# National Institute for Health and Care Excellence

Final

# Epilepsies in children, young people and adults

## [K] Effectiveness of antiseizure therapies in the treatment of Dravet syndrome

*NICE guideline NG217*

*Evidence reviews underpinning recommendations 6.1.1-6.1.8 in the 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*

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ISBN: 978-1-4731-4513-9

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# Effectiveness of antiseizure therapies in the treatment of Dravet syndrome

## Review question

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

### Introduction

Dravet syndrome is a developmental and epileptic encephalopathy with early onset, presenting in the first year of life. Presentation is usually with reoccurring fever related prolonged hemiclonic seizures with afebrile generalised tonic clinic seizures, myoclonic seizures and absence seizures. Children are developmentally normal prior to seizure onset but development begins to slow from 18 months and severe learning disability, impaired language, impaired mobility and feeding develop over time. The majority of patients (85%) have a mutation in SCN1A sodium channel gene, although SCN1A mutations can also be associated with less severe forms of epilepsy, such as generalised epilepsy with febrile seizures (GEFS). The aim of this review is to determine which antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome.

### Summary of the protocol

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

**Table 1: Summary of the protocol (PICO table)**

| | |
|---|---|
| **Population** | Children, young people and adults with confirmed Dravet syndrome |
| **Intervention** | • Potassium bromide<br>• Midazolam<br>• Cannabidiol<br>• Clobazam<br>• Diazepam<br>• Levetiracetam<br>• Fenfluramine<br>• Sodium valproate<br>• Stiripentol<br>• Topiramate<br>• Steroids<br>• Zonisamide<br>• Ketogenic diet<br><br>Interventions may be monotherapy or add-on therapy |
| **Comparison** | • No treatment/placebo<br>• Comparison between the listed interventions (monotherapy or add-on therapy)<br>• Different doses of the listed interventions |
| **Outcomes** | **Critical**<br>• Reduction in seizure frequency >50%<br>• Reduction in clonic or tonic-clonic attack frequency |

| | |
|---|---|
| | • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)<br>• Adverse events, as assessed by:<br>○ % of patients with reported side effects (trial defined adverse and serious adverse events)<br>○ Mortality<br><br>**Important**<br>• 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)<br>• Health-related quality of life (measured using validated tools) |

*IQ: Intelligence quotient; VABS: Vineland Adaptive Behaviour Scale*

For further details see the review protocol in appendix A.

## Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

## Clinical evidence

### Included studies

Three randomised controlled trials (RCTs) were identified for inclusion in this review (Chiron 2000, Lagae 2019, Nabbout 2019).

One RCT compared stiripentol to placebo as an add-on therapy; 1 RCT compared fenfluramine (0.2 mg/kg/day and 0.7 mg/kg/day) to placebo, and 1 RCT compared fenfluramine (0.4 mg/kg/day) to placebo.

The included studies are summarised from Table 2 to Table 4.

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

### Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

## Summary of clinical studies included in the evidence review

Summary of the studies that were included in this review are presented from Table 2 to Table 4.

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

| Study | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Chiron 2000 | N = 42 | Add-on stiripentol (STP) | Add-on placebo<br>n=20 | • Reduction in clonic or tonic-clonic sei- |

| Study | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| RCT<br><br>France | Mean age<br>STP: 9.4 years (range 3 to 16.7)<br><br>Placebo: 9.3 years (range 3.2 to 20.7) | n=22<br><br>Dose: 50 mg/kg/day<br><br>Co-medication was limited to 30 mg/kg/day for valproate and 0.5 mg/kg/day for clobazam | Co-medication was limited to 30 mg/kg/day for valproate and 0.5 mg/kg/day for clobazam | zure frequency >50%<br>• Mean change from baseline in seizure frequency<br>• Clonic or tonic-clonic seizure freedom<br>• Number of patients who withdrew from treatment because of adverse events<br>• Adverse events: % of patients with reported side effects (trial defined serious) |

*Kg: kilogram; mg: milligram; STP: Stiripentol*

**Table 3: Summary of included studies. Comparisons 2 and 3: fenfluramine (0.2 and 0.7 mg/kg/day) versus placebo**

| Study | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Lagae 2019<br><br>RCT<br><br>US, Canada, western Europe, Australia | N=119 children with Dravet syndrome<br><br>Mean age (SD), years: fenfluramine 0.2 mg/kg/day 9.0 (4.5); fenfluramine 0.7 mg/kg/day 8.8 (4.4); placebo 9.2 (5.1) | Fenfluramine 0.2 mg/kg/day<br>n=39<br><br>Fenfluramine 0.7 mg/kg/day<br>n=40<br><br>Maximum daily dose limited to 30 mg | Placebo<br>n=40 | • Reduction in seizure frequency >50%<br>• Reduction in clonic or tonic-clonic attack frequency<br>• Mortality<br>• Adverse events: % of patients with reported side effects (trial defined serious)<br>• Neurodevelopment outcomes<br>• Social functioning changes<br>• Health-related quality of life |

*Kg: kilogram; mg: milligram; SD: standard deviation*

**Table 4: Summary of included studies. Comparison 4: fenfluramine (0.4 mg/kg/day) versus placebo**

| Study | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Nabbout 2019<br><br>RCT<br><br>France, Germany, Netherlands, Spain, United Kingdom, US | N=87 children and young people with Dravet syndrome<br><br>Age, years, mean (SD) [range]: Fenfluramine 8.8 (4.6) [2-18]; placebo 9.4 | Fenfluramine<br>n=43<br><br>Twice-daily fenfluramine (administered as a fenfluramine hydrochloride oral solution containing 2.2 mg/mL of fenfluramine)<br><br>Maximum daily | Placebo<br>n=44 | • Reduction in seizure frequency >50%<br>• Seizure freedom<br>• Adverse events: % of patients with reported side effects (trial defined serious)<br>• Social functioning changes<br>• Health-related quality of life (measured using validated tools) |

| Study | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| | (5.1) [2-19]; total 9.1 (4.8) [2-19], | dose limited to 0.4 mg/kg/day | | |

*Kg: kilogram; mg: milligram; SD: standard deviation*

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

## Summary of the clinical evidence

Moderate to low quality evidence showed that add-on stiripentol (to clobazam and valproate) was associated with clinically important reductions in clonic or tonic-clonic seizure frequency > 50%, and mean seizure frequency (compared to baseline); and a clinically important increase in the number of patients who achieved seizure freedom.

High to low quality evidence showed that, when compared to placebo, fenfluramine (0.2 mg/kg/day, 0.7 mg/kg/day) was associated with clinically important benefits in reduction of seizure frequency > 50%; assessments of executive function, cognition and quality of life; and caregiver/parent and investigator ratings of improvement from baseline.

Similarly, low to high quality evidence showed that in patients whose seizures were poorly controlled with a current treatment plan that included stiripentol plus clobazam or valproic acid; fenfluramine 0.4 mg/kg/day was associated with clinically important benefits reduction of seizure frequency >50%; and caregiver/parent and investigator ratings of improvement from baseline.

No evidence was identified for outcomes such as neurodevelopmental, social functioning changes or health-related quality of life

## Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

## Economic evidence

### Included studies

One relevant study was identified in a literature review of published economic evidence on this topic (Elliott 2018; see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of stiripentol as an adjunctive treatment to clobazam and valproate for treatment of Dravet syndrome compared with clobazam and valproate alone. The study considered a population representative of patients with Dravet syndrome who had not previously responded to concomitant treatment with clobazam and valproate.

The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs). The analysis adopted the perspective of the Canadian healthcare system.

### Excluded studies

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

## Summary of studies included in the economic evidence review

The base-case results of Elliott 2018 suggest that stiripentol as an adjunctive to clobazam and valproate is more effective and more costly than clobazam and valproate alone in patients with Dravet syndrome, who had not previously responded to concomitant treatment with clobazam and valproate. The estimated base-case incremental cost-effectiveness ratio (ICER) of Canadian dollars ($Can) 151,310 per QALY is well above the conventional threshold range specified by NICE to represent cost-effective use of resources of £20,000 per QALY.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis. Results were found to be sensitive to the patient age, and the cost of stiripentol treatment. However as stated in the paper, while the patient age varied the results to an extent that their final interpretation of would not change; results were very sensitive to the cost of stiripentol, and this was likely to change the cost-effectiveness results (that is Stiripentol would be considered cost effective at a willingness-to-pay threshold of $Can 50,000 if its price was reduced by 61.4%). In probabilistic sensitivity analysis adjunctive stiripentol was found to have 5.2% probability of being cost-effective at a threshold of $Can 50,000 per QALY, and 20.7% probability of being cost-effective at a threshold of $Can 100,000 per QALY.

As it was not based in the UK, the study was considered to be partly applicable to this guideline review. This is because the Canadian evaluation context is likely to change the conclusions about cost effectiveness results. The study was deemed to have minor limitations, as it meets most of the requirements of an adequate economic evaluation (see Developing NICE guidelines: appendix H).

## Economic model

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

## Evidence statements

- There was evidence from 1 Canadian cost utility analysis showing adjunctive stiripentol not being cost effective to clobazam and valproate alone in people with Dravet syndrome who had not previously responded to concomitant treatment with clobazam and valproate. The study was partially applicable to the decision problem and was deemed to only have minor methodological liitations.

## Summary of the economic evidence

One relevant study was identified in the literature review of published cost effectiveness analyses on this topic (Elliott 2018). This was a cost-utility study, partially applicable to the decision problem and with minor methodological limitations, comparing the cost effectiveness of stiripentol as an adjunctive therapy to clobazam and valproate with clobazam and valproate alone in people with Dravet syndrome, who had not previously responded to concomitant treatment with clobazam and valproate. Adjunctive stiripentol was not deemed to be a cost-effective intervention compared to clobazam and valproate alone, with an ICER of Canadian dollars ($Can) 151,310 per QALY gained. Probabilistic sensitivity analysis estimated a lower 5.2% probability of adjunctive stiripentol being cost effective when QALYs are valued at $Can 50,000 per QALY.

## The committee's discussion of the evidence

### Interpreting the evidence

### The outcomes that matter most

Dravet syndrome is a lifelong form of epilepsy for which complete seizure freedom is unlikely and treatment is therefore focused on controlling seizures as much as possible whilst minimising the risk of adverse events. The committee therefore agreed that reduction in seizure frequency >50%, time to withdrawal of treatment or change of medication, and adverse events (as assessed by trial-defined adverse and serious adverse events and mortality) should be designated as critical outcomes for this review. As patients with Dravet syndrome experience seizures characterised by stiffness and/or jerking, the committee also agreed that reduction in clonic or tonic clonic seizures specifically should be included as a critical outcome.

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

### The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The majority of outcomes were considered moderate or very low quality indicating high uncertainty in the reliability of the data. Outcomes were generally downgraded due to risk of bias, methods were poorly reported, particularly in regard to outcome reporting as the study authors did not pre-register a protocol prior conducting the study, therefore the analysis intentions were not available. Data were also downgraded due to imprecision. The included studies only included a small number of participants; therefore, overall the data should be regarded with some caution. Additionally, not all outcomes as specified in the protocol were reported by all the trials.

