data could be extracted for inclusion. References checked for inclusion
Rolston, J. D., Englot, D. J., Wang, D. D., Garcia, P. A., Chang, E. F., Corpus callosotomy versus vagus nerve stimulation for atonic seizures and drop attacks: A systematic review, Epilepsy and Behavior, 51, 13-17, 2015	Systematic review. No relevant data could be extracted for inclusion. References checked for inclusion
Rosati, A., Ilvento, L., Lucenteforte, E., Pugi, A., Crescioli, G., McGreevy, K. S., Virgili, G., Mugelli, A., De Masi, S., Guerrini, R., Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis, Epilepsia, 59, 297-314, 2018	Network meta-analysis. No relevant data could be extracted for inclusion. References checked for inclusion
Sharma, S., Goel, S., Jain, P., Agarwala, A., Aneja, S., Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: A randomized controlled trial, Epilepsy Research, 127, 152-159, 2016	RCT on children with refractory epilepsy. Subgroup analyses for epilepsy with myoclonic-atonic seizures was not reported. No relevant data
Sharma, S., Sankhyan, N., Gulati, S., Agarwala, A., Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial, Epilepsia, 54, 481-486, 2013	RCT on children with refractory epilepsy. Subgroup analysis for epilepsy with myoclonic-atonic seizures not reported. No relevant data
Sheth, R. D., Gidal, B. E., Intravenous valproic acid for myoclonic status epilepticus, Neurology, 54, 1201, 2000	Study design does not meet inclusion criteria - case report
Singh, Kanika, Aggarwal, Anju, Faridi, M. M. A., Sharma, Sangeeta, IV Levetiracetam versus IV Phenytoin in Childhood Seizures: A Randomized Controlled Trial, Journal of pediatric neurosciences, 13, 158-164, 2018	Comparison not relevant, does not include data on epilepsy with myoclonic-atonic seizures or patients with Doose syndrome
Treiman, D. M., Efficacy and safety of antiepileptic drugs: A review of controlled trials, Epilepsia, 28, S1-S8, 1987	Narrative review
Tudur Smith, Catrin, Marson, Anthony G., Chadwick, David W., Williamson, Paula R., Multiple treatment comparisons in epilepsy monotherapy trials, Trials, 8, 34, 2007	Does not include data on epilepsy with myoclonic-atonic seizures or patients with Doose syndrome
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
Yagi, K., Overview of Japanese experience-controlled and uncontrolled trials, Seizure, 13 Suppl 1, S11-5; discussion S16, 2004	Narrative review and case studies
Zhou, S., Zhan, Q., Wu, X., Effect of levetiracetam on cognitive function and clonic seizure frequency in children with epilepsy, Current molecular medicine., 29, 2019	Sample did not include patients with Doose syndrome

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 epilepsy with myoclonic-atonic seizures (Doose Syndrome)?

Research question:

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

Why this is important

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

Table 4: Research recommendation rationale

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

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

N/A: not applicable

Table 5: Research recommendation modified PICO table

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

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

Study design	Multicentre/UK wide RCT

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

RCT: randomised controlled trial