National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[Q] Effectiveness of ASMs for self-limited epilepsy with centrotemporal spikes

NICE guideline number tbc

Evidence reviews underpinning recommendations 6.4.1-6.4.8 in the NICE guideline

November 2021

Draft for Consultation

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

Disclaimer

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

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

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ISBN:

Contents

Effectiveness of antiseizure medications for self-limited epilepsy with centrotemporal spikes

Review question

What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Introduction

Self-limited epilepsy with centrotemporal spikes (SeLECTS) is a common focal epilepsy in childhood in which there may be infrequent seizures. Children grow out of this epilepsy by early teenage years; therefore, one of the main considerations is whether to treat the child with antiseizure medications (ASMs). Understanding the effectiveness and the potential adverse effects is important in clinical practice, and to inform discussions and decisions with families. The aim of this review is to determine which ASMs improve outcomes in those with SeLECTS.

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 and young people with confirmed self-limited epilepsy with centrotemporal spikes
Intervention	The following ASMs and their combinations will be considered: • Carbamazepine • Clobazam • Gabapentin • Lacosamide • Levetiracetam • Oxcarbazepine • Sodium Valproate • Sulthiame • Topiramate • Lamotrigine • Zonisamide
Comparison	• Any of the above and their combinations • No treatment/placebo
Outcomes	**Critical** • Seizure freedom (12 months data and short term [minimum 3 months with 100% freedom] of starting treatment) • Reduction of seizure frequency >50% • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • Side effects, as assessed by:

	○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event [dichotomous outcome only]) **Important** • Neuropsychological changes (IQ testing, or other validated tools) • Social functioning changes (behaviour reported by parents/caregivers/school or validated tools) • EEG outcomes (ESES, CSWS or spike wave index)

ASMs: antiseizure medications; CSWS: continuous spike-wave of slow-wave sleep; ESES: electrical status epilepticus in sleep; EEG: electroencephalogram; IQ: intelligence quotient

When this review was originally conducted, the name of the epilepsy syndrome used in the searches and the review was childhood epilepsy with centrotemporal spikes (CECTS) and benign epilepsy with centrotemporal spikes (BEBCTS), however the name of this epilepsy syndrome changed during guideline development to self-limited epilepsy with centrotemporal spikes (SeLECTS), and amendments to reflect this change were done as appropriate throughout this report.

For further details see the review protocol in appendix A.

Methods and process

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

Clinical evidence

Included studies

Nine studies reporting on 8 randomised controlled trials (RCTs) were identified for inclusion in this review (Ahadi 2020, Borggraefe 2013, Coppola 2007, Kang 2007, Kwon 2013, Mitsudame 1997, Rating 2000, Suo 2021, Tacke 2018); 2 of these provided data from the same study (Borggraefe 2013, Tacke 2018).

Two studies compared levetiracetam (LEV) to sulthiame (STM) (Borggraefe 2013, Tacke 2018), 2 studies compared LEV to oxcarbazepine (OXC) (Coppola 2007, Suo 2021), 1 study compared LEV to carbamazepine (CBZ), 1 study compared topiramate (TPM) to CBZ (Kang 2007), 1 study compared clonazepam (CZP) to valproate (VAL) and CBZ (Mitsudame 1997), 1 study compared STM to placebo (Rating 2000) and 1 study compared OXC to no treatment.

The included studies are summarised from Table 2 to Table 7.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented from Table 2 to Table 7.

Table 2: Summary of included studies. Comparison 1: levetiracetam versus carbamazepine

Study	Population	Intervention	Comparison	Outcomes
Ahadi 2020 RCT Iran	N=92 children with a clinical diagnosis of benign childhood epilepsy with centro temporal spikes and an EEG showing characteristics of rolandic epilepsy Age, years, mean (SD): levetiracetam 8.7 (2.76); carbamazepine 8.36 (2.25), p=0.514.	Levetiracetam n=46 Levebel (levetiracetam) oral solution 100 mg/ml at initial dose of 25-30 mg/kg/day.	Carbamazepine n=46 Tegretol (carbamazepine) syrup 20 mg/ml at initial dose of 15-20 mg/kg/day.	• Seizure freedom • Side effects

EEG: electroencephalogram; kg: kilogram; mg: milligram; ml: millilitre; RCT: randomised controlled trial; SD: standard deviation

Table 3: Summary of included studies. Comparison 2: levetiracetam versus sulthiame

Study	Population	Intervention	Comparison	Outcomes
Borggraefe 2013 Multi-centre double blind RCT Germany	N = 44 children with benign epilepsy with centrotemporal spikes Mean age LEV: 8.7 years (SD 1.7) STM: 9.0 years (SD 1.5)	Levetiracetam (LEV) n=21 Starting dose: 10mg/kg Final dose: 30mg/kg Down dosing to 20mg/kg was permitted in case of AE	Sulthiame (STM) n=22 Starting dose:2mg/kg Final dose: 6mg/kg Down dosing to 4mg/kg was permitted in case of AEs	• Seizure freedom (study defined treatment failure as occurrence of a seizure in 24 weeks) • Serious events leading to treatment withdrawal
Tacke 2018 Multi-centre double blind	See Borggraefe 2013	See Borggraefe 2013	See Borggraefe 2013	• Absence of rolandic discharge on EEG

Study	Population	Intervention	Comparison	Outcomes
RCT Germany				

AEs: adverse events; EEG: electroencephalogram; RCT: randomised controlled trial; SD: standard deviation

Table 4: Summary of included studies. Comparison 3: levetiracetam versus oxcarbazepine

Study	Population	Intervention	Comparison	Outcomes
Coppola 2007 Open label pilot RCT Italy	N = 39 children with bening epilepsy with centrotemporal spikes Mean age LEV: 10.5 years OXC: 8.4 years	Levetiracetam (LEV) n=21 Starting dose of 5mg/kg Final dose of 20mg/kg	Oxcarbazepine (OXC) n=18 Starting dose of 5mg/kg Final dose of 20mg/kg	• Seizure freedom (number of participants free from seizures at 18 months) • Adverse events leading to withdrawal • Adverse events (total AEs recorded, excluding those leading to withdrawal)
Suo 2021 RCT China	N=70 children with bening epilepsy with centrotemporal spikes (n=64 included in final analysis) Age, years: Intervention group 8.47 ± 2.13; control group 8.62 ± 2.21, Age at onset, years: Intervention group 6.98 ± 1.82; control group 7.13 ± 1.75	Levetiracetam n=35 (n=32 included in final analysis) 250 mg tablets (Keppra). Initial dose set at 10 mg/kg/day. Dose increased once every 7 days and maintained at 20–60 mg/kg/day.	Oxcarbazepine (OXC) n=35 (n=32 included in final analysis) 150 mg tablets. Initial dose set at 8–10 mg/kg/day, orally administered twice a day at an interval of 12 hours. Dose increased to 5–10 mg/kg/day every 5–7 days and maintained at 20–46 mg/kg/day.	• Seizure freedom • Normalisation of EEG • Adverse events

AEs: adverse events; RCT: randomised controlled trial

Table 5: Summary of included studies. Comparison 4: topiramate versus carbamazepine

Study	Population	Intervention	Comparison	Outcomes
Kang 2007	N = 112 children	Topiramate (TPM)	Carbamazepine	• Seizure freedom

Study	Population	Intervention	Comparison	Outcomes
Multi-centre, open label RCT Korea	with be-ningn epi-lepsy with centrotem-poral spikes Mean age TPM: 8.7 years (SD 1.9) CBZ: 8.7 years (SD 2.0)	n=58 Starting dose: 12.5mg/day Final dose of at least 50mg/day if weighed <30kg, or at least 75mg/day if weighed >30kg	(CBZ) n=54 Starting dose: 10mg/kg/day Final dose of at least 20/kg/day	(number of partici-pant free of seizures over 28 weeks) • Adverse events (total AEs recorded, ex-cluding those which led to withdrawal) • Adverse events lead-ing to withdrawal

AEs: adverse events; RCT: randomised controlled trial

Table 6: Summary of included studies. Comparison 5, 6, and 7: clonazepam versus valproate/ carbamazepine