### Benefits and harms

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

Dravet syndrome is a developmental and epileptic encephalopathy which has early onset and is characterised by reoccurring fever related prolonged hemiclonic seizures with afebrile generalised tonic clinic seizures, myoclonic seizures and absence seizures. Over time, children with Dravet syndrome develop severe learning disabilities, impaired language and feeding difficulties. Given the difficulties in treating Dravet syndrome, the range of seizures it can feature, and the impact it can have on quality of life both for children with Dravet syndrome and their carers, the committee agreed to recommend that people with Dravet syndrome should have an adult or paediatric neurologist with expertise in epilepsy involved in their care with the aim of facilitating diagnosis, improving access to further investigations, and ensuring that appropriate treatment is provided. Involvement of a neurologist with expertise in epilepsy in the care of people with Dravet syndrome is standard current practice, therefore the committee did not think this recommendation would lead to increased costs or resource use.

The committee agreed that, prior to starting antiseizure therapy there should be a discussion with the person, their family and carers, if appropriate, about an individualised strategy according to their syndrome type, treatment goals and the preferences of the person and their family or carers as appropriate. Treatment plans should be regularly reassessed, and its

agreement should include a transparent explanation of the epilepsy type, severity and duration of adverse effects that the person with epilepsy may experience and how should these be managed. The person, their family and carers, should also be made aware that they should be taking the least amount of medicines as possible to be effective due to the side effects of being on numerous medications.

No evidence was found assessing the effectiveness of monotherapy or first-line therapy, so the committee agreed, based on their expert opinion, that sodium valproate should be the first-line treatment in people with a confirmed diagnosis of Dravet syndrome because it is effectively used in clinical practice to treat generalised seizures, including Dravet syndrome, and because the severity of the syndrome and the lack of evidence for alternative first-line options. The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children, yet agreed that it should be offered as first line treatment as Dravet Syndrome's neurodevelopmental consequences mean that pregnancy is unusual. Additionally, the committee agreed that the severity of the syndrome and the lack of evidence to support alternative first-line treatment options meant that the potential benefits of sodium valproate could outweigh risks associated with sodium valproate where the likelihood of pregnancy is very low. However, the committee agreed that, for women and girls who are able to have children, sodium valproate should only be prescribed after a full and clear discussion with them or their families/carers, as appropriate, ensuring they understand all the potential risks and benefits. If sodium valproate is prescribed to women and girls able to have children, clinicians must follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a pregnancy prevention programme, if appropriate.

The evidence showed that stiripentol as an add-on therapy to sodium valproate and clobazam was associated with an improvement in seizure frequency in children and young people who had not previously responded to concomitant treatment with clobazam and sodium valproate. Based on the available evidence, the committee recommended this treatment as first-line add-on therapy if seizures continued after sodium valproate had been started. The committee emphasised that monotherapy should be used in the first instance and warned about the potential sedative effects of stiripentol and clobazam in combination. They agreed that clobazam should be titrated according to clinical response with the main aim to bring seizures under control as quickly as possible while avoiding side effects. Stiripentol requires close monitoring of adverse effects associated with this medication.

The recommendation regarding cannabidiol was adopted from the NICE Technology Appraisal Cannabidiol for adjuvant treatment of seizures associated with Dravet Syndrome (NICE TA 614).

Based on their expert opinion, the committee recommended alternative treatments that could be used if seizures continued or the child is under 2 years. They emphasised that these treatments should only be considered with guidance from ketogenic diet team or a neurologist with expertise in epilepsy. This is because response to drugs may differ according to the person with epilepsy. The choice of antiseizure therapy would be tailored to each individual, according to their age and their ability to tolerate higher doses. Ketogenic diets are successfully used in clinical practice in cases which are difficult to treat. The committee emphasised that these should only be prescribed under the guidance or supervision of a neurologist with expertise in epilepsy as these are calculated individually, and the person's weight and ketone levels need to be monitored.

The committee agreed that, if all other treatment options are unsuccessful, potassium bromide should be considered under the guidance of a neurologist with expertise in epilepsy. Potassium bromide is used in clinical practice in people with refractory Dravet syndrome. Although it is not licenced in the UK, it can be obtained on a named-patient basis and requires close monitoring of adverse effects associated with this medication.

The committee agreed it should be highlighted that certain antiseizure medications may exacerbate seizures in people with Dravet Syndrome. Therefore, they agreed to draft a recommendation stating this.

### Cost effectiveness and resource use

No economic evidence was identified for monotherapy, so the committee agreed, based on their expert opinion, that sodium valproate should be the first drug of choice in people with a confirmed diagnosis of Dravet syndrome.

One economic evaluation was identified and considered by the committee in making recommendations for this question, as for add-on therapy. The study was a cost utility analysis conducted from the perspective of the Canadian healthcare system. A Markov model was developed to assess the cost-effectiveness of stiripentol as an adjunctive treatment to clobazam and valproate for treatment of Dravet syndrome compared with clobazam and valproate alone in a hypothetical cohort of adult patients with Dravet syndrome who had not previously responded to concomitant treatment with clobazam and valproate. Although the analysis was deemed to have minor limitations, it was considered to be only partly applicable to this guideline question, as the Canadian evaluation context is likely to change the conclusions about cost-effectiveness results.

In the analysis outcomes in terms of cost per QALY, strongly suggested that the adjunctive use of stiripentol is not cost effective in patients with Dravet syndrome, at a willingness-to-pay threshold of Canadian dollars ($Can) 50,000 ($Can 151,310 per additional QALY compared to clobazam and valproate alone). The committee noted that these cost effectiveness results were very sensitive to the price of stiripentol considered in the analysis (that is stiripentol would be considered cost effective at a willingness-to-pay threshold of $Can 50,000 if its price was reduced by 61.4%), and this was likely to vary with the healthcare setting. Whilst the conclusions may not be directly applicable to the NHS & PSS the cost of stiripentol is significantly cheaper in the UK where it is available off-patent. Stiripentol was also recommended first line in the previous NICE guideline and represents current practice. Therefore, based on the available evidence and their clinical expertise, the committee agreed to recommend the sequential adjunctive use of stiripentol and then clobazam, when seizures continue with careful titration and frequent review with monitoring of adverse effects.

All recommendations reinforce current practice and will not lead to any significant 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.

The committee discussed that guidance on the use of fenfluramine for people with Dravet syndrome should be based on NICE's forthcoming technology appraisal on fenfluramine for treating seizures associated with Dravet syndrome.

## Recommendations supported by this evidence review

This evidence review supports recommendations 6.1.1-6.1.8 and the research recommendation on complex epilepsy syndromes.

# References

**Chiron 2000**

Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G, STICLO Study Group. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. The Lancet. 2000; 356(9242):1638-42.

**Elliott 2018**

Elliott J, McCoy B, Clifford T, Wells GA, Coyle D. Economic evaluation of stiripentol for Dravet syndrome: a cost-utility analysis. Pharmacoeconomics. 2018; 36:1253–61.

**Lagae 2019**

Lagae, L., Sullivan, J., Knupp, K., Laux, L., Polster, T., Nikanorova, M., Devinsky, O., Cross, J. H., Guerrini, R., Talwar, D., Miller, I., Farfel, G., Galer, B. S., Gammaitoni, A., Mistry, A., Morrison, G., Lock, M., Agarwal, A., Lai, W. W., Ceulemans, B., Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial, The Lancet, 394, 2243-2254, 2019

**Nabbout 2019**

Nabbout, R., Mistry, A., Zuberi, S., Villeneuve, N., Gil-Nagel, A., Sanchez-Carpintero, R., Stephani, U., Laux, L., Wirrell, E., Knupp, K., et al., Fenfluramine for Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: a Randomized Clinical Trial, JAMA Neurology, 2019

# Appendices

## Appendix A – Review protocols

### Review protocol for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome?

**Table 5: Review protocol for effectiveness of antiseizure therapies in treatment of seizures in those with Dravet syndrome**

| Field | Content |
|---|---|
| PROSPERO registration number | Not registered |
| Review title | Effectiveness of antiseizure therapies in treatment of seizures in those with Dravet syndrome. |
| Review question | What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome? |
| Objective | The objective of this review is to determine which antiseizure therapies improve outcomes in those with seizures in Dravet syndrome.<br><br>This review will determine the effectiveness of therapies given alone or in combination (add-on therapy). |
| 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 |

| Field | Content |
|---|---|
| | 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 | Dravet syndrome |
| Population | Inclusion: children, young people and adults with confirmed Dravet syndrome. |
| Intervention | • Potassium bromide<br>• Midazolam<br>• Cannabidiol<br>• Clobazam<br>• Diazepam<br>• Levetiracetam<br>• Fenfluramine<br>• Sodium valproate<br>• Stiripentol<br>• Topiramate<br>• Steroids<br>• Zonisamide<br>• Ketogenic diet<br>• Interventions may be monotherapy or add-on therapy |
| Comparator/Reference standard/Confounding factors | • No treatment/placebo<br>• Comparison between the listed interventions (monotherapy or add-on therapy)<br>• Different doses of the listed interventions |
| Types of study to be included | • Systematic Reviews of RCTs |

| Field | Content |
|---|---|
| | • RCTs |
| Other exclusion criteria | Studies with a mixed population (this is, including children, young people and adults with Dravet syndrome and other types of epilepsy) will be excluded, unless subgroup analysis for Dravet syndrome has been reported.<br><br>Conference abstracts will not be included because these do not typically provide sufficient information to fully assess risk of bias. |
| Context | Recommendations will apply to those receiving care in healthcare settings (for example, community, primary, secondary care). |
| Primary outcomes (critical outcomes) | • Reduction in seizure frequency >50%<br>• Reduction in clonic or tonic-clonic attack frequency.<br>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)<br>Adverse events, as assessed by:<br>• % of patients with reported side effects (trial defined adverse and serious adverse events)<br>• Mortality<br>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)<br>• Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)<br>• Health-related quality of life (measured using 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: |

| Field | Content |
|---|---|
| | • 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. |
| Strategy for data synthesis | Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.<br><br>Data synthesis<br>• Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm. Mean differences or standardised mean differences will be presented for continuous outcomes.<br><br>Heterogeneity<br>Heterogeneity in the effect estimates of the individual studies will be assessed using the $I^2$ statistic. $I^2$ values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively.<br><br>In the presence of heterogeneity, sub-group analysis will be conducted:<br>• according to the risk of bias of individual studies<br>• by age (older people/adults/children)<br>• study location<br><br>Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies.<br><br>Minimal important differences (MIDs)<br>Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes<br>• For risk ratios: 0.8 and 1.25.<br>• For continuous outcomes: |

| Field | Content | |
|---|---|---|
| | • For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm.<br>• For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used.<br>• For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD.<br>• For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.<br><br>Validity<br>The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ | |
| Analysis of sub-groups (Stratification) | 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 | 30 July 2019 | |
| Anticipated completion date | 7th April 2021 | |

| Field | Content | | |
|---|---|---|---|
| Stage of review at time of this submission | Review stage | Started | Completed |
| | Preliminary searches | ☑ | ☑ |
| | Piloting of the study selection process | ☑ | ☑ |
| | Formal screening of search results against eligibility criteria | ☑ | ☑ |
| | Data extraction | ☑ | ☑ |
| | Risk of bias (quality) assessment | ☑ | ☑ |
| | Data analysis | ☑ | ☑ |
| Named contact | 5a. Named contact<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 | | |

| Field | Content |
|---|---|
| | interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/gid-ng10112/documents/committee-member-list |
| Other registration details | Not applicable |
| URL for published protocol | Not registered in PROSPERO |
| 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, Dravet syndrome, severe myoclonic epilepsy of infancy, Children, adults, young people, antiseizure medication. |
| 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; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SD: Standard Deviation.*

