# 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 recommendation section 6.5.1-6.5.7 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*

## 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<br>• Clonazepam<br>• Ethosuximide<br>• Ketogenic diet<br>• Lamotrigine<br>• Levetiracetam<br>• Rufinamide<br>• Topiramate<br>• Vagus Nerve Stimulation<br>• Valproate<br>• Zonisamide<br><br>Intervention could be individual drug or combination |
| **Comparison** | • No treatment/placebo<br>• Comparison between the listed intervention (individually or combination) |

| Outcome | Critical<br>• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment).<br>• Reduction of seizure frequency >50%<br>• Reduction in drop attacks/atonic attacks<br>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)<br>• Side effects, as assessed by:<br>○ % of patients with reported side effects (trial defined adverse and serious adverse effects)<br>○ treatment cessation due to adverse events [dichotomous outcome only])<br>○ Mortality<br><br>Important<br>• Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS<br>• 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. However, the committee agreed that sodium valproate should only be prescribed to a woman or girl who is able to have children after a full and clear discussion with them or their families and carers, if appropriate, ensuring they understand all the potential risks and benefits. If sodium valproate is prescribed to women and girls able to have children, clinicians must follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a pregnancy prevention programme, if appropriate.

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 6.5.1-6.5.7 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.<br><br>This review will determine the effectiveness of antiseizure therapies given alone or in combination. |

| Field | Content |
|---|---|
| Searches | The following databases will be searched:<br>• CDSR<br>• CENTRAL<br>• DARE<br>• HTA<br>• MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations<br>• Embase<br>• EMCare<br><br>Searches will be restricted by:<br>• Date: No date limit<br>• English language studies<br>• Human studies<br>• 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<br>• Clonazepam<br>• Ethosuximide<br>• Ketogenic diet<br>• Lamotrigine<br>• Levetiracetam<br>• Rufinamide<br>• Topiramate<br>• Vagus Nerve Stimulation<br>• Valproate<br>• Zonisamide<br>Intervention could be individual or combination |
| Comparator | • No treatment/placebo<br>• Comparison between the listed intervention (individually or combination). |

| Field | Content |
|---|---|
| Types of study to be included | • Systematic Reviews of RCT<br>• 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.<br><br>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.<br><br>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).<br>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.<br>• Reduction of seizure frequency >50%<br>• Reduction in drop attacks/atonic attacks<br>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)<br>• Side effects, as assessed by:<br>o % of patients with reported side effects (trial defined adverse and serious adverse effects)<br>o mortality<br>o treatment cessation due to adverse events (dichotomous outcome only)<br><br>NB: Outcomes are in line with those described in the core outcome set for epilepsy ( http://www.comet-initiative.org/studies/searchresults) |

| Field | Content | |
|---|---|---|
| Secondary outcomes (important outcomes) | • Neurodevelopment outcomes, as assessed by validated developmental/IQ tools, for example the VABS (Vineland Adaptive Behaviour Scale)<br>• 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.<br>• 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.<br>• 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.<br>• 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:<br>• ROBIS tool for systematic reviews<br>• Cochrane RoB tool v.2 for RCTs and quasi-RCTs<br>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 | |

| Field | Content | | |
|---|---|---|---|
| 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<br>National Guideline Alliance<br><br>5b. Named contact e-mail<br>epilepsies@nice.org.uk<br><br>5c. Organisational affiliation of the review<br>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. | | |

| Field | Content |
|---|---|
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112 |
| Other registration details | Not applicable |
| URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019146519 |
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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 |
| 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. |
| 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 |

| # | searches |
|---|---|
| | topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab. |
| 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. |
| 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 |

| # | searches |
|---|---|
| 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 |
| 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 |

| # | searches |
|---|---|
| 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 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. |
| 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 |

| # | searches |
|---|---|
| | value of life/ |
| 23 | 22 use ppez |
| 24 | budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/ |
| 25 | 24 use emczd |
| 26 | budget*.ti,ab. |
| 27 | cost*.ti. |
| 28 | (economic* or pharmaco economic* or pharmacoeconomic*).ti. |
| 29 | (price* or pricing*).ti,ab. |
| 30 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 31 | (financ* or fee or fees).ti,ab. |
| 32 | (value adj2 (money or monetary)).ti,ab. |
| 33 | or/23,25-32 |
| 34 | 21 and 33 |
| 25 | limit 34 to engish language |