Study	Population	Intervention	Comparison	Outcomes
Mitsudome 1997 RCT Japan	N = 40 children with benign epilepsy with cen-trotemporal spikes Mean age CZP: 7.3 years (range 3.11- 9.11) VPA: 8.6 years (range 4.0 – 10.11) CBZ: 8.6 years (range 5.5 – 10.3)	Clonazepam (CZP) n=20 Dose: 0.35-1.0mg/day	Valproate (VPA) n=10 Dose: 250-600mg/day Carbamazepine (CBZ) n= 10 Dose: 100-200mg/day	• EEG (disappearance of RD)

AEs: adverse events; EEG: electroencephalogram; RCT: randomised controlled trial; RD: rolandic dis-charge

Table 7: Summary of included studies. Comparison 8: sulthiame versus pla-cebo

Study	Population	Intervention	Comparison	Outcomes
Rating 2000 Double blind RCT Germany	N = 66 children with with benign childhood epilepsy with cen-trotemporal spikes	Sulthiame (STM) n=31 5mg/kg/day (in 3 administrations per day)	Placebo n=35	• Seizure freedom (defined as treat-ment failure, no sei-zure in first 7 days, no AEs or withdraw-al) • EEG reading (de-fined as specific pa-thology)

Study	Population	Intervention	Comparison	Outcomes
	Mean age STM: 8 years (range 3-10) Placebo: 8 years (range 3-10)			

EEG: electroencephalogram; RCT: randomised controlled trial

Table 8: Summary of included studies. Comparison XX: Oxcarbazepine versus no treatment

Study	Population	Intervention	Comparison	Outcomes
Kwon 2013 RCT South Korea	N=39 children with newly diagnosed benign partial epilepsy Age, mean, years: intervention group 8.2 ±2.3; control group 8.5±2.3.	Oxcarbazepine n=13 Initially administered once or twice a day at a dose of 5-10 mg/kg/day and titrated to 10-20 mg/kg/day over a week.	No treatment n=16	• Seizure frequency • Reduction of seizure frequency >50% • Normalisation of sleep EEG • EEG spike index • Full-scale intelligence quotient

EEG: electroencephalogram; RCT: randomised controlled trial; 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 evidence

Across all the comparisons identified in this review, the majority showed no important difference between the interventions compared (for example, levetiracetam versus sulthiame, levetiracetam versus oxcarbazepine, topiramate versus carbamazepine or valproate versus carbamazepine). Exceptions included clonazepam versus valproate, and clonazepam versus carbamazepine, where clonazepam had an important benefit in terms of outcome rolandic discharge on electroencephalogram (EEG), and sulthiame versus placebo, where sulthiame had an important benefit in terms of outcome treatment failure.

Typically, the comparisons where no difference in outcomes between interventions was found included less participants and had very serious imprecision, therefore they should not be taken as definitive evidence of no difference between the interventions. There were also a number of outcomes in the protocol that were not reported on by any studies, including neuropsychological and social functioning changes. For the comparison of sulthiame versus placebo, the findings were precise and high quality therefore this is indicative that the true effect size is similar to the estimated effect reported by the study.

See appendix F for full GRADE tables.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

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

Excluded studies

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

Summary of studies included in the economic evidence review

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

Economic model

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the seizures associated with SeLECTS often stop around the age of puberty, it is not clear whether it is necessary to prescribe ASMs to all children who present with this condition. The committee therefore agreed that seizure freedom and reduction in seizure frequency should be included as critical outcomes for this review in order to evaluate the effectiveness of antiseizure medications for this condition. However, as there is a risk of side effects the committee agreed that time to withdrawal of treatment and adverse events should also be included as critical outcomes.

Neuropsychological changes and social functioning changes were included as important outcomes as deterioration in these areas could indicate progression to a different form of epilepsy or an adverse reaction to treatment. EEG readings were also included as an important outcome as changes on these can also indicate progression of the condition and there is a risk that certain medications may exacerbate abnormal features seen on EEG.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The majority of outcomes were considered very low or low quality indicating high uncertainly in the reliability of the data. Data was generally downgraded due to risk of bias, methods were poorly reported, specifically in regard to the randomisation processes and measurement of outcomes. Data was also downgraded due to impreci-

sion. Studies only included a small number of participants; therefore, overall the data should be regarded with some caution.

Benefits and harms

Self-limited epilepsy with centrotemporal spikes is an age-related epilepsy syndrome which subsides by early teenage years. Seizures can be infrequent and confined to sleep with limited impact on the child's well-being which means the main decision is whether to treat with ASMs. The committee agreed the decision should be individually tailored following discussion between the clinician, the child and their parent/carer on the risks and benefits of treatment and non-treatment. For some children, seizures can be frequent and severe with effects on well-being and daily function, and risk injury or death. The committee stated that death is very rare, and the discussion should not cause undue worry to the child or parent/carer. Some children will have infrequent seizures, and therefore the side effects of daily therapy may be more detrimental to the child than the epilepsy itself.

The committee agreed that, if antiseizure medications are started in self-limited epilepsy with centrotemportal spikes, there should be a discussion with the person, their family and carers, if appropriate, about an individualised antiseizure medication strategy according to their epilepsy syndrome, treatment goals and the preferences of the person and their family or carers as appropriate. Treatment plans should be regularly reassessed, and its agreement should include a transparent explanation of the epilepsy syndome, 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.

The committee agreed that, overall, the evidence was limited and insufficient to make firm recommendations; therefore, they also relied on clinical experience and knowledge as well as on the existing evidence in evidence report E for focal seizures. The committee considered it was appropriate to extrapolate from this population as focal seizures are common in self-limited epilepsy with centrotemporal spikes. On this basis, the committee agreed that lamotrigine and levetiracetam should be considered as first-line treatment. There was high quality evidence that lamotrigine and levetiracetam were most effective in increasing the time to treatment withdrawal and, in particular, time to treatment withdrawal due to adverse events, suggesting these were better tolerated and more effective than other options. As second-line treatment, carbamazepine, oxcarbazepine and zonisamide were recommended as these appeared to be the next most effective. The precise choice between these options will be dependent on the preferences and the particular circumstances of the person being treated.

The Rating 2000 study was considered to be at low risk of bias, and this study showed sulthiame was superior to placebo for reducing seizures; however, since this treatment is not licenced in the UK, it is difficult to recommend this as a first line therapy. As such, the committee agreed that prescription of sulthiame as an add-on or alternative treatment should only be undertaken in discussion with a tertiary paediatric neurologist, to ensure that sulthiame is not widely over-prescribed. The committee also questioned whether other drugs would show the same performance as sulthiame if they had been tested in the same way.

The committee emphasised that, monotherapy should be used in the first instance. When starting alternative antiseizure medications, the dose of the new antiseizure medication should be slowly increased, whilst the existing antiseizure medication is

tapered off. When starting add-on antiseizure medications, the additional antiseizure medication should be carefully titrated, in line with the BNF guidance, adverse events monitored, and there should be a frequent treatment review.

The evidence did not provide data on all treatments which are currently available, therefore making recommendations on specific antiseizure medications was difficult. The committee agreed that, in their experience, carbamazepine, oxcarbazepine and lamotrigine may rarely lead to increased seizures and/or the evolution to another epilepsy syndrome with greater effects on cognitive function.

The committee also agreed that if there is concern regarding school performance, advice should be sought from an epilepsy specialist. School performance is a good indicator of cognition since it reflects performance both in processing and retention of information. If any deterioration is noted, an EEG should be performed to exclude electrical status epilepticus in sleep (ESES)/ continuous spike-wave of slow-wave sleep (CSWS). A neuropsychology assessment to review academic performance should also be performed.

As noted previously, this is an age-related condition and therefore consideration should be given to the timing of discontinuation of treatment. When the child has been free of seizures for 2 years, dicontinuation of treatment can be considered. The committee agreed that seizures will generally stop by early teenage years; if treatment has not already ceased, then it should be discontinued when the child reaches 14.

The committee were not surprised that in an epilepsy syndrome in which seizures may be infrequent and, only at night, there were a limited number of studies. Although evidence is scarce, the committee did not prioritise this topic for a research recommendation as they were able to base the recommendations for first- and second-line treatment on the evidence for treating focal seizures.