# Appendix B – Literature search strategies

## Literature search strategies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome?

### Clinical

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

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

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

| # | searches |
|---|---|
| 1 | severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez |
| 2 | (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. |
| 3 | or/1-2 |
| 4 | 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. |
| 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 | levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam or "ucb l 059" or ucb l059).ti,ab. |
| 12 | exp steroid/ use emczd, emcr or steroids/ use ppez or steroid*.sh. or steroid*.ti,ab. |
| 13 | 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. |
| 14 | zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab. |
| 15 | bromide/ use emczd, emcr or exp bromides/ use ppez or (bromid* or hydrobromide*).ti,ab. |
| 16 | midazolam/ use emczd, emcr,ppez or (buccolam or dalam or doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or midacum or midazo or midazol or midazolam or midolam or miloz or versed).ti,ab. |

| # | searches |
|---|---|
| 17 | cannabidiol/ use emczd, emcr,ppez or (cannabidiol or epidiolex or nabidiolex).ti,ab. |
| 18 | diazepam/ use emczd, emcr,ppez or (alboral or aliseum or alupram or amiprol or ansiolin or antenex or anxionil or apaurin* or apozepam or armonil or arzepam or assival or atensine or audium or azedipamin or benzopin or betapam or bialzepam or bialzepan or calmpose or caudel or cercin* or cersine or chlordiazepam or compaz or desconet or diaceplex or dialag or dialar or diano or diapam or diapanil or diapax or diapin or diapine or diapo or diaquel or diastat or diazelium or diazem or diazemuls or diazepa* or diazepin or diazidem or dipaz or dipezona or dizac or doval or drenian or ducene or dupin or duxen or elcion or eridan or euphorin or eurosan or evacalm or fanstan or faustan or gewacalm or gubex or kratium or lamra or lembrol or lipodiazepam or lorinon or lovium or melode or mentalium or methyldiazepinon or methyldiazepinone or morosan or neocalme or neurolytril or nivalen or noan or novazam or ortopsique or paceum or pacitran or paxum or placidox or plidan or propam or psychopax or q-pam or radizepam or relanium or reliver or reposepan or saromet or sedapam or seduxen or serendin or setonil or sibazon or simasedan or sipam or sonacon or stesolid or stesolin or tanquo tablinen or tensium or tranimul or tranquirit or tranquo puren or trazepam or umbrium or valaxona or valiquid or valium or valpam or valrelease or vanconin or vatran or vazen or vival or vivol or zetran).ti,ab. |
| 19 | fenfluramine/ use emczd, emcr or (adipomin or fenflurami* or fenured or kataline or minifage or moderex or obedrex or pesos or phenfluoramine or phenylethylamine or ponderal or ponderax or ponderex or pondimin or ponflural or rotondin).ti,ab. |
| 20 | stiripentol/ use emczd, emcr or (stiripentol* or diacomit).ti,ab. |
| 21 | topiramate/ use emczd, emcr,ppez or (epitomax or topamax or topiramat* 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. |
| 22 | or/4,10--21 |
| 23 | 3 and 22 |
| 24 | 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. |
| 25 | 24 use ppez |
| 26 | (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. |
| 27 | 26 use ppez |
| 28 | 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. |
| 29 | 28 use emczd, emcr |
| 30 | or/25,27,29 |
| 31 | meta-analysis/ |
| 32 | meta-analysis as topic/ or systematic reviews as topic/ |
| 33 | "systematic review"/ |
| 34 | meta-analysis/ |
| 35 | (meta analy* or metanaly* or metaanaly*).ti,ab. |
| 36 | ((systematic or evidence) adj2 (review* or overview*)).ti,ab. |
| 37 | ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. |
| 38 | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 39 | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 40 | (search* adj4 literature).ab. |
| 41 | (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. |
| 42 | cochrane.jw. |
| 43 | ((pool* or combined) adj2 (data or trials or studies or results)).ab. |
| 44 | (or/31-32,35,37-43) use ppez |
| 45 | (or/33-34,38-43) use emczd, emcr |
| 46 | or/44-45 |
| 47 | or/30,46 |
| 48 | 23 and 47 |

| # | searches |
|---|---|
| 49 | limit 48 to english language |
| 50 | ((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.) |
| 51 | 50 use emez |
| 52 | ((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.) |
| 53 | 52 use mesz |
| 54 | 51 or 53 |
| 55 | 49 not 54 |

## Database(s): Cochrane Library

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

| # | searches |
|---|---|
| 1 | mesh descriptor: [epilepsies, myoclonic] explode all trees |
| 2 | ((dravet* or ("intractable childhood epilepsy" near/2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei)):ti,ab,kw |
| 3 | #1 or #2 |
| 4 | mesh descriptor: [bromides] explode all trees |
| 5 | ((bromid* or hydrobromide*)):ti,ab,kw |
| 6 | mesh descriptor: [midazolam] this term only |
| 7 | ((buccolam or dalam or doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or midacum or midazo or midazol or midazolam or midolam or miloz or versed)):ti,ab,kw |
| 8 | mesh descriptor: [cannabidiol] this term only |
| 9 | ((cannabidiol or epidiolex or nabidiolex)):ti,ab,kw |
| 10 | mesh descriptor: [clobazam] explode all trees |
| 11 | ((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab,kw |
| 12 | mesh descriptor: [diazepam] explode all trees |
| 13 | ((alboral or aliseum or alupram or amiprol or ansiolin or antenex or anxionil or apaurin* or apozepam or armonil or arzepam or assival or atensine or audium or azedipamin or benzopin or betapam or bialzepam or bialzepan or calmpose or caudel or cercin* or cersine or chlordiazepam or compaz or desconet or diaceplex or dialag or dialar or diano or diapam or diapanil or diapax or diapin or diapine or diapo or diaquel or diastat or diazelium or diazem or diazemuls or diazepa* or diazepin or diazidem or dipaz or dipezona or dizac or doval or drenian or ducene or dupin or duxen or elcion or eridan or euphorin or eurosan or evacalm or fanstan or faustan or gewacalm or gubex or kratium or lamra or lembrol or lipodiazepam or lorinon or lovium or melode or mentalium or methyldiazepinon or methyldiazepinone or morosan or neocalme or neurolytril or nivalen or noan or novazam or ortopsique or paceum or pacitran or paxum or placidox or plidan or propam or psychopax or "q-pam" or radizepam or relanium or reliver or reposepan or saromet or sedapam or seduxen or serendin or setonil or sibazon or simasedan or sipam or sonacon or stesolid or stesolin or tanquo tablinen or tensium or tranimul or tranquirit or "tranquo puren" or trazepam or umbrium or valaxona or valiquid or valium or valpam or valrelease or vanconin or vatran or vazen or vival or vivol or zetran)):ti,ab,kw |
| 14 | mesh descriptor: [fenfluramine] explode all trees |
| 15 | ((adipomin or fenflurami* or fenured or kataline or minifage or moderex or obedrex or pesos or phenfluoramine or phenylethylamine or ponderal or ponderax or ponderex or pondimin or ponflural or rotondin)):ti,ab,kw |
| 16 | mesh descriptor: [valproic acid] explode all trees |
| 17 | ((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 |

| # | searches |
|---|---|
| | acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or" dipropylacetic acid" or diprosin or divalproex or epilam or epilex or "epilim chrono" or "epilim chronosphere" or "epilim enteric" or epilim or episenta or "epival cr" or ergenyl or "ergenyl chrono" or "ergenyl chronosphere" or "ergenyl retard" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or "n dipropylacetic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propyl-valerate" or "sodium di n propyl acetate" or "sodium di n propylacetate" or "sodium dipropy acetate" or "sodium dipropylacetate" or "sodium n dipropylacetate" or stavzor or "valberg pr" or valcote or valepil or valeptol or valerin or "valhel pr" or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)):ti,ab,kw |
| 18 | ((stiripentol* or diacomit)):ti,ab,kw |
| 19 | mesh descriptor: [topiramate] explode all trees |
| 20 | ((epitomax or topamax or topiramat* or acomicil or ecuram or epiramat or epitomax or epitoram or er-ravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)):ti,ab,kw |
| 21 | mesh descriptor: [zonisamide] this term only |
| 22 | ((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw |
| 23 | mesh descriptor: [steroids] this term only |
| 24 | (steroid*):ti,ab,kw |
| 25 | mesh descriptor: [levetiracetam] this term only |
| 26 | ((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw |
| 27 | mesh descriptor: [diet, carbohydrate-restricted] this term only |
| 28 | mesh descriptor: [dietary fats] explode all trees |
| 29 | mesh descriptor: [glycemic index] this term only |
| 30 | mesh descriptor: [diet, ketogenic] this term only |
| 31 | mesh descriptor: [triglycerides] explode all trees |
| 32 | (((adequate near/3 protein*) or atkin* or keto* or kd* or (carbohydrate* near/5 (restrict* or low* or re-duc*)) 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,kw (word var-iations have been searched) |
| 33 | {or #4-#32} |
| 34 | #3 and #33 |

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

| # | Searches |
|---|---|
| 1 | mesh descriptor epilepsies, myoclonic explode all trees |
| 2 | ((dravet* or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (se-vere near2 (myoclonic or polymorphic) near2 epilepsy near/2 infancy) or smeb or smei)) |
| 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 |
|---|---|

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

| # | searches |
|---|---|
| 31 | (financ* or fee or fees).ti,ab. |
| 32 | (value adj2 (money or monetary)).ti,ab. |
| 33 | or/23,25-32 |
| 34 | 21 and 33 |
| 25 | limit 34 to engish language |