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

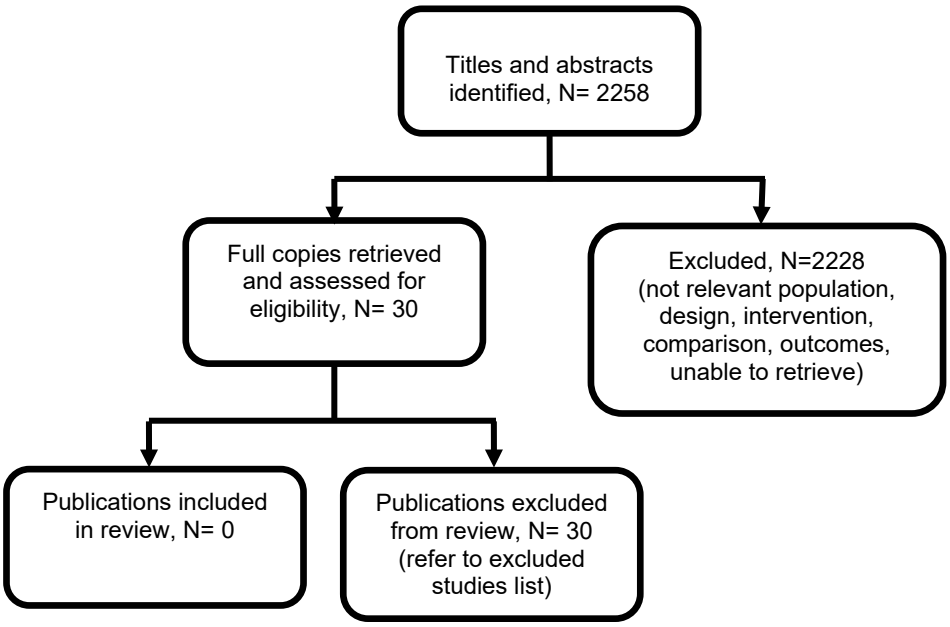
| # | searches |
|---|---|
| 1 | mesh descriptor epilepsy explode all trees |
| 2 | mesh descriptor seizures this term only |
| 3 | mesh descriptor seizures, febrile this term only |
| 4 | mesh descriptor status epilepticus explode all trees |
| 5 | (epilep* or seizure* or convuls*) or (“continous spike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

| # | searches |
|---|---|
| 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 |
| 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: | Does not include data on epilepsy with myoclonic-atonic seizures or patients with Doose syndrome |

| Study | Reason for Exclusion |
|---|---|
| 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 | |
| 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 |
| 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. No relevant data could be extracted for inclusion. References checked for inclusion |

| Study | Reason for Exclusion |
|---|---|
| network meta-analysis, Epilepsia, 59, 297-314, 2018 | |
| 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 |
| **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<br>• Dietary treatments<br>• Novel treatments<br>• Surgical therapies |
| **Comparator** | • Placebo<br>• No treatment<br>• Combinations of above |
| **Outcomes** | Important outcomes:<br>• Reduction in seizure frequency >50%<br>• Ongoing seizures<br><br>Tolerability:<br>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures, intolerable side effects, behavioural changes)<br>• Adverse events, as assessed by:<br>  ○ % of patients with reported side effects (as defined by trialists)<br>  ○ Treatment cessation due to adverse medication effects<br><br>Other outcomes:<br>• Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)<br>• Overall quality of life (reported by caregiver/the individual with epilepsy and as measured with a validated scale) |
| **Study design** | Multicentre/UK wide RCT |
| **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*