Cost effectiveness and resource use

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

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

Other factors the committee took into account

The committee noted that, in line with the BNF, carbamazepine and oxcarbazepine should not be offered to people of European or Japanese family background because of the risks of serious complications, unless the person meets the pre-treatment screening advice for people from these groups. In addition, in line with the MHRA, the committee emphasised that long-term treatment with carbamazepine can cause decreased bone mineral density and increased risk of osteomalacia. The committee noted that appropriate supplementation should be considered for those at risk.

Recommendations supported by this evidence review

This evidence review supports recommendations 6.4.1-6.4.8.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Table 9: Review protocol

Field	Content
PROSPERO registration number	CRD42019146620
Review title	Effectiveness of ASMs for self-limited epilepsy with centrotemporal spikes (SeLECTS)
Review question	What ASMs (individually or in combination) are effective in the treatment of seizures in self-limited epilepsy with centrotemporal spikes?
Objective	The objective of this review is to determine which antiseizure medications (ASMs) improve outcomes in those with self-limited epilepsy with centrotemporal spikes. This review will determine the effectiveness of drugs given alone or in combination.
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by:

Field	Content
	• Date: No date limit • English language studies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Self-limited epilepsy with centrotemporal spikes (SeLECTS)
Population	Inclusion: children and young people with confirmed self-limited epilepsy with centrotemporal spikes
Intervention/Exposure/Test	The following ASMs and their combinations will be considered: • Carbamazepine • Clobazam • Gabapentin • Lacosamide • Levetiracetam • Oxcarbazepine • Sodium Valproate • Sulthiame • Topiramate • Lamotrigine • Zonisamide
Comparator/Reference standard/Confounding factors	• Any of the above and their combinations • No treatment/placebo
Types of study to be included	• Systematic review of RCTs • RCTs
Other exclusion criteria	• Studies with a mixed population (this is, including children and young people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported • Studies with a mixed population (this is, including children, and young people with SeLECTS and other types of epilepsy) will be excluded, unless subgroup analysis for epilepsy with SeLECTS has been reported

Field	Content
	• Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care)
Primary outcomes (critical outcomes)	• Seizure freedom (12 months data and short term [minimum 3 months with 100% freedom] of starting treatment). *Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as "time to 12 months seizure freedom", (this is, time to event: HR or mean time) followed by "achievement of 12 months seizure freedom" (RR). Minimum follow up data of 3 months will be included.* • Reduction of seizure frequency >50% • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • Side effects, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event (dichotomous outcome only) Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/searchresults
Secondary outcomes (important outcomes)	• Neuropsychological changes (IQ testing, or other validated tools) • Social functioning changes (behaviour reported by parents/caregivers/school or validated tools) • EEG outcomes (ESES, CSWS, or spike wave index)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised

Field	Content
	form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs 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. <u>Data synthesis</u> 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. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • those with and without learning disabilities • by age (older people/adults/children) • study location Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. <u>Minimal important differences (MIDs):</u> • Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or

Field	Content			
	other MIDs for specific outcomes • For risk ratios: 0.8 and 1.25. • For continuous outcomes: +/-0.5 times the baseline SD of the control arm. If there are 2 studies, the MID is calculated as +/- 0.5 times the mean of the SDs of the control arms at baseline. • Validity • The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/			
Analysis of sub-groups (stratification)	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	6th Aug 2019			
Anticipated completion date	7th April 2021			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑

Field	Content		
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact National Guideline Alliance 5b. Named contact e-mail epilepsies@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	The National Guideline Alliance technical team		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112		
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019146620		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such		

Field	Content	
	as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Epilepsy; Childhood; Centrotemporal spikes; Antiepileptic Drug	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

ASM: antiseizure medication; CSWS: contiuous spike-wave of slow-wave sleep; EEG: electroencephalogram; ESES: electrical status epilepticus in sleep; IQ: intelligence quotient

Appendix B – Literature search strategies

Literature search strategies for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Clinical

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

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

Date of last search: 03 March 2021

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

#	searches
1	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.
2	carbamazepine/ use emczd, emcr or exp carbamazepine/ use ppez or carbamazepin*.sh. or (amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol).ti,ab.
3	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.
4	gabapentin/ use emczd, emcr or gabapentin/ use ppez or gabapentin*.sh. or (apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin).ti,ab.
5	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
6	lamotrigine/ use emczd, emcr or lamotrigine/ use ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium).ti,ab.
7	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
8	oxcarbazepine/ use emczd, emcr or oxcarbazepine/ use ppez or oxcarbazepin*.sh. or (apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin).ti,ab.
9	sultiame/ use emczd, emcr or (conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or trolone).ti,ab.
10	topiramate/ use emczd, emcr,ppez or (epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab.
11	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.
12	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonis-

#	searches
	amid*).ti,ab.
13	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.
14	13 use ppez
15	(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.
16	15 use ppez
17	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.
18	17 use emczd, emcr
19	or/14,16,18
20	meta-analysis/
21	meta-analysis as topic/ or systematic reviews as topic/
22	"systematic review"/
23	meta-analysis/
24	(meta analy* or metanaly* or metaanaly*).ti,ab.
25	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
26	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
27	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
28	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
29	(search* adj4 literature).ab.
30	(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.
31	cochrane.jw.
32	((pool* or combined) adj2 (data or trials or studies or results)).ab.
33	(or/20-21,24,26-32) use ppez
34	(or/22-23,24-25,27-32) use emczd, emcr
35	or/33-34
36	or/19,35
37	1 and 36 and or/2-12
38	limit 37 to english language
39	((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.)
40	39 use emez
41	((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.)
42	41 use mesz
43	40 or 42
44	38 not 43

Database(s): Cochrane Library

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

Date of last search: 03 March 2021

#	searches
1	mesh descriptor: [epilepsy, rolandic] this term only
2	(“epilepsy, rolandic “ or bcects or bects or brec or “benign epilepsy” or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near/1 (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab

#	searches
3	#1 or #2
4	mesh descriptor: [carbamazepine] explode all trees
5	((amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol)):ti,ab,kw
6	mesh descriptor: [clobazam] explode all trees
7	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl)):ti,ab
8	mesh descriptor: [gabapentin] this term only
9	((apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin)):ti,ab,kw
10	mesh descriptor: [lacosamide] this term only
11	((erlosamide or harkoseride or lacosamide or vimpat)):ti,ab,kw
12	mesh descriptor: [levetiracetam] this term only
13	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
14	mesh descriptor: [oxcarbazepine] this term only
15	(apydan or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin):ti,ab
16	(conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or trolone):ti,ab
17	mesh descriptor: [topiramate] this term only
18	(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
19	mesh descriptor: [valproic acid] this term only
20	(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
21	mesh descriptor: [lamotrigine] this term only
22	(crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium):ti,ab
23	mesh descriptor: [zonisamide] this term only
24	(excegran or excemid or zonegran or zonisamid*):ti,ab
25	{or #4-#24}
26	#3 and #25

Database(s): DARE; HTA database - CRD

Date of last search: 03 March 2021

#	searches
1	mesh descriptor epilepsy, rolandic“ this term only
2	(“epilepsy, rolandic “ or 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*) near/2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near1 (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
3	#1 or #2