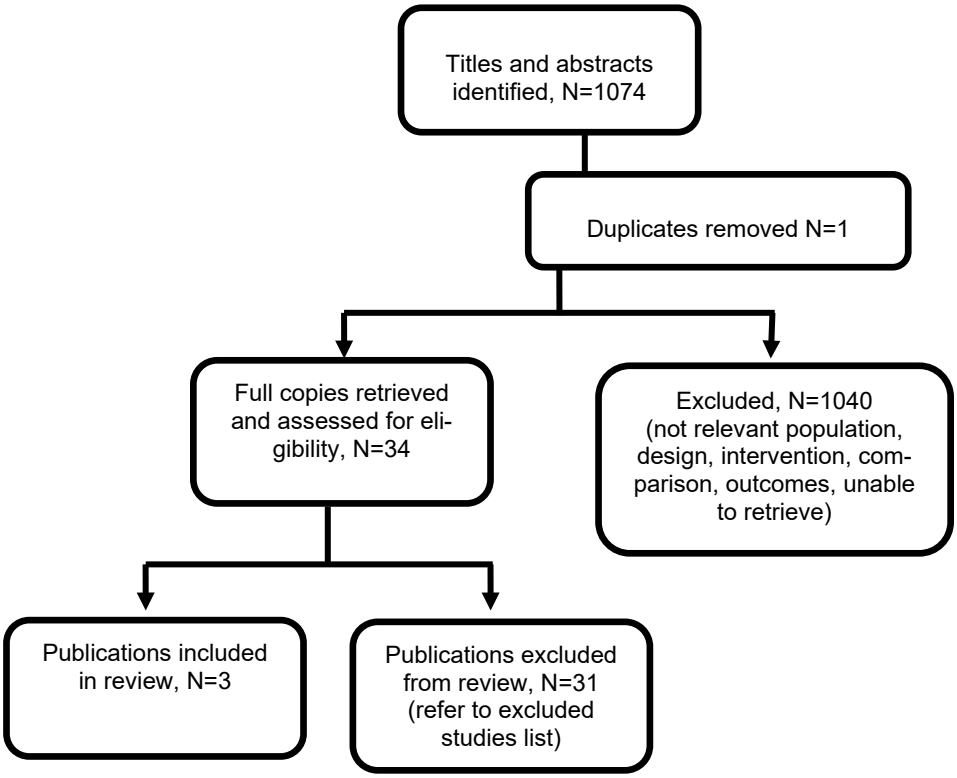
**Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD**
Date of last search: 31 March 2021