Economic

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

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

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

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

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

Date of last search: 31 March 2021

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

#	searches
	vere 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

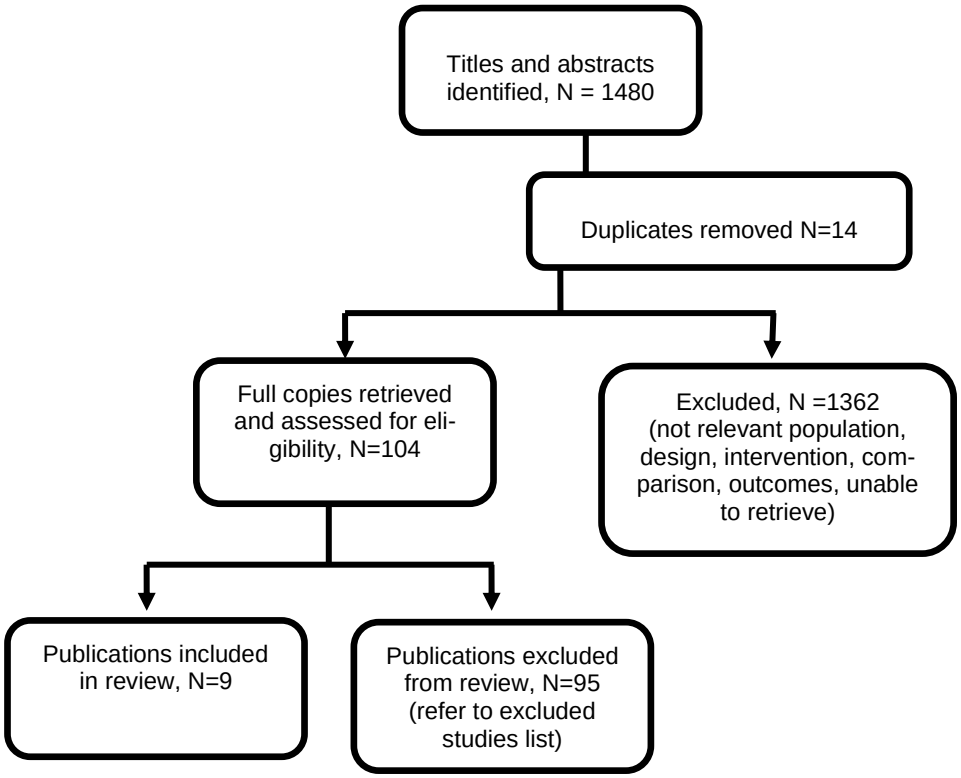
1

2

Appendix C – Clinical evidence study selection

Clinical study selection for: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Figure 1: Study selection flowchart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Table 10: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Ahadi, P., Nasiri, J., Ghazavi, M., Mosavian, T., Mansouri, V., A comparative study on the efficacy of levetiracetam and carbamazepine in the treatment of rolandic seizures in children: An open-label randomized controlled trial, Journal of Research in Pharmacy Practice, 9, 68-72, 2020 **Ref Id** 1291164. **Country/ies where the study was carried out** Iran. **Study type** Randomised con-	**Sample size** N=92. Levetiracetam n=46; carbamazepine n=46. **Characteristics** Children with a clinical diagnosis of benign childhood epilepsy with centro temporal spikes and an EEG showing characteristics of rolandic epilepsy. Sex: Male - levetiracetam n=26; carbamazepine n=28, female - levetiracetam n=20; carbamazepine n=18, p=0.832. Age, years, mean (SD): levetiracetam 8.7 (2.766); carbamazepine 8.36 (2.250), p=0.514. Weight, kg,	**Interventions** Levebel (levetiracetam) oral solution 100 mg/ml at initial dose of 25-30 mg/kg/day versus tegretol (carbamazepine) syrup 20 mg/ml at initial dose of 15-20 mg/kg/day. The levetiracetam and carbamazepine dosages ranged from 27.07 to 31.57 mg/kg/daily and from 12.78 to 13.13 mg/kg/daily (differences due to rounding the amount of daily prescribed drug), respectively.	**Details** Consecutive selection of patients referred to paediatric neurology department at one hospital. Computer generated random numbers. Participants who had a severe reaction to either treatment were excluded from the study and treated with other medications. Open label/participants and investigators were not blinded to treatment allocation. Seizure freedom defined as absence of seizures for at least 1 month. Follow-up by a paediatric neurologist took place every 2 months for a period of 6 months after the start of treatment.	**Results** **Critical outcomes** Seizure freedom at 6 months: Levetiracetam n=47/47; carbamazepine n=47/47. Adverse events – leading to change in medication: levetiracetam n=1/47; carbamazepine n=1/47. NB. Authors report that decreased appetite was most common adverse event. These two patients were excluded from the study.	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 1.1: Yes, computer generated randomisation. 1.2: No information is provided regarding concealment of allocation however it is unlikely that the enrolling investigator or the participant had knowledge of the forthcoming allocation. 1.3: No, there were no significant differences between groups at baseline.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
trolled trial. **Aim of the study** To "... investigate whether levetiracetam should be preferred to carbamazepine as a treatment choice for benign childhood epilepsy with centro Temporal spikes ..." p 68 **Study dates** 2018 - 2020. **Source of funding** Isfahan University of Medical Sciences (Project Number: 398460).	mean (SD): levetiracetam 28.45 (9.306); carbamazepine 28.72 (8.754), p=0.882. Seizure frequency before starting treatment (mean): 1 per month. **Inclusion criteria** • More than two attacks per year. • Normal MRI. • Between the ages of 4 and 12 years. **Exclusion criteria** • 'Under' multi drug therapy. • A history of severe side effects or reaction to levetiracetam or carbamazepine.		Frequency and duration of seizures and side effects recorded using a predesigned checklist. Follow-up: 6 months (no measure of variability was reported)		**Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, participants were aware of their treatment allocation. 2.2: Yes, carers and those delivering interventions were aware of treatment allocation. 2.3 Probably no, changes to the intervention occurred due to adverse events which is consistent with trial protocol. 2.6 Probably no, patients who changed treatments due to adverse events were excluded from final analysis of some outcome data. 2.7 Probably no, it is unlikely that the exclusion of data from patients who changed treatments due to adverse events would have had a substantial effect on the results. **Domain 3: Missing outcome data: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					3.1: Probably yes, although missing outcome data is not reported on specifically, it appears that data were available for all outcomes and participants (with the exception of those excluded from the final analysis due to adverse event related treatment cessation. **Domain 4: Measurement of the outcome: Low risk** 4.1: No, methods of outcome measurement are appropriate. 4.2: No, measurement of the outcome is unlikely to have differed between intervention groups. **Domain 5: Selection of the reported result: Some concerns** 5.1: No information, analysis plans are not reported in sufficient detail to enable assessment although it is unlikely that selective reporting due to unblinded outcome data was an issue.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					5.2: No information, analysis plans are not reported in sufficient detail to enable assessment, and there is more than one way in which the outcome domain could have been measured. 5.3 No information, analysis plans are not available, however it is unlikely that selective reporting of analyses was an issues **Domain 6: Overall judgment of bias: High risk.** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Full citation Borggraefe, I., Bonfert, M., Bast, T., Neubauer, B. A., Schotten, K. J., Maßmann, K., Noachtar, S., Tuxhorn, I., May, T. W., Heinen, F., Levetiracetam vs. sulthiame in benign epilepsy with centrotemporal spikes in childhood: a double-blinded, randomized, controlled	**Sample size** Total recruited: N = 44 Analysis conducted: N = 43 Levetiracetam (n=21), Sulthiame (n=22) **Characteristics** Mean age Levetiracetam: 8.7 years (SD 1.7), Sulthiame: 9.0 years (SD	**Interventions** Levetiracetam Starting dose: 10mg/kg body weight (weekly increments of 10mg/kg body weight) Final dose: 30mg/kg body weight Sulthiame Starting dose: 2mg/kg body weight (weekly	**Details** Medication which looked the same for both treatments was produced by Haupt Pharma Wuelfing, Germany Outcomes were assessed at baseline, after 4 weeks, 12 weeks, and 27 weeks	**Results** **Critical outcomes** Occurrence of treatment failure (occurrence of a seizure in the 24 week observation period after reaching target dose) Levetiracetam: n=4 (19.0%) Sulthiame: n=2 (9.1%).	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk** 1.1: Yes, patients were randomly allocated to treatments