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

# Appendix C – Clinical evidence study selection

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

**Figure 1: Study selection flow chart**



# Appendix D – Clinical evidence tables

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

**Table 6: Clinical evidence tables**

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| **Full citation**<br>Chiron, C., Marchand, M. C., Tran, A., Rey, E., d'Athis, P., Vincent, J., Dulac, O., Pons, G., Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group, Lancet (london, england), 356, 1638-1642, 2000<br><br>**Ref Id**<br>1080135<br><br>**Country/ies where the study was carried out**<br>France<br><br>**Study type**<br>Double-blind placebo controlled trial<br><br>**Aim of the study**<br>To assess the effectiveness of stiripentol as compared with placebo as an add-on treatment | **Sample size**<br><br>N=42; n=22 allocated to stiripentol (STP) and n=20 allocated to placebo<br><br>**Characteristics**<br>Mean age<br>Intervention: 9.4 years (range 3 to 16.7 years), Control: 9.3 years (range 3.2 to 20.7 years)<br><br>Number of females<br>Intervention: n= 15 (68.1%), Control: n=9 (45%)<br><br>Median number of monthly seizures<br>Intervention: 18 (range 4-73), Control:19 (range 4-76)<br><br>No statistically differences seen between the treatment groups (p values not provid- | **Interventions**<br><br>Intervention group: add-on STP 50mg/kg/day<br><br>Control group: add on placebo<br><br>Co-medication was limited to 30 mg/kg a day for vaproate and 0.5 mg/kg a day for clobazam.<br><br>Doses could be decreased by 10 mg/kg daily for valproate in case of loss of appetite and by 25% for clobazam in case of drowsiness or hyperexcitability. | **Details**<br>After 1 month baseline, patients were randomly allocated to STP or placebo as an add-on therapy using a computer generated list.<br><br>Assessments took place monthly during the double blind period for 2 months and in subsequent open treatment for at least 1 month (the trial lasted 22 months, but all the reported results are from the double blind phase. During the open label phase, all patients received STP).<br><br>A patient could be withdrawn from the study if seizure frequency increased above 50% as compared with baseline or if adverse events were | **Results**<br><br>*Primary outcomes*<br><br>Reduction in clonic or tonic-clonic seizure frequency >50% (defined as 50% reduction of clonic or tonic-clonic seizure frequency during the second month of the double-blind period compared with baseline)<br>Intervention group: 15/21<br>Control group: 1/20<br><br>Mean change (SD) from baseline in seizure frequency<br>Intervention group: -69 (41), n=21<br>Control group: 7 (38), n=20<br><br>Clonic or tonic-clonic seizure freedom<br>Intervention group: 9/21<br>Control group: 0/20<br><br>Number of patients who withdrew from treatment because of adverse | **Limitations**<br><br>Methodological limitations assessed using the Cochrane Risk of Bias Tool for Randomised Trials (Version 2.0)<br><br>**Domain 1: Randomisation: Low** risk<br>1.1: Yes, a predetermined randomisation code was used<br>1.2: Yes, a computer-generated list to allocate interventions to participants was used<br>1.3: No, no significant differences between groups at baseline were reported<br><br>**Domain 2: Deviations from intended interventions: Low risk**<br>2.1: No, double blind study<br>2.2: No, double blind |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| to valproate and clobazam in patients with Dravet Syndrome<br><br>**Study dates**<br>October 1996 to August 1998<br><br>**Source of funding**<br>Not reported | ed)<br><br>**Inclusion criteria**<br>• ≥3 years old with severe myoclonic epilepsy of infancy (SMEI) defined as onset of clonic or tonic-clonic generalised seizures in the first year of life but normal psychomotor development and normal EEG<br>• Appearance of myoclonia after 1 year of age<br>• Atypical absences<br>• Generalised spikes and waves on EEG<br>• Mental delay<br>• At least 4 clonic or tonic-clonic seizures a month<br>• Valproate and clobazam as ongoing epileptic drugs<br><br>**Exclusion criteria**<br>• Those receiving other antiseizure medications (except progabide)<br>• Those whose parents were not able to comply with drug delivery and seizure | | experienced.<br><br>Follow-up: 2 months (no measure of variability was reported) | events<br>Intervention group: 0/21<br>Control group: 1/20<br><br>Adverse events: % of patients with reported side effects (trial defined serious)<br>Intervention group: 5/21<br>Control group: 1/20 | study<br><br>**Domain 3: Missing outcome data: Low risk**<br>3.1: Yes, data was available for all participants randomised<br><br>**Domain 4: Measurement of the outcome: Low risk**<br>4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom<br>4.2: Probably no, outcomes included seizure frequency and reduction, and these are unlikely to differ between treatment arms<br>4.3: No, double blind study<br><br>**Domain 5: Selection of the reported result: Some concerns**<br>5.1: Probably no, the study authors do not make reference to any study protocol<br>5.2: No information, analysis intentions are not available and there is more than |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | diary | | | | one way in which the outcomes could have been measured<br>5.3: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured<br><br>**Domain 6: Overall judgment of bias: Some concerns**<br>The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain<br><br>**Other information**<br>The deaths reported by the study (n=2) have not been reported as part of the results because these took place at follow-up, during the open label phase of STP. |
| **Full citation**<br>Lagae, L., Sullivan, J., Knupp, K., Laux, L., Polster, T., Nikanorova, M., Devinsky, O., Cross, J. H., Guerrini, R., Talwar, D., Miller, I., Farfel, G., Galer, B. S., Gammaitoni, A., Mistry, A., | **Sample size**<br>N=119 randomised.<br>Placebo n=40.<br>Fenfluramine 0.2 mg/kg/day n=39.<br>Fenfluramine 0.7 mg/kg/day n=40. | **Interventions**<br>Placebo<br>Fenfluramine hydrochloride 0.2 mg/kg per day (base equivalent 0.17 mg/kg per day),<br>Fenfluramine hydro- | **Details**<br>Seizures were documented by parents or caregivers in an electronic diary, including date, time of day, duration, and seizure type.<br>Based on data from two | **Results**<br>*Critical outcomes*<br>Reduction in seizure frequency >50%:<br>fenfluramine 0.7 mg/kg/day n=27/40;<br>fenfluramine 0.2 mg/kg/day n=15/39; | Methodological limitations assessed using the Cochrane Risk of Bias Tool for Randomised Trials (Version 2.0)<br><br>**Domain 1: Randomisation: Low risk** |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Morrison, G., Lock, M., Agarwal, A., Lai, W. W., Ceulemans, B., Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial, The Lancet, 394, 2243-2254, 2019<br><br>**Ref Id**<br>1213802<br><br>**Country/ies where the study was carried out**<br>USA, Canada, western Europe, Australia<br><br>**Study type**<br>Double-blind placebo randomised controlled trial<br><br>**Aim of the study**<br>To "… assess the efficacy and safety of fenfluramine in patients with Dravet syndrome." P 2243<br><br>**Study dates**<br>Jan 2016, to Aug 2017<br><br>**Source of funding**<br>Zogenix | **Characteristics**<br>Children with Dravet syndrome.<br><br>Age, years, mean (SD): fenfluramine 0.7 mg/kg/day 8.8 (4.4); fenfluramine 0.2 mg/kg/day 9.0 (4.5); placebo 9.2 (5.1); 9.0 (4.7).<br>Patients younger than 6 years: fenfluramine 0.7 mg/kg/day n=11 (28%); fenfluramine 0.2 mg/kg/day n=9 (23%); placebo n=11 (28%); total n=31 (26%).<br><br>Male: fenfluramine 0.7 mg/kg/day n=21 (52%); fenfluramine 0.2 mg/kg/day n=22 (56%); placebo n=21 (52%); total n=64 (54%).<br><br>Race<br>White - fenfluramine 0.7 mg/kg/day n=34 (85%); fenfluramine 0.2 mg/kg/day n=33 (85%); placebo n=31 (78%); total n=98 (82%)<br>Asian - fenfluramine 0.7 mg/kg/day n=1 | chloride 0.7 mg/kg per day (base equivalent 0.69 mg/kg per day), with the maximum daily dose limited to 30 mg per day (base equivalent 25.9 mg). All doses of fenfluramine are expressed in the manuscript as base-equivalent doses.<br><br>Fenfluramine administered as an oral solution of fenfluramine hydrochloride containing 2.2 mg/Ml fenfluramine.<br>Daily doses administered orally with food in two equal doses—one in the morning and one in the evening, approximately 12 hours apart.<br>During the first 2 weeks (titration period), patients in the fenfluramine 0.7 mg/kg per day group were titrated to their final dose, starting with 0.2 mg/kg per day for 4 days, 0.4 mg/kg per day for 4 days, and then reaching the final | phase 3 RCTs (NCT02682927, NCT02826863) comparing two different doses of fenfluramine to placebo. The datasets were merged due to incomplete enrolment in both studies.<br>Online randomisation with a 1:1:1 ratio (stratified by age, <6 years, ≥6 years) produced by independent statistician.<br>The original protocol stated that each age group was to include at least 40% of enrolled patients, but during the drafting of the statistical analysis plan and after observing the age distribution of the study population in a study of Dravet syndrome, the stratification regimen was changed in the statistical analysis plan to achieve an age distribution of 25% in patients younger than 6 years.<br>All patients, caregivers, investigators, and other people involved in acquiring and assessing were masked to treat- | placebo n=5/40.<br><br>NB Defined as reduction in convulsive seizures - hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs.<br><br>100% reduction in convulsive seizure frequency:<br>fenfluramine 0.7 mg/kg/day n=3/40;<br>fenfluramine 0.2 mg/kg/day n=3/39;<br>placebo n=0/40<br><br>Patients with at least 1 adverse event:<br>fenfluramine 0.7 mg/kg/day n=38/40;<br>0.2 mg/kg/day n=37/39;<br>placebo n=26/40.<br><br>Mortality:<br>fenfluramine 0.7 mg/kg/day n=0/40;<br>0.2 mg/kg/day n=0/39;<br>placebo n=0/40.<br><br>Serious adverse events:<br>fenfluramine 0.7 mg/kg/day n=5/40;<br>0.2 mg/kg/day n=4/39; | 1.1: Yes, online randomisation<br>1.2: Yes, randomisation schedule produced by independent staistician<br>1.3: No, no significant differences between groups at baseline were reported<br><br>**Domain 2: Deviations from intended interventions: Low risk**<br>2.1: No, double blind trial<br>2.2: No, double blind trial<br><br>**Domain 3: Missing outcome data: Low risk**<br>3.1: Yes, data available for all randomised participants<br><br>**Domain 4: Measurement of the outcome: Low risk**<br>4.1: No, methods of measuring outcomes were appropriate<br>4.2: No, measurement of outcomes is unlikely to have differed between groups<br>4.3: No, double blind trial |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | (3%); fenfluramine 0.2 mg/kg/day n=2 (5%); placebo n=4 (10%); total n=7 (6%)<br>Other or not reported - fenfluramine 0.7 mg/kg/day n=5 (12%); fenfluramine 0.2 mg/kg/day n=4 (10%); placebo n=5 (12%); total n=14 (12%)<br>Bodyweight (kg), mean (SD): fenfluramine 0.7 mg/kg/day 31.8 (13.5); fenfluramine 0.2 mg/kg/day 35.1 (19.6); placebo 31.7 (16.2); total 32.9 (16.5).<br>BMI (kg/m²), mean (SD): fenfluramine 0.7 mg/kg/day 18.5 (3.5); fenfluramine 0.2 mg/kg/day 19.3 (5.7); placebo 18.0 (3.8); total 18.6 (4.4).<br><br>**Inclusion criteria**<br>• 2–18 years of age<br>• Medical history supporting a clinical diagnosis of Dravet syndrome<br>• Incomplete control of seizures with current treatment<br>• At least 4 convulsive seizures in a 4-week | dose. The other groups underwent dummy titrations.<br><br>After the titration period, patients were maintained on their final dose for an additional 12 weeks (maintenance period). At the conclusion of the 14-week treatment period (titration plus maintenance), eligible patients choosing to continue in an optional open-label extension study underwent a blinded 2-week transition period, and patients exiting the study underwent a 2-week taper of medication and a safety follow-up, 3–6 months after the last dose of active study medication, depending on the duration of exposure.<br><br>All patients reached the target dose, but 6 patients did not tolerate the 0.7 mg/kg per day dose as add-on therapy and either | ment group assignment.<br>Nine patients withdrew before completion of the trial - placebo n=3 (lack of efficacy n=1, patient or guardian decision n=2); fenfluramine 0.7 mg/kg/day n=6 (adverse events n=5, patient or guardian decision n=1).<br><br>Follow-up: 14 weeks (no measure of variability was reported) | placebo n=4/40.<br>Included hospital admission for status epilepticus.<br><br>*Important outcomes*<br><u>Neurodevelopment outcomes</u><br><br><u>Behavioral Rating Inventory of Executive Function - Behavioral Regulatory Index, change from baseline, mean (SD) 95% CI:</u><br>fenfluramine 0.7 mg/kg/day –4.4 (10.5) –8.34 to –0.52;<br>fenfluramine 0.2 mg/kg/day –3.4 (8.6) –6.82 to 0.01; placebo 3.0 (8.7) –0.54 to 6.62.<br>Because some countries do not have normative populations for BRIEF, only raw scores are presented here. Lower values indicate better function.<br><br><u>Neurodevelopment outcomes</u><br><u>Metacognition Index - Change from baseline, mean (SD) 95% CI:</u><br>fenfluramine 0.7 mg/kg/day –6.6 (20.7) –14.32 to 1.12; fenfluramine 0.2 mg/kg/day –1.0 (16.4) –7.51 to 5.44; placebo 5.9 (19.1) –2.02 to 13.78. | **Domain 5: Selection of the reported result: Low risk**<br>5.1: Yes, the data were analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data<br>5.2: No, there is evidence (statistical analysis plan available online) that all eligible reported results correspond to all intended outcome measurements<br>5.3: No, there is evidence (statistical analysis plan available online) that all eligible reported results correspond to all intended analyses<br><br>**Domain 6: Overall judgment of bias: Low risk**<br>The study is judged to be at low risk of bias for all domains for this result. |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | period during the 12 weeks before entering screening (baseline) period of trial and at least 6 convulsive<br>• seizures during the baseline period with at least two in the first 3 weeks and at least two in the last 3 weeks.<br>• All medications or interventions for epilepsy must have been stable for at least 4 weeks before screening and were expected to remain stable throughout trial participation.<br><br>NB. Convulsive seizures defined as hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs.<br>Genetic testing was done for all patients where possible, however a positive SCN1A mutation was not required for enrolment.<br><br>**Exclusion criteria**<br>• History of: - | reduced the dose (three patients) or discontinued the trial (n=3).<br>Overall mean compliance to study medication was more than 90% in each treatment group, as reported by caretakers in the daily diary and verified against returned medication. | | <u>Neurodevelopment outcomes</u><br><u>Global Executive Composite - Change from baseline, mean (SD) 95% CI:</u><br>fenfluramine 0.7 mg/kg/day –11.0 (29.1) –21.91 to –0.15;<br>fenfluramine 0.2 mg/kg/day –4.4 (22.3) –13.27 to 4.38;<br>placebo 8.9 (24.9) –1.35 to 19.19.<br><br><u>Social functioning changes - Clinical Global Impression of Improvement - parent or caregiver rating - very much improved or much improved:</u><br>fenfluramine 0.7 mg/kg/day n=22/40;<br>fenfluramine 0.2 mg/kg/day n=16/39;<br>placebo n=4/40.<br><br><u>Social functioning changes - Clinical Global Impression of Improvement - investigator rating - very much improved or much improved:</u><br>fenfluramine 0.7 mg/kg/day n=25/40;<br>fenfluramine 0.2 mg/kg/day n=16/39;<br>placebo n=4/40. | |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | • pulmonary hypertension; cardiovascular or cerebrovascular disease (including aortic or mitral valve regurgitation) as established by echocardiographic examination, myocardial infarction, or stroke.<br>• Current treatment with centrally acting anorectic agents, monoamine oxidase inhibitors, or any centrally acting agent with serotonin agonist or antagonist properties.<br>• Treatment with stiripentol within 21 days before screening.<br>• Positive urine test for tetrahydrocannabinol and a positive whole blood test for cannabidiol at screening. | | | Health-related quality of life - Quality of Life in Childhood Epilepsy - Overall Quality of Life (higher values indicate better quality of life), change from baseline, mean (SD):<br>fenfluramine 0.7 mg/kg/day 5.8 (11.7);<br>fenfluramine 0.2 mg/kg/day 0.8 (11.8);<br>placebo 1.5 (8.7).<br><br>Health-related quality of life - Pediatric Quality of Life Inventory Total Score (higher values indicate better quality of life), change from baseline, mean (SD):<br>fenfluramine 0.7 mg/kg/day 5.9 (15.1);<br>fenfluramine 0.2 mg/kg/day 6.8 (11.2);<br>placebo –1.6 (10.4). | |
| **Full citation**<br>Nabbout, R., Mistry, A., Zuberi, S., Villeneuve, N., Gil-Nagel, A., Sanchez-Carpintero, R., Stephani, U., Laux, L., Wirrell, E., Knupp, K., et al., Fenfluramine for | **Sample size**<br>N=87 randomised. Fenfluramine n=43; placebo n=44.<br><br>**Characteristics**<br>Patients with Dravet Syndrome seizures | **Interventions**<br>Fenfluramine versus placebo.<br><br>Twice-daily fenfluramine (administered as a fenfluramine | **Details**<br>28 sites.<br>Patients randomised after a 6-week period to establish baseline seizure frequency (1:1 randomisation ratio, stratified across ages | **Results**<br><br>*Critical outcomes*<br><br>≥50% reduction in mean convulsive seizure frequency: | **Limitations**<br><br>Methodological limitations assessed using the Cochrane Risk of Bias Tool for Randomised Trials (Version 2.0) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: a Randomized Clinical Trial, JAMA Neurology, 2019<br><br>**Ref Id** 1213874.<br><br>**Country/ies where the study was carried out**<br>Canada, France, Germany, Netherlands, Spain, United Kingdom, United States.<br><br>**Study type** Phase 3, double-blind randomised controlled trial.<br><br>**Aim of the study** To "… To determine whether fenfluramine reduced monthly convulsive seizure frequency relative to placebo in patients with Dravet syndrome who were taking stiripentol-inclusive regimens." p 300<br><br>**Study dates**<br>Not reported<br><br>**Source of funding**<br>Zogenix | that were poorly controlled with current treatment, which had to include stiripentol plus clobazam or valproic acid.<br><br>Age, years, mean (SD) [range]: Fenfluramine 8.8 (4.6) [2-18]; placebo 9.4 (5.1) [2-19]; total 9.1 (4.8) [2-19], p = .57.<br>Male, n: Fenfluramine n=23/43; placebo n=27/44; total n=50/87, p = .52<br>Race, n: p = .66<br>White - Fenfluramine n=23; placebo n=29; total n=52<br>Black/African American - Fenfluramine n=1; placebo n=2; total n=3.<br>Asian - Fenfluramine n=2; placebo n=1; total n=3.<br>Other - Fenfluramine n=3; placebo n=1; total n=4.<br>Not reported or missing - Fenfluramine n=13; placebo n=11; total n=24.<br>Unknown - Fenfluramine n=1; placebo | hydrochloride oral solution containing 2.2 mg/mL of fenfluramine) added to a stiripentol-inclusive ASM regimen (plus valproate or clobazam, at a minimum).<br>Starting dosage was 0.2mg/kg/din 2 equal doses, with a gradual blinded titration to 0.4 mg/kg/d (maximum, 17 mg/d) over 3 weeks.<br>Patients maintained their use of fenfluramine or placebo for an additional 12 weeks at a stable dosage, then either continued treatment in an open-label extension study or discontinued treatment with a blinded, downward dose–tapering protocol.<br>Caregivers recorded doses, any rescue medication in handheld electronic diaries. | <6 years versus ≥6 years, web-based system).<br>Safety analyses performed on all randomised patients who received 1 or more doses of fenfluramine or placebo. The primary endpoint analysis and the key secondary analyses performed on the modified intent-to-treat population included all randomised patients who received 1 or more doses of fenfluramine or placebo with 1week or more of seizure diary data.<br>Frequency of treatment-emergent adverse events and serious adverse events were presented by treatment group using the Preferred Term from the Medical Dictionary for Regulatory Activities.<br>Caregivers recorded doses, any rescue medication, and the number and type of seizures in handheld electronic diaries.<br>Of those randomised, 3 in the placebo group and 7 in the fenflu- | Fenfluramine 23/43; placebo 2/44.<br><br><u>Seizure freedom:</u><br>fenfluramine 1/43; placebo 0/44.<br><br><u>Patients with ≥1 treatment-emergent adverse event:</u><br>Fenfluramine 42/43; placebo 42/44.<br><br><u>Patients with ≥1 serious treatment-emergent adverse event:</u><br>Fenfluramine 6/43; placebo 7/44.<br><br><u>Clinical global impression of improvement - very much improved or much improved - parent/caregiver rating (at end of treatment + maintenance period):</u><br>Fenfluramine 14/43; placebo 9/44.<br><br><u>Clinical global impression of improvement - very much improved or much improved - investigator rating (at end of treatment + maintenance period):</u><br>Fenfluramine 19/43; placebo 7/44.<br><br><u>Clinical global impression</u> | **Domain 1: Randomisation: Low risk**<br>1.1: Yes, online randomisation<br>1.2: Probably yes<br>1.3: No, no significant differences between groups at baseline were reported<br><br>**Domain 2: Deviations from intended interventions: Low risk**<br>2.1: No, double blind tria<br>2.2: No, double blind trial<br><br>**Domain 3: Missing outcome data: Low risk**<br>3.1: Yes, data available for all randomised participants<br><br>**Domain 4: Measurement of the outcome: Low risk**<br>4.1: No, methods of measuring outcomes were appropriate<br>4.2: No, measurement of outcomes is unlikely to have differed between groups<br>4.3: No, double blind trial |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | n=0; total n=1.<br>BMI, mean (SD): Fenfluramine 17.3 (2.7); placebo 19.1 (4.9); total 18.2 (4.0), p = .11.<br><br>**Inclusion criteria**<br>• Aged 2 to 18 years (inclusive)<br>• Receiving a stable, stiripentol-inclusive treatment regimen<br>• Free of cardiovascular disease on an echocardiogram, electrocardiogram, or physical examination.<br><br>Diagnosis of Dravet Syndrome validated by a central committee, the Epilepsy Study Consortium.<br><br>**Exclusion criteria**<br>• Pulmonary arterial hypertension or a current condition<br>• History of cardiovascular or cerebrovascular disease (for example, cardiac valvulopathy, myocardial infarction, stroke) and con- | | ramine group withdrew early.<br><br>Follow-up: 15 weeks (no measure of variability was reported) | <u>of improvement – any improvement – parent/caregiver rating (at end of treatment + maintenance period)</u>:<br>Fenfluramine 26/43; placebo 16/44.<br><br><u>Clinical global impression of improvement – any improvement - investigator rating (at end of treatment + maintenance period):</u><br>Fenfluramine 31/43; placebo 14/44. | **Domain 5: Selection of the reported result: Low risk**<br>5.1: Yes, the data were analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data<br>5.2: No, there is evidence (statistical analysis plan available online) that all eligible reported results correspond to all intended outcome measurements<br>5.3: No, there is evidence (statistical analysis plan available online) that all eligible reported results correspond to all intended analyses<br><br>**Domain 6: Overall judgment of bias: Low risk**<br>The study is judged to be at low risk of bias for all domains for this result<br><br>**Other information**<br>The authors report in the narrative that |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | comitant treatment with modulators of serotonergic activity, antiseizure medications with sodium channel antagonist activity, or cannabinoid products. | | | | there were no significant differences between groups on the Quality of Life in Childhood Epilepsy Scale, the Pediatric Quality of Life Inventory, and the Behavior Rating Inventory of Executive Function; however no data are included. |