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
trial (German HEAD Study), European journal of paediatric neurology: EJPN, 17, 507-514, 2013 **Ref Id** 1082298 **Country/ies where the study was carried out** Germany **Study type** Multi-centre double blind randomized controlled trial **Aim of the study** To determine the efficacy, tolerability and safety of levetiracetam and sulthiame in participants with Benign childhood epilepsy with centrotemporal spikes (BECTS) **Study dates** 2006 to 2008 **Source of funding** The study was part funded by UCB Pharma SA, Brussels, Belgium	1.5) Number of females Levetiracetam: n=6 (28.6%), Sulthiame: n=10 45.5%) Mean number of seizures (before study entry) Levetiracetam: 6.4 (SD 8.3), Sulthiame: 5.2 (SD 10.2) No statistically differences seen between the treatment groups (p values not provided) **Inclusion criteria** • Male and female participants • Aged between 6 and 12 years • Diagnosed with BECTS, who had experienced two or more seizures within the past 6 months **Exclusion criteria**	increments of 2mg/kg body weight) Final dose: 6mg/kg body weight Down dosing to 20mg/kg (Levetiracetam) or 4mg/kg (Sulthiame) body weight was allowed in case of adverse events	(end of observation period) After an observation period of 24 weeks, the study was unblinded and participants could choose to continue treatment or not. Data analysed according to intention to treat Follow-up: 27 weeks (no measure of variability was reported)	<u>Serious adverse event, leading to treatment dropout</u> Levetiracetam: n= 5 (23.8%) Sulthiame: n= 1 (4.5%)	1.2: Yes, randomisation was conducted in a central randomisation centre using permuted blocks 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, only data from one participant was not included in the analysis **Domain 4: Measurement of the outcome: Low risk** 4.1: No information, outcomes clearly defined, but no information was provided on how they were assessed, or by whom 4.2: Probably no, outcomes included seizure occurrence and ad-

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	• Coincidence of other epilepsy forms • Participation in another clinical study (within 30 days prior to study starting) • Mental retardation				verse events, unlikely to differ between treatment arms 4.3: No, double blind study **Domain 5: Selection of the reported result: Some concerns** 5.1: No, the study did not meet the required number of participants to conduct the planned analysis 5.2: No, descriptive data presented 5.3: No, data presented as expected **Domain 6: Overall judgment of bias: Some concerns** The study did not recruit the 120 sample size needed for the primary outcome - leading to overall bias result
Full citation Coppola, G., Franzoni, E., Verrotti, A., Garone, C., Sarajlija, J., Operto, F. F., Pascotto, A., Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy	**Sample size** Total recruited: N= 39 Levetiracetam: n=21 Oxcarbazepine: n= 18 **Characteristics** Mean age	**Interventions** Levetiracetam and Oxcarbazepine Starting dose: 5mg/kg, with 3 day incremental increase of 5mg/kg Final dose: 20mg/kg	**Details** In case of seizure recurrence daily does of Levetiracetam could be increased to 30mg/kg In case of seizure recurrence, the daily dose of Oxcarbazepine could be increased to	**Results** **Critical outcomes** Seizure freedom (18 months) Levetiracetam: n=19 (90.5%), Oxcarbazpine: n = 13 (72.2%) Adverse events leading	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some con-**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
of childhood with centrotemporal spikes (BECTS): An open-label, parallel group trial, Brain and Development, 29, 281-284, 2007 **Ref Id** 1082322 **Country/ies where the study was carried out** Italy **Study type** Open label pilot study **Aim of the study** To determine the efficacy and tolerability of levetiracetam and oxcarbazepine for participants with benign epilepsy with centrotemporal spikes **Study dates** Not stated **Source of funding** Not stated	Levetiracetam: 10.5 years, oxcarbazepine: 8.4 years Number of females Levetiracetam: n=10 (41.6%), oxcarbazepine: n=8 (44.4%) Mean number of seizure (during baseline period) Levetiracetam: 1.8 seizures/month, oxcarbazepine: 1.5 seizures/month **Inclusion criteria** • Males and females • Aged 3 to 12 years • Newly diagnosed with BECTS (according to LIAE classification) • Frequent seizures in the last 6 months (seizures to occur during wakefulness) • Partial motor seizures (hemifacial or hemiclonic) with or without generalisation		35mg/kg Data analysed according to intention to treat Mean follow-up (range): 18.5 (12–24) months	<u>to withdrawal of medication</u> Levetiracetam: n=1/21, Oxcarbazpine: n = 1/18 <u>Adverse events (not leading to withdrawal)</u> Levetiracetam: n=2/21, Oxcarbazpine: n = 1/18	**cerns** 1.1: Yes, children were randomised 1.2: No information, no details on allocation concealment provided 1.3: Probably yes, baseline characteristics given, no statistical data provided but there appear to be some differences; however, children were matched so this may not be an issue **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, an open label pilot study 2.2: Yes, an open label pilot study 2.3: No information, no details provided about deviations from the protocol **Domain 3: Missing outcome data: Low risk** 3.1: No information, no details provided on missing data 3.2: Probably yes, in-

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	• EEG features of peculiar focal or multifocal centrotemporal spikes • MRI with normal or slight abnormal results • absence of neurological and mental deficits • No previous therapy • Provided informed consent **Exclusion criteria** • Poor compliance by parents or caregivers to complete seizure diary • progressive neurological and or systemic disease • Those with associated pseudoseizures during MRI scan				tention to treat analysis was carried out **Domain 4: Measurement of the outcome: Some concerns** 4.1: Probably no, outcome data recorded in diaries by parents/carers 4.2: Probably no, data collected methods consistent across arms 4.3: Yes, open label pilot study 4.4: Probably yes, data recorded by parents/carers; therefore, knowledge of medication could lead to bias 4.5: No information, unclear what information parents/carers were given about the treatment; therefore, it is difficult to determine if their beliefs about the medication influenced recording of data **Domain 5: Selection of the reported result: Low risk** 5.1: Probably yes, Study states ITT analysis conducted

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					5.2: No, data provided as expected 5.3: No, data provided as expected **Domain 6: Overall judgment of bias: Some concerns**
Full citation Kang, H. C., Eun, B. L., Wu Lee, C., Ku Moon, H., Kim, J. S., Wook Kim, D., Soo Lee, J., Young Chae, K., Ho Cha, B., Sook Suh, E., et al., The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy, Epilepsia, 48, 1716-1723, 2007 **Ref Id** 1082380 **Country/ies where the study was carried out** Korea **Study type** Multi-centre, open label randomised trial	**Sample size** Total enrolled: N=112 Topiramate: n=58, Carbamazepine: n=54 Total completed: n=88 **Characteristics** Mean age Topiramate: 8.7 years (SD 1.9), Carbamazepine: 8.7 years (SD 2.0) Number of females Topiramate: n=26 (44.8%), Carbamazepine: n=22 (40.7%) **Inclusion criteria** • Normal intelligence • Aged 5 to 15 years • Had at least 2 partial seizures during 6 months at baseline • Clinical and EEG findings compatible	**Interventions** <u>Topiramate</u> Starting dose: 12.5mg/day, incremental increases over 4 weeks Final dose of at least 50mg/day if weighed under 30kg, or at least 75mg/day if weighed over 30kg <u>Carbamazepine</u> Starting dose: 10mg/kg/day, incremental increases over 4 weeks Final dose of at least 20/kg/day	**Details** The study had a baseline 6 month phase followed a one week screening phase to determine eligibility And a four week dose escalation phase, and a 6 week maintenance phase where dose was kept stable Average daily dose during the maintenance phase was 3.4mg/kg/day TPM and 21.6mg/kg/day CBZ Follow-up: 28 weeks (no measure of variability reported)	**Results** **Critical outcomes** <u>Seizure free (mean follow-up 28 weeks)</u> Topiramate: n=40, Carbamazepine: n=38 <u>Number of patients who experienced an adverse event (follow-up mean 28 weeks)</u> Topiramate: n=16/58 Carbamazepine: n=19/54 <u>Number of patients who withdrew due to adverse events</u> Topiramate: n=6/58 Carbamazepine: n=5/54	**Limitations** <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u> **Domain 1: Randomisation: Some concerns** 1.1: Yes, each study center had a randomisation plan 1.2: No information, no details provided on concealment of allocation 1.3: Probably no, no clearly reported differences at baseline; however, no p values provided so difficult to be certain **Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes, an open label