*BMI: body mass index; EEG: Electroencephalogram; STP: Stiripentol*

# Appendix E – Forest plots

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

No meta-analysis was conducted, the quality assessment for these outcomes is provided in the GRADE profiles in appendix F.

# Appendix F – GRADE tables

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

**Table 7: Clinical evidence profile. Comparison 1: add-on stiripentol versus placebo**

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Add-on stiripentol | Add-on placebo | Relative (95% CI) | Absolute | Quality | Importance |
| **Reduction in clonic or tonic-clonic seizure frequency >50% (during the second month of the double-blind period, which lasted 2 months)** | | | | | | | | | | | | |
| 1 (Chiron 2000) | RCT | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15/21 (71.4%) | 1/20 (5%) | RR 14.29 (2.07 to 98.36) | 664 more per 1000 (from 53 more to 1000 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Mean change from baseline in seizure frequency (Better indicated by lower values) (follow-up 2 months)** | | | | | | | | | | | | |
| 1 (Chiron 2000) | RCT | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 21 | 20 | - | MD 76 lower (100.18 to 51.82 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Clonic or tonic-clonic seizure freedom (follow-up 2 months)** | | | | | | | | | | | | |
| 1 (Chiron 2000) | RCT | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 9/21 (42.9%) | 0/20 (0%) | POR 11.48 (2.66 to 49.49) | 430 more per 1000 (from 210 more to 650 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Number of patients who withdrew from treatment because of adverse events (follow-up 2 months)** | | | | | | | | | | | | |
| 1 (Chiron 2000) | RCT | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 0/21 (0%) | 1/20 (5%) | RR 0.32 (0.01 to 7.38) | 34 fewer per 1000 (from 49 fewer to 319 more) | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Add-on stiripentol | Add-on placebo | Relative (95% CI) | Absolute | Quality | Importance |
| **Adverse events: % of patients with reported side effects (trial defined serious) (follow-up 2 months)** | | | | | | | | | | | | |
| 1 (Chiron 2000) | RCT | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 5/21 (23.8%) | 1/20 (5%) | RR 4.76 (0.61 to 37.28) | 188 more per 1000 (from 20 fewer to 1000 more) | ⊕OOO VERY LOW | CRITICAL |

*1 Serious risk of bias in the evidence contributing to the outcomes as per RoB2*
*2 95% CI crosses 2 MIDs (0.8 and 1.25)*

**Table 8: Clinical evidence profile. Comparison 2: fenfluramine 0.2 mg/kg/day versus placebo**

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.2 mg/kg/day | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| **Reduction in seizure frequency >50%** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 15/39 (38.5%) | 5/40 (12.5%) | RR 3.08 (1.24 to 7.65) | 260 more per 1000 (from 30 more to 831 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **100% reduction in convulsive seizure frequency (seizure freedom)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/39 (7.7%) | 0/40 (0%) | RD 0.08 (-0.02 to | 80 more per 1000 | ⊕⊕⊕O MODERATE | CRITICAL |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.2 mg/kg/day | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| | | risk of bias | | | | | | | 0.17) | (from 20 fewer to 17 more) | | |
| **Patients with at least 1 adverse event** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 37/39 (94.9%) | 26/40 (65%) | RR 1.46 (1.15 to 1.85) | 299 more per 1000 (from 97 more to 553 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 0/39 (0%) | 0/40 (0%) | RD 0 (-0.05 to 0.05) | 0 fewer per 1000 (from 50 fewer to 50 more) | ⊕⊕OO LOW | CRITICAL |
| **Serious adverse events** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 4/39 (10.3%) | 4/40 (10%) | RR 1.03 (0.28 to 3.82) | 3 more per 1000 (from 72 fewer to 282 more) | ⊕⊕OO LOW | CRITICAL |
| **Behavioral Rating Inventory of Executive Function - Behavioral Regulatory Index, change from baseline (better indicated by lower values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 39 | 40 | - | MD 6.4 lower (10.21 to 2.59 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Metacognition Index - change from baseline (better indicated by lower values)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.2 mg/kg/day | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 39 | 40 | - | MD 6.9 lower (14.74 lower to 0.94 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Global Executive Composite - change from baseline (better indicated by lower values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 39 | 40 | - | MD 13.3 lower (23.72 to 2.88 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Clinical Global Impression of Improvement - parent or caregiver rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 16/39 (41%) | 4/40 (10%) | RR 4.1 (1.5 to 11.18) | 310 more per 1000 (from 50 more to 1000 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Clinical Global Impression of Improvement - investigator rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 16/39 (41%) | 4/40 (10%) | RR 4.1 (1.5 to 11.18) | 310 more per 1000 (from 50 more to 1000 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Quality of Life in Childhood Epilepsy - Overall Quality of Life, change from baseline (better indicated by higher values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of | no serious inconsistency | no serious indirectness | serious[4] | none | 39 | 40 | - | MD 0.7 lower (5.28 | ⊕⊕⊕O MODERATE | IMPORTANT |

| Quality assessment | | | | | | | Number of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.2 mg/kg/day | Placebo | Relative (95% CI) | Absolute | | |
| | | bias | | | | | | | | lower to 3.88 higher) | | |
| **Pediatric Quality of Life Inventory Total Score, change from baseline (better indicated by higher values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 39 | 40 | - | MD 8.4 higher (3.63 to 13.17 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |

*1 95% CI crosses 1 MID (1.25)*
*2 Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)*
*3 95% CI crosses 2 MIDs (0.8 and 1.25)*
*4 95% CI crosses 1 MID (+/-0.5x control group SD, for Behavioral Rating Inventory of Executive Function - Behavioral Regulatory Index = +/- 9.05; for metacognition index = +/- 12.55; for global executive composite = +/- 20.1; for Quality of Life in Childhood Epilepsy = +/- 5.2; for Pediatric Quality of Life Total Inventory Score = +/- 8.55)*

**Table 9: Clinical evidence profile. Comparison 3: fenfluramine 0.7 mg/kg/day versus placebo**

| Quality assessment | | | | | | | Number of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.7 mg | Placebo | Relative (95% CI) | Absolute | | |
| **Reduction in seizure frequency >50% (convulsive)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious | no serious inconsistency | no serious indirectness | no serious imprecision | none | 27/40 (67.5%) | 5/40 (12.5%) | RR 5.4 (2.31 to 12.6) | 550 more per 1000 (from 164 | ⊕⊕⊕⊕ HIGH | CRITICAL |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.7 mg | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| | | risk of bias | | | | | | | | more to 1000 more) | | |
| **100% reduction in convulsive seizure frequency (seizure freedom)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 3/40 (7.5%) | 0/40 (0%) | RD 0.07 (-0.02 to 0.17) | 70 more per 1000 (from 20 fewer to 170 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Patients with at least 1 adverse event** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 38/40 (95%) | 26/40 (65%) | RR 1.46 (1.15 to 1.85) | 299 more per 1000 (from 97 more to 553 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 0/40 (0%) | 0/40 (0%) | RD 0 (-0.05 to 0.05) | 0 fewer per 1000 (from 50 fewer to 50 more) | ⊕⊕OO LOW | CRITICAL |
| **Serious adverse events** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 5/40 (12.5%) | 4/40 (10%) | RR 1.25 (0.36 to 4.32) | 25 more per 1000 (from 64 fewer to 332 more) | ⊕⊕⊕O MODERATE | CRITICAL |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.7 mg | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| **Behavioral Rating Inventory of Executive Function - Behavioral Regulatory Index, change from baseline (better indicated by lower values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 40 | 40 | - | MD 7.4 lower (11.63 to 3.17 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Metacognition Index - change from baseline (better indicated by lower values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 40 | 40 | - | MD 12.5 lower (21.23 to 3.77 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Global Executive Composite - change from baseline (better indicated by lower values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 40 | 40 | - | MD 19.9 lower (31.77 to 8.03 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Clinical Global Impression of Improvement - parent or caregiver rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 22/40 (55%) | 4/40 (10%) | RR 5.5 (2.08 to 14.52) | 450 more per 1000 (from 108 more to 1000 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Clinical Global Impression of Improvement - investigator rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 25/40 (62.5%) | 4/40 (10%) | RR 6.25 (2.39 to 16.33) | 525 more per 1000 (from 139 more to | ⊕⊕⊕⊕ HIGH | IMPORTANT |

| Quality assessment | | | | | | | Number of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.7 mg | Placebo | Relative (95% CI) | Absolute | | |
| | | | | | | | | | | 1000 more) | | |
| **Quality of Life in Childhood Epilepsy - Overall Quality of Life, change from baseline (better indicated by higher values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 40 | 40 | - | MD 4.3 higher (0.22 lower to 8.82 higher) | ⊕⊕⊕O MODERATE | IM-PORTANT |
| **Pediatric Quality of Life Inventory Total Score, change from baseline, (better indicated by higher values)** | | | | | | | | | | | | |
| 1 (Lagae 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 40 | 40 | - | MD 7.5 higher (1.82 to 13.18 higher) | ⊕⊕⊕O MODERATE | IM-PORTANT |

*1Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)*
*2 95% CI crosses 1 MID (1.25)*
*3 95% CI crosses 2 MIDs (0.8 and 1.25)*
*4 95% CI crosses 1 MID (+/-0.5x control group SD, for Behavioral Rating Inventory of Executive Function - Behavioral Regulatory Index = +/- 9.05; for metacognition index = +/- 12.55; for Global Executive Composite = +/- 20.1; for Quality of Life in Childhood Epilepsy - Overall Quality of Life = +/- 5.2; for Pediatric Quality of Life Inventory Total Score = +/- 8.55)*

**Table 10: Clinical evidence profile. Comparison 5: fenfluramine 0.4 mg/kg/day versus placebo**

| Quality assessment | Number of patients | Effect | Quality | Importance |
|---|---|---|---|---|

| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.4 mg | Placebo | Relative (95% CI) | Absolute | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reduction in seizure frequency ≥50%** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 23/43 (53.5%) | 2/44 (4.5%) | RR 11.77 (2.95 to 46.89) | 490 more per 1000 (from 89 more to 1000 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Seizure freedom** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 1/43 (2.3%) | 0/44 (0%) | RD 0.02 (-0.04 to 0.09) | 20 more per 1000 (from 40 fewer to 90 more) | ⊕⊕OO LOW | CRITICAL |
| **% of patients with reported side effects - Patients with ≥1 treatment-emergent adverse event** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 42/43 (97.7%) | 42/44 (95.5%) | RR 1.02 (0.95 to 1.11) | 19 more per 1000 (from 48 fewer to 105 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **% of patients with reported side effects - Patients with ≥1 serious treatment-emergent adverse event** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 6/43 (14%) | 7/44 (15.9%) | RR 0.88 (0.32 to 2.4) | 19 fewer per 1000 (from 108 fewer to 223 more) | ⊕⊕OO LOW | CRITICAL |
| **Clinical Global Impression of Improvement – parent/caregiver rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 14/43 (32.6%) | 9/44 (20.5%) | RR 1.59 (0.77 to 3.28) | 121 more per 1000 (from 47 fewer to 466 more) | ⊕⊕OO LOW | IMPORTANT |

| Quality assessment | | | | | | | Number of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Fenfluramine 0.4 mg | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| **Clinical Global Impression of Improvement - investigator rating - very much improved or much improved from baseline** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 19/43 (44.2%) | 7/44 (15.9%) | RR 2.78 (1.3 to 5.93) | 283 more per 1000 (from 48 more to 784 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Clinical Global Impression of Improvement – parent/caregiver rating – any improvement from baseline** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 26/43 (60.5%) | 16/44 (36.4%) | RR 1.66 (1.05 to 2.63) | 240 more per 1000 (from 18 more to 593 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Clinical Global Impression of Improvement - investigator rating – any improvement from baseline** | | | | | | | | | | | | |
| 1 (Nabbout 2019) | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 31/43 (72.1%) | 14/44 (31.8%) | RR 2.27 (1.41 to 3.63) | 404 more per 1000 (from 130 more to 837 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

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

# Appendix G – Economic evidence study selection

## Economic evidence study selection for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

# Appendix H – Economic evidence tables

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

**Table 11: Economic evidence tables for stiripentol as an adjunctive treatment to clobazam and valproate in the treatment of patients with Dravet syndrome.**

| Study details | Treatment strategies | Study population, design and data sources | Results | Comments |
|---|---|---|---|---|
| **Author & year:**<br>• Elliott 2018<br><br>**Country:**<br>• Canada<br><br>**Type of economic analysis:**<br>• Cost Utility Analysis<br><br>**Source of funding:**<br>• None | **Interventions in detail:**<br>• Adjunctive stiripentol<br><br>Stiripentol as an adjunctive to clobazam and valproate<br><br>• Clobazam plus valproate<br><br>Stiripentol as an adjunctive therapy was compared with clobazam and valproate alone<br><br>*Notes:*<br>Patients were assumed to be taking the maximum recommended dose of each agent as recommended by the Canadian guidelines:<br>stiripentol 50 mg/kg/day<br>clobazam 1 mg/kg/day up to a maximum of 40 | **Population characteristics:**<br>• All patients enter the model with diagnosed Dravet syndrome, who had not previously responded to concomitant treatment with clobazam and valproate. In the base case, the typical patient was based on the 'STICLO' France study (Chiron 2000), an RCT including children with Dravet syndrome.<br><br>**Modelling approach:**<br>• Markov model<br><br>**Source of base-line and effectiveness data:**<br>• Estimates of base-line clinical data were obtained from a review of published literature, including a previous NICE guideline on management of epilepsy (CG137), and the STICLO France RCT (Chiron 2000).<br><br>**Source of cost data:**<br>Cost data were obtained from different | **QALYs**<br>• 4.37 QALYs for adjunctive stiripentol group<br>• 3.77 QALYs for clobazam plus valproate group<br><br>**Incremental costs with adjunctive stiripentol:**<br>• $Can 99,062<br><br>**Incremental QALYs with adjunctive stiripentol:**<br>• 0.60 QALYs<br><br>**ICER:**<br>• $Can 151,310<br><br>**Deterministic sensitivity analysis:**<br>The results were sensitive to:<br>• Price of stiripentol (with reduced prices leading to lower ICERs)<br>• Patient age (with lower ages leading to lower ICERs)<br>ICERs not report but as noted by the au- | **Perspective:**<br>• Health care System<br><br>**Currency:**<br>• Canadian dollars ($Can)<br><br>**Cost year:**<br>• 2017<br><br>**Time horizon:**<br>• 10 years<br><br>**Discounting:**<br>• 1.5% per year<br><br>**Applicability:**<br>• This study was deemed as partly applicable, as the study failed to meet 1 applicability criterion, named the evaluation context, |

| Study details | Treatment strategies | Study population, design and data sources | Results | Comments |
|---|---|---|---|---|
| | mg/day<br>valproate 60 mg/kg/day | sources:<br>• Costs associated with stiripentol, clobazam, lorazepam and valproate treatment were taken from provincial formularies (this is, Ontario Drug Benefit Formulary)<br>• Resource use (for example, emergency department visits, general practitioner visits, and neurologist visits) by seizure status among patients with Dravet syndrome was assumed to be consistent with that described in a previous NICE guideline on management of paediatric epilepsy (CG137)<br>• The unit costs of each resource were obtained from the Ontario Schedule of Benefits<br><br>Costs were all inflated to 2017 Canadian dollars<br><br>**Source of QoL data:**<br>• Utilities estimates (based on EQ-5D data) for baseline QoL associated with medical treatment by seizure status among patients with Dravet syndrome were derived from another severe form of pediatric epilepsy (this is, Lennox–Gastaut syndrome), by using data from Verdian 2008* | thors, while the patient age varied the results to an extent that their final interpretation of would not change; results were very sensitive to the cost of stiripentol (this is, Stiripentol would be considered cost effective at a willingness-to-pay threshold of $Can50,000 if its price was reduced by 61.4%)<br><br>**Probabilistic sensitivity analysis:**<br>Stiripentol as an adjunctive treatment to clobazam and valproate in the treatment of patients with Dravet syndrome was found to have:<br>• 5.2% probability of being cost-effective at a threshold of $Can 50,000 per QALY<br>• 20.7% probability of being cost-effective at a threshold of $Can 100,000 per QALY | and this was likely to change the conclusions about cost effectiveness<br><br>**Limitations:**<br>• The study meets most quality criteria. The only potential limitation was associated the estimates of the effect of interventions under evaluations.<br><br>*<br>Verdian L, Oyee J, Heyes A, Tolley K, Yi Y. Eliciting preferences for health states associated with Lennox-Gastaut syndrome (LGS) [abstract no. 1.352]. 62nd meeting of the American Epilepsy society; 5–9 Dec 2008; Seattle. |

*CG: clinical guideline; CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; NICE: National Institute for Health and Care Excellence; QALY: quality adjusted life year; QoL: quality of life; $Can: Canadian dollars*

# Appendix I – Economic evidence profiles

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

**Table 12: Economic evidence profiles for stiripentol as an adjunctive treatment to clobazam and valproate in the treatment of patients with Dravet syndrome.**

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| **Author & year:**<br>Elliott 2018<br><br>**Country:**<br>Canada<br><br>**Interventions:**<br>Stiripentol as an adjunctive to clobazam and valproate<br>*versus*<br>clobazam and valproate alone | Minor limitations[1] | Partly applicable[2] | **Type of economic analysis:**<br>CUA<br><br>**Time horizon:**<br>10 years<br><br>**Primary measure of outcome:**<br>QALY | $Can 99,062 | 0.60 QALYs | $Can 151,310 | **Deterministic sensitivity analyses:**<br>The results were sensitive to:<br>• Price of stiripentol (with reduced prices leading to lower ICERs)[3]<br>• Patient age (with lower ages leading to lower ICERs)[3]<br><br>**PSA:**<br>Adjunctive stiripentol was found to have<br>• 5.2% probability of being cost-effective at a threshold of $Can 50,000 per QALY<br>• 20.7% probability of being cost-effective at a threshold of $Can 100,000 per QALY |

*CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.*
*1 The study meets most quality criteria. The only potential limitation was associated the estimates of the effect of interventions under evaluations. These were not derived from a systematic review, but were considered similar in magnitude to the best available estimates*
*2 Being a non-UK study considering the Canadian healthcare system perspective, the study was considered to be partly applicable. This is because it does directly address the review question posed in the guideline, but the non-UK evaluation context was likely to change the conclusions about cost effectiveness results. Qualty of life values were also derived from a different form of severe pediatric epilepsy (Lennox-Gastaut).*
*3 As noted by the authors, while the patient age varied the results of the economic model to an extent that their final interpretation of would not change; results were very sensitive to the cost of stiripentol (this is, Stiripentol would be considered cost effective at a willingness-to-pay threshold of $Can50,000 if its price was reduced by 61.4%)*

# Appendix J – Economic analysis

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

No economic analysis was conducted for this review question.