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To determine the cognitive and behavioural effects of Topiramate (TPM) as compared to carbamazepine (CBZ) in children with benign Rolandic epilepsy **Study dates** Not stated **Source of funding** The study was supported by a grant from Janssen, Korea limited, a Johnson and Johnson company	with benign Rolandic epilepsy • Plus, at least one of the following: • Parent or patient wanted to take ASM • daytime seizures • at least 1 episode of a convulsive seizure during 6 months at baseline **Exclusion criteria** • Evidence of progressive cerebral lesion • Neurodegenerative metabolic disorder • Cognitive impairment that could interfere with cognitive testing • History of psychiatric disorder requiring tranquilizers in the past 6 months • Regular use of antihistamines or CNS active compounds in the past 6 months • History of poor drug compliance				study, only the observer was blinded 2.2: Probably no, states that the observer is blinded, but no details given 2/3: Probably no, no deviations from the intended protocol were reported **Domain 3: Missing outcome data: Low risk** 3.1: Probably no, drop-outs are reported, and data analysis conducted as intention to treat 3.2: Probably yes, Intention to treat analysis conducted **Domain 4: Measurement of the outcome: Low risk** 4.1: Probably no, outcomes measured using validated tools 4.2: Probably no, same tools used across the groups 4.3: No, observers were blind to treatment **Domain 5: Selection of the reported result:**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	• Inability to maintain a seizure calendar • History of nephrolithiasis • Previously treated with TPM or CBZ				**High risk** 5.1: probably yes, data analysis described 5.2: Probably yes, a number of tools were used to assess neuropsychological outcomes, data was unclearly reported making interpretation difficult 5.3: No information: Data on neuropsychological outcomes was unclearly reported making interpretation difficult **Domain 6: Overall judgment of bias: High risk** **Other information** Some data were presented in a way that could not be extracted (this is, change in seizure frequency and neuropsychological test results)
Full citation Kwon, Soonhak, Hwang, Tae Gyu, Lee, Junhwa, Kim, Doo-Kwun, Seo, Hye-Eun, Benign childhood epilepsy with centrotem-	**Sample size** N=39 randomised. Intervention group n=13 Control n=16	**Interventions** Intervention group: Oxcarbazepine initially administered once or twice a day at a dose of 5-10 mg/kg/day and	**Details** The study consisted of screening, randomization and a 30 week treatment phase. Each center was given a	**Results** **Primary outcomes** Seizure freedom (6 months) Intervention group n=7/13; control group	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
poral spikes: to treat or not to treat, Journal of epilepsy research, 3, 1-6, 2013 **Ref Id** 1310611 **Country/ies where the study was carried out** South Korea **Study type** Randomised controlled trial (multi-centre) **Aim of the study** To determine the "…the benefits and risks of oxcarbazepine (OXC) monotherapy as a first-line AED in children with newly diagnosed BCECT were evaluated based on clinico-electrical and neuro-psychological findings over time." p 1 **Study dates** Not reported **Source of funding** Novartis Korea	**Characteristics** Childern with newly diagnosed, benign partial epilepsy recruited from 4 tertiary medical centers functioning as referral centres in 4 different regions of South Korea. Age, mean, years: intervention group 8.2 ±2.3; control group 8.5±2.3. Sex: Intervention group male n=6, female n=7; control group male n=11; female n=8. **Inclusion criteria** • Aged between 5 and 15 years • 2 or more seizures over the past 6 months • Diagnosed with BECTS by pediatric neurologists. **Exclusion criteria** • Primary generalised seizures • Partial epilepsies of a	titrated to 10-20 mg/kg/day over a week. This allowed dosages to be increased to a therapeutic range if the patients experienced increased frequency or severity of seizures in comparison to baseline. Control group: No treatment.	separate and independent randomization protocol using a random code assignment. EEGs read by 2 or more experienced specialists. Location and frequency of spikes were quantified for each patient. Spike index was calculated by dividing the total number of spikes by the total time the patient was evaluated. Full-scale intelligence quotient derived from scores on Korean versions of Wechsler Intelligence Scale for Children III. Follow-up: 6 months (no measure of variabil-ity reported)	n=8/16. <u>Reduction of seizure frequency >50%</u> Intervention group n=3/13; control group n=3/16. **Secondary outcomes** <u>Normalisation of sleep EEG (6 months)</u> Intervention group n=2/13; control group n=3/16. <u>EEG spike index - left (6 months, frequency/minute):</u> Intervention group 26.2±18.0; control group 11.8±20.0. <u>EEG spike index - right (6 months, frequency/minute):</u> intervention group 19.1±18.4; control group 3.8±7.9. <u>Full-scale intelligence quotient (6 months):</u> intervention group 97.6±7.5; control group 111.4±18.6.	**Domain 1: Randomisation: Low risk** 1.1: Yes, each centre had a randomisation protocol 1.2: Yes. Randomisation protocol provided by external agency. 1.3: Probably no. Only minimal demographic data provided however baseline values for clinical data are also provided and these do not suggest that any issues with randomisation arose. **Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes. Participants were aware of their assigned intervention. 2.2: Yes. Parents/carers and individuals delivering the interventions were aware of assigned interventions. 2.3: Probably no. No deviations are reported and any that arose would be unlikely to do so as a result of the trial context. 2.6: Yes. An an appro-

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	symptomatic Etiology • Neurodegenerative conditions • History of psychiatric conditions • History of taking antiepileptic drugs over previous 3 months.			Although baseline values for all outcomes are reported insufficient data is reported to allow presentation of change scores.	priate analysis was used. **Domain 3: Missing outcome data: Low risk** 3.1: Yes. Outcome data available for all patients. **Domain 4: Measurement of the outcome: Some concerns** 4.1: No. Method of measuring outcome was appropriate. 4.2: No. Measurement of the outcome did not differ between intervention groups. 4.3: No information. No details provided regarding blinding of outcome assessors. 4.4: Probably yes. Outcome assessment ssessment could be influenced by knowledged of the intervention received. 4.5: Probably no. It is unlikely that assessment of the outcome was influenced by knowledge of intervention received.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					Domain 5: Selection of the reported result: Some concerns 5.1: No information. Analysis plans not provided. 5.2: No information. Analysis plans are not provided. 5.3: No information. Analysis plans not provided. **Domain 6: Overall judgment of bias: Some concerns.** **The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.**
Full citation Mitsudome, A., Ohfu, M., Yasumoto, S., Ogawa, A., Hirose, S., Ogata, H., Yamada, T., The effectiveness of clonazepam on the Rolandic discharges, Brain and Development, 19, 274-278, 1997	**Sample size** EEG Total: N= 40 Clonazepam (CZP): n=20 Valproate (VPA): n=10 Carbamazepine (CBZ): n=10 **Characteristics** Mean age	**Interventions** Dose of clonazepam: 0.35-1.0mg/day Dose of valproate: 250-600mg/day Dose of carbamazepine: 100-200mg/day	**Details** The first EEG was recorded before administration of drug, the second after 4 weeks of medication Follow-up: 4 weeks (no measure of variability reported)	**Results** **Important outcomes** Disappearance of Rolandic discharge on EEG Clonazepam: n=15 (75%) Valproate: n=1 (10%) Carbamazepine: n=0 (0%)	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: High risk** 1.1: Yes, children were randomly sorted

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 1082416 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial **Aim of the study** To determine the effect of Clonazepam compared to Valproate and Carbamazepine on Rolandic discharge on Electroencephalography (EEG) **Study dates** Not stated **Source of funding** Not stated	CZP: 7.3 years (range 3.11 to 9.11), VPA: 8.6 years (range 4.0 - 10.11), CBZ: 8.6 years (range 5.5 - 10.3) Number of females CZP: n=9 (45%0, VPA: n=4 (40%), CBZ: n= 5 (50%) **Inclusion criteria** • Newly diagnosed with benign epilepsy in childhood with centrotemporal spikes (BECTS) • With typical Rolandic discharge of EEG • Not treated for BECTS prior to study **Exclusion criteria** • None stated				1.2: No information, no details provided on allocation concealment 1.3: Probably yes, no baseline differences between groups were demonstrated; however, double the number of participants were allocated to the clonazepam group **Domain 2: Deviations from intended interventions: Some concerns** 2.1: No information 2.2: No information 2.3: No information **Domain 3: Missing outcome data: High risk** 3.1: No information, no details on missing data provided 3.2: Probably no, no information, unequal balance of participants in the arms may indicated bias in the research 3.3: No information 3.4: No information **Domain 4: Measure-**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					ment of the outcome: High risk 4.1: No, outcome data measured by EEG, and two investigators agreed the reading 4.2: Probably no, data collection methods consistent across arms 4.3: No information 4.4: Probably yes, potential bias of observer could influence their reading of the EEG 4.5: No information **Domain 5: Selection of the reported result: Some concerns** 5.1: No information, no data analysis plan provided 5.2: No, EEG readings provided as expected 5.3: No, decision on EEG data provided as expected. **Domain 6: Overall judgment of bias: High risk** **Other information** Brief publication with little detail on methods

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Rating, D., Wolf, C., Bast, T., Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: A 6-month randomized, double-blind, placebo-controlled study, Epilepsia, 41, 1284-1288, 2000 **Ref Id** 1082446 **Country/ies where the study was carried out** Germany **Study type** Double-blind, placebo randomised trial **Aim of the study** To determine the efficacy of Sulthiame in preventing seizures in children with Benign childhood epilepsy with centrotemporal spikes (BECTS) **Study dates** 1996 to 1999	**Sample size** Total randomised: N=66. Sulthiame: n=31, placebo: n= 35 **Characteristics** Mean age Sulthiame: 8 years (range 3-10), placebo: 8 years (range 3-10) Number of females Sulthiame: n=15 (48.4%), placebo: n=11 (31.4%) Total number of seizures prior to study date Sulthiame: n=4 (range 2-20), placebo: n=3 (range 2-80) **Inclusion criteria** • Diagnosed with BECTS • Had 2 or more seizures in the past 6 months • Aged between 3 and 10 years	**Interventions** **Sulthiame** 5mg/kg/day given in three administrations per day Relative dose administered varied from 3.1 to 5.7mg/kg/day	**Details** Patients assessed at screening, day 14, day 28, and at 3 and 6 months Follow-up: 6 months (no measure of variability was reported)	**Results** **Critical outcomes** Treatment failure (defined as no seizure in first 7 days, no adverse event or withdrawal Sulthiame: n=6, placebo: n=25 **Important outcomes** EEG awake, Specific pathology (follow-up mean 6 months) Sulthiame: n= 10/25, placebo: n=5/10 EEG awake, normal - EEG (follow-up mean 6 months) Sulthiame: 11/25, placebo: 2/10. EEG sleep, specific pathology (follow-up mean 6 months) Sulthiame: 10/25, placebo: 6/10. EEG sleep, normal - (follow-up mean 6 months) Sulthiame: 10/25, placebo: 1/10.	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk** 1.1: Yes, participants randomized into blocks of four using a prepared list. 1.2: Yes, the randomisation codes were in sealed envelopes. 1.3: Yes, there were no significant differences between the groups at baseline. **Domain 2: Deviations from intended** interventions: Low risk 2.1: Probably no, the study states it was double blind; however, no details are provided 2.2: Probably no, the study states it was double blind; however, no details are provided **Domain 3: Missing outcome data: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Not stated	**Exclusion criteria** • Presence of severe organic disease • acute porphyria • somatic signs of puberty • relevant hypersensitivity • history of mental illness • relevant renal, thyroid or hepatic dysfunction				3.1: Yes, the paper reports dropouts and data presented for the time period of the study, data on EEG is missing in placebo group over time. **Domain 4: Measurement of the outcome: Low risk** 4.1: No information, the outcome "treatment failure" was defined but there was no information on how this was assessed. 4.2: No 4.3: Probably no, the study claims to be double blind **Domain 5: Selection of the reported result: Low risk** 5.1: Probably yes, the data analysis was described, with ITT at interim time point once 60 participants recruited 5.2: No, only one set of measurements for outcomes **Domain 6: Overall**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					judgment of bias: Low risk
Full citation Suo, G. H., Zheng, Y. Q., Wu, Y. J., Tang, J. H., Effects of levetiracetam and oxcarbazepine monotherapy on intellectual and cognitive development in children with benign epilepsy with centrotemporal spikes, Acta Neurologica Belgica, 2021 **Ref Id** 1310603 **Country/ies where the study was carried out** China. **Study type** Randomised controlled trial. **Aim of the study** To "…the efficacy of LEV and OXC monotherapy for the treatment of children with BCECTS, and the effect of these treatments on intelligence and cognitive development …" p 2	**Sample size** N=70 randomised (n=64 completed/analysed). Intervention group n=35 randomised (n=32 completed/analysed). Control group n=35 (n=32 completed/analysed). **Characteristics** Children diagnosed with BECTS in the outpatient department of the Affiliated Hospital of Nantong University. **Inclusion criteria** Age, years: Intervention group 8.47 ± 2.13; control group 8.62 ± 2.21, *p* = 0.783 Age at onset, years: Intervention group 6.98 ± 1.82; control group 7.13 ± 1.75, *p* = 0.738 Gender, male, (%): Intervention group n=21	**Interventions** Intervention: Levetiracetam – 250 mg tablets (Keppra). Initial dose set at 10 mg/kg/day. Dose increased once every 7 days and maintained at 20–60 mg/kg/day. Control: Oxcarbazepine – 150 mg tablets. Initial dose set at 8–10 mg/kg/day, orally administered twice a day at an interval of 12 hours. Dose increased to 5–10 mg/kg/day every 5–7 days and maintained at 20–46 mg/kg/day. All children started treatment at a low dose and returned to the clinic for assessment once a week at the beginning of treatment. During the treatment, clinical reactions in each child were closely observed, and the dosage of drug was appropriately adjusted according to the weight	**Details** 1:1 randomisation. Follow-up at 1, 3, and 6 months. No information provided regarding handling of missing data. Follow-up: 6 months (no measure of variability was reported)	**Results** Seizure freedom (3 months): Intervention group n=12/32; control group n=16/32. Seizure freedom (6 months): Intervention group n=17/32; control group n=25/32. EEG – normal (3 months): Intervention group n=10/32; control group n=13/32. EEG – normal (6 months): Intervention group n=14/32; control group n=19/32. Adverse events – number of patients experiencing any adverse event (timescale not reported): Intervention group n=6/32; control group	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk** 1.1: Yes. Random number table. 1.2: No information. No details on allocation concealment are reported. 1.3: No. No significant differences at baseline. **Domain 2: Deviations from intended interventions**: Some concerns 2.1: No information. Not clear whether particiapnts were aware of assigned interventions. 2.2: No information. Not clear carers or those delivering were aware of assigned interventions. 2.3: Probably no. Deviations not reported clearly however any

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates October 2018 – February 2020. **Source of funding** Suzhou Science and Technology Plan (People's Livelihood Science and Technology), the Scientific Research Project of Jiangsu Health Commission, and the Nantong Science and Technology Project.	(65.63); control group n=19 (59.38), *p* = 0.606 **Inclusion criteria** • diagnosis of BECTS according to 2017 ILAE criteria • EEG features showing that seizure during an epileptic attack was partial or was generalised to the whole body and that the background rhythm was normal • at least 2 convulsions before recruitment • no abnormality in head MRI or CT examination • normal liver and kidney function prior to commencement of medication. **Exclusion criteria** • Encephalitis, brain injury, cerebralhemorrhage, and other organic diseases of the nervous system • functional insufficiency of the liver, lung, kidney or other important organs • emergence of mental	of the child and his/her seizure status. If a child exhibited obvious adverse events, the treatment was adjusted.		n=7/32.	arising would not be likely to do so as a result of the trial context. 2.6: No. Participants lost to follow-up/those who discontinued have been excluded from final analysis. 2.7: Probably no. Exclusion of these patients is unlikely to have influenced the results. **Domain 3: Missing outcome data: Low risk** 3.1: No. Six patients were excluded from analyses due to discontinuation/loss to follow-up. 3.2: No. No details regarding sensitivity analyses or methods to correct for missing outcome data are reported. 3.3 Probably no. Unlikely that missingness in outcome data depends on true value. **Domain 4: Measurement of the outcome: Low risk** 4.1: Yes. Methods of outcome measurement