# Appendix K – Excluded studies

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

### Clinical studies

**Table 13: Excluded studies and reasons for their exclusion**

| Study | Reason for Exclusion |
|---|---|
| ZX008 (fenfluramine HCL oral solution) significantly reduces frequency of generalized tonic-clonic seizures in Dravet syndrome: pooled analysis from two phase 3 clinical trials, Annals of Neurology, 86, S59â□□S60, 2019 | Conference Abstract |
| ZX008 (low dose fenfluramine hydrochloride oral solution) significantly reduces frequency of generalized tonic-clonic seizures in Dravet syndrome: pooled analysis from two phase 3 clinical trials, Developmental Medicine and Child Neurology, 62, 21â□□, 2020 | Conference Abstract |
| Efficacy and safety of low dose fenfluramine hydrochloride oral solution in the treatment of Dravet syndrome: pooled analysis of two Phase 3 clinical studies, Developmental Medicine and Child Neurology, 62, 14, 2020 | Conference Abstract |
| Brigo, F., Igwe, S. C., Bragazzi, N. L., Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy, Cochrane Database of Systematic Reviews, 2017 | Systematic review; one of the studies included had already been included in this systematic review (Chiron 2000) and the second one (Guerrini 2002) is a study abstract |
| Buck, M. L., Goodkin, H. P., Stiripentol: A Novel Antiseizure Medication for the Management of Dravet Syndrome, Annals of Pharmacotherapy., 2019 | Narrative review - included studies checked. |
| Chiron, C., Marchand, M. C., d'Athis, P., Rey, E., Vincent, J., Dulac, O., Pons, G., Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled trial, Epilepsia, 40, 180, 1999 | Study abstract |
| Christe, W., Krämer, G., Vigonius, U., Pohlmann, H., Steinhoff, B. J., Brodie, M. J., Moore, A., A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy, Epilepsy Research, 26, 451â□□460, 1997 | Patients with Dravet syndrome were not included |
| Cross, H., Zuberi, S., Anand, I., Sunny, P., Hughes, E., Desurkar, A., Riney, K., Deepak, G., Scheffer, I. E., Lagae, L., Mistry, A., Galer, B., Morrison, G., Gammaitoni, A., Farfel, G., Pagano, K., | Conference Abstract |

| Study | Reason for Exclusion |
|---|---|
| Effect of ZX008 (Fenfluramine HCl Oral Solution) on Total Seizures in Dravet Syndrome, Epilepsy and Behavior, Part B. Conference: 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. Francis Crick Institute, 2019 | |
| Dozieres-Puyravel, B., Auvin, S., Fenfluramine hydrochloride for the treatment of Dravet syndrome, Expert Opinion on Orphan Drugs, 8, 121-126, 2020 | Systematic review. Included studies checked. |
| Euctr, D. E., A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2), http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-000474-38-DE, 2016 | Study registry, no results reported |
| Euctr, I. T., A MULTICENTRE RANDOMIZED CONTROLLED TRIAL COMPARING TOPIRAMATE, STIRIPENTOL AND CLOBAZAM AS ADJUNCTIVE THERAPY TO VALPROATE AND CLOBAZAM IN PAEDIATRIC PATIENTS WITH DRAVET'S SYNDROME (SMEI) NOT ADEQUATELY CONTROLLED WITH CLOBAZAM AND VALPROATE, AND AUXILIARY PHARMACOGENETIC STUDY - ND, Http://www.who.int/trialsearch/trial2.aspx ? Trialid=euctr2007-003702-95-it, 2007 | Study registry, no results reported |
| Euctr, I. T., A MULTICENTRE RANDOMIZED CONTROLLED TRIAL COMPARING TOPIRAMATE, STIRIPENTOL AND CLOBAZAM AT THE MAXIMAL TOLERATED DOSAGE, AS ADJUNCTIVE THERAPY TO VALPROATE AND CLOBAZAM IN PAEDIATRIC PATIENTS WITH DRAVET`S SYNDROME (SMEI), AND AUXILIARY PHARMACOGENETIC STUDY, Http://www.who.int/trialsearch/trial2.aspx ? Trialid=euctr2007-002198-30-it, 2012 | Study registry, no results reported |
| Euctr, S. E., Study to evaluate the safety and effectiveness of Fenfluramine as adjunct therapy in children and young adults with Dravet Syndrome, http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015-004167-37-SE, | Study registry, no results reported |

| Study | Reason for Exclusion |
|---|---|
| 2016 | |
| Frampton, J. E., Stiripentol: A Review in Dravet Syndrome, Drugs, 79, 1785-1796, 2019 | Systematic review. Included studies checked. |
| Guerrini, R., Tonnelier, S., d'Athis, P., Rey, E., Vincent, J., Pons, G., Dalla Bernardina, B., Ferrari, A. R., Veggiotti, P., Veneselli, E., et al.,, Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial, Epilepsia, 43 Suppl 8, 155, 2002 | Study abstract |
| Hagopian, S. J., Marsh, E. D., Cannabidiol for epilepsy: A new indication for an old drug, Future Neurology, 13, 181-190, 2018 | Narrative review, references checked for inclusion |
| Lambrechts, D. A., de Kinderen, R. J., Vles, J. S., de Louw, A. J., Aldenkamp, A. P., Majoie, H. J., A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta Neurologica Scandinavica, 135, 231â□□239, 2017 | Not all patients presented with Dravet syndrome |
| Nabbout, R., Mistry, A., Zuberi, S., Villeneuve, N., Gil-Nagel, A., Sanchez-Carpintero, R., Stephani, U., Laux, L., Wirrell, E., Knupp, K., Chiron, C., Farfel, G., Galer, B. S., Morrison, G., Lock, M., Agarwal, A., Auvin, S., Fenfluramine for Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial, JAMA Neurology, 77, 300-308, 2020 | Duplicate of Nabbout 2019 which has been included in this review. |
| Nct,, GWPCARE2 A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome, Https://clinicaltrials.gov/show/nct02224703, 2014 | Trial registry, no relevant peer-reviewed publications |
| Polster, T., Lagae, L., Sullivan, J., Brandl, U., Herting, A., Jacobs, J., Kluger, G., Mayer, T., Panzer, A., Pringsheim, M., et al.,, ZX008 (Fenfluramine) in Dravet's Syndrome: first results of a phase 3 randomized, double-blind, placebo-controlled trial, Neuropediatrics, 49, 2018 | Study abstract |
| Schoonjans, A. S., Lagae, L., Ceulemans, B., Low-dose fenfluramine in the treatment of neurologic disorders: Experience in Dravet syndrome, Therapeutic Advances in Neurological Disorders, 8, 328-338, 2015 | Prospective uncontrolled study |
| Sharawat, I. K., Panda, P. K., Kasinathan, A., Panda, P., Dawman, L., Joshi, K., Efficacy and tolerability of fenfluramine in patients with Dravet syndrome: | Systematic review - both RCTs (Lagae 2019; Nabbout 2019) already included in this review. |

| Study | Reason for Exclusion |
|---|---|
| A systematic review and meta-analysis, Seizure, 85, 119-126, 2021 | |
| Specchio, N., Pietrafusa, N., Ferretti, A., Trivisano, M., Vigevano, F., Successful use of fenfluramine in nonconvulsive status epilepticus of Dravet syndrome, Epilepsia, 61, 831-833, 2020 | Case report. |
| Specchio, Nicola, Pietrafusa, Nicola, Ferretti, Alessandro, Trivisano, Marina, Vigevano, Federico, Successful use of fenfluramine in nonconvulsive status epilepticus of Dravet syndrome, Epilepsia, 61, 831-833, 2020 | Case report. |
| Strzelczyk, A., Schubert-Bast, S., Therapeutic advances in Dravet syndrome: a targeted literature review, Expert Review of Neurotherapeutics, 20, 1065-1079, 2020 | Review - included studies checked. |
| Sundqvist, A., Nilsson, B. Y., Tomson, T., Valproate monotherapy in juvenile myoclonic epilepsy: dose-related effects on electroencephalographic and other neurophysiologic tests, Therapeutic Drug Monitoring, 21, 91-6, 1999 | Conference presentation |
| Sundqvist, A., Tomson, T., Lundkvist, B., Valproate as monotherapy for juvenile myoclonic epilepsy: Dose-effect study, Therapeutic Drug Monitoring, 20, 149-157, 1998 | Conference presentation |
| Ulamek-Koziol, M., Czuczwar, S. J., Pluta, R., Januszewski, S., Ketogenic diet and epilepsy, Nutrients, 11 (10) (no pagination), 2019 | Narrative review - references checked. |
| Wang, Y. Q., Fang, Z. X., Zhang, Y. W., Xie, L. L., Jiang, L., Efficacy of the ketogenic diet in patients with Dravet syndrome: A meta-analysis, Seizure, 81, 36-42, 2020 | Meta-analysis - included studies checked |
| Zhang, L., Li, W., Wang, C., Efficacy and safety of fenfluramine in patients with Dravet syndrome: A meta-analysis, Acta Neurologica Scandinavica, 143, 339-348, 2021 | Systematic review - both RCTs (Lagae 2019; Nabbout 2019) already included in this review. |
| Zuberi, S., Knupp, K., Lagae, L., Thiele, E., Nabbout, R., Galer, B., Farfel, G., Gammaitoni, A., ZX008 (Fenfluramine) provides clinically meaningful reduction in seizure frequency irrespective of concomitant AEDs commonly used in Dravet syndrome, Developmental Medicine and Child Neurology, 63, 68, 2021 | Conference Abstract |

## Economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

# Appendix L – Research recommendations

## Research recommendations for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of seizures in Dravet syndrome?

### Research question:

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

### Why this is important

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

**Table 14: Research recommendation rationale**

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

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

*N/A: not applicable*

**Table 15: Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | People with complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) |
| **Intervention** | • Antiseizure medications<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*