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	'retardation' • presence of cranial space-occupying lesions • poor medication compliance • any relevant drug contraindications.				are appropriate. 4.2: No. Unlikely to have differed between groups. 4.3: No information. Not clear whether outcome assessors were blinded. 4.4: Probably no. Assessment of the outcome unlikely to have been influenced by knowledge of interventions received. **Domain 5: Selection of the reported result: Some concerns** 5.1: No information. Pre-specified data analysis intentions not reported. 5.2: No information. Pre-specified data analysis intentions not reported. 5.3: No information. Pre-specified data analysis intentions not reported. **Domain 6: Overall judgment of bias: Some concerns.** The study is judged to raise some concerns in

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					at least one domain for this result, but not to be at high risk of bias for any domain. **Other information** A number of scales relating to intelligence and cognitive function are reported however no summary outcome is reported and as these each relate to very specific components of intelligence and cognition these results have not been extracted.
Full citation Tacke, M., Borggraefe, I., Gerstl, L., Heinen, F., Vill, K., J et al., Effects of Levetiracetam and Sulthiame on EEG in benign epilepsy with centrotemporal spikes: A randomized controlled trial, Seizure, 56, 115-120, 2018 **Ref Id** 1082470 **Country/ies where the study was carried out** Germany	**Sample size** see Borggraefe 2013 **Characteristics** see Borggraefe 2013 **Inclusion criteria** see Borggraefe 2013 **Exclusion criteria** see Borggraefe 2013	**Interventions** see Borggraefe 2013	**Details** see Borggraefe 2013	**Results** **Important outcomes** <u>Absence of EEG discharges in all available EEGs (27 weeks)</u> Levetiracetam: n=8/13 Sulthiame: n=11/21	**Limitations** see Borggraefe 2013 **Other information** see Borggraefe 2013

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type see Borggraefe 2013 **Aim of the study** To compare the effects of Levetiracetam and Sulthiame on EEG in benign childhood epilepsy with centrotemporal spikes (BECTS) - secondary publication from the HEAD study (Borggraefe 2013) **Study dates** see Borggraefe 2013 **Source of funding** see Borggraefe 2013					

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Appendix E – Forest plots

Forest plots for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here, but the quality assessement for these outcomes is provided in the GRADE profiles in appendix F.

Comparison 3: levetiracetam versus oxcarbamazepine

Figure 2: adverse events

Appendix F – GRADE tables

GRADE tables for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Table 11: Clinical evidence profile. Comparison 1: levetiracetam versus carbamazepine

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	CBZ	Relative (95% CI)	Absolute	Quality	Importance
Seizure freedom at 6 months												
1 (Ahadi 2020)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/47 (100%)	47/47 (100%)	RR 1.00 (0.96 to 1.04)	0 fewer per 1000 (from 40 fewer to 40 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events – leading to change in medication												
1 (Ahadi 2020)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/47 (2.1%)	1/47 (2.1%)	RR 1.00 (0.06 to 15.52)	0 fewer per 1000 (from 20 fewer to 309 more)	⨁◯◯◯ VERY LOW	CRITICAL

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Confidence interval crosses both MIDs (0.8 and 1.25)*

Table 12: Clinical evidence profile. Comparison 2: levetiracetam versus sulthiame

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	STM	Relative (95% CI)	Absolute		
Treatment failure (follow-up mean 24 weeks)												
1 (Borggraefe 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/21 (19%)	2/22 (9.1%)	RR 2.1 (0.43 to 10.26)	100 more per 1000 (from 52 fewer to 842 more)	⊕OOO VERY LOW	CRITICAL
Adverse event leading to withdrawal (follow-up mean 24 weeks)												
1 (Borggraefe 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/21 (23.8%)	1/22 (4.5%)	RR 5.24 (0.67 to 41.18)	193 more per 1000 (from 15 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Normal EEG (absence of EEG discharge at 27 weeks) (follow-up mean 27 weeks)												
1 (Tacke 2018)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/13 (61.5%)	11/21 (52.4%)	RR 1.17 (0.65 to 2.12)	89 more per 1000 (from 183 fewer to 587 more)	⊕OOO VERY LOW	IMPORTANT

1 [1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *Confidence intervals cross both MIDs (0.8 and 1.25)*

3 **Table 13: Clinical evidence profile. Comparison 3: levetiracetam versus oxcarbazepine**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	OXC	Relative (95% CI)	Absolute	Quality	Importance

1

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	OXC	Relative (95% CI)	Absolute	Quality	Importance
Seizure freedom (3 months)												
1 (Suo 2021)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/32 (37.5%)	16/32 (50%)	RR 0.75 (0.43 to 1.32)	125 fewer per 1000 (from 285 fewer to 160 more)	⊕OOO VERY LOW	CRITICAL
Seizure freedom (6 months)												
1 (Suo 2021)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17/32 (53.1%)	25/32 (78.1%)	RR 0.68 (0.47 to 0.99)	250 fewer per 1000 (from 8 fewer to 414 fewer)	⊕⊕OO LOW	CRITICAL
Seizure freedom (18 months)												
1 (Coppola 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19/21 (90.5%)	13/18 (72.2%)	RR 1.25 (0.91 to 1.72)	181 more per 1000 (from 65 fewer to 520 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
2 (Coppola 2007, Suo 2021)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/53 (15.1%)	8/50 (16%)	RR 0.97 (0.4 to 2.37)	5 fewer per 1000 (from 96 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
Adverse events leading to withdrawal of medication												
1 (Coppola 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/21 (4.8%)	1/18 (5.6%)	RR 0.86 (0.06 to 12.75)	8 fewer per 1000 (from 52 fewer to 653 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	OXC	Relative (95% CI)	Absolute	Quality	Importance
EEG normal (3 months)												
1 (Suo 2021)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/32 (31.3%)	13/32 (40.6%)	RR 0.77 (0.4 to 1.49)	93 fewer per 1000 (from 244 fewer to 199 more)	⊕OOO VERY LOW	IMPORTANT
EEG normal (6 months)												
1 (Suo 2021)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/32 (43.8%)	19/32 (59.4%)	RR 0.74 (0.45 to 1.2)	154 fewer per 1000 (from 327 fewer to 119 more)	⊕⊕OO LOW	IMPORTANT

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *2 Confidence interval crosses both MIDs (0.8 and 1.25)*
3 *3 Confidence interval crosses 1 MID (0.8 or 1.25)*

4 **Table 14: Clinical evidence profile. Comparison 4: topiramate versus carbamazepine**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TPM	CBZ	Relative (95% CI)	Absolute	Quality	Importance
Number of participants seizure free (mean follow-up 28 weeks)												
1	RCT	serious[1]	no serious	no serious	serious[2]	none	40/58	38/54	RR 0.98	14 fewer	⊕⊕OO	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TPM	CBZ	Relative (95% CI)	Absolute	Quality	Importance
(Kang 2007)			inconsistency	indirectness			(69%)	(70.4%)	(0.77 to 1.25)	per 1000 (from 162 fewer to 176 more)	LOW	
Number of patients who experienced an adverse event (follow-up mean 28 weeks)												
1 (Kang 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/58 (27.6%)	19/54 (35.2%)	RR 0.78 (0.45 to 1.36)	77 fewer per 1000 (from 194 fewer to 127 more)	⨁OOO VERY LOW	CRITICAL
Number of patients who withdrew due to adverse events (follow-up mean 28 weeks)												
1 (Kang 2007)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/58 (10.3%)	5/54 (9.3%)	RR 1.12 (0.36 to 3.45)	11 more per 1000 (from 59 fewer to 227 more)	⨁OOO VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Confidence interval crosses 1 MID (0.8 or 1.25)*
[3] *Confidence intervals cross both MIDs (0.8 and 1.25)*

Table 15: Clinical evidence profile. Comparison 5. oxcarbazepine versus no treatment

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OXC	No treat-ment	Relative (95% CI)	Absolute		
Seizure freedom (6 months)												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/13 (53.8%)	8/16 (50%)	RR 1.08 (0.53 to 2.17)	40 more per 1000 (from 235 fewer to 585 more)	⊕OOO VERY LOW	CRITICAL
Reduction of seizure frequency > 50%												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/13 (23.1%)	3/16 (18.8%)	RR 1.23 (0.3 to 5.11)	43 more per 1000 (from 131 fewer to 771 more)	⊕OOO VERY LOW	CRITICAL
Normalisation of sleep EEG (6 months)												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/13 (15.4%)	3/16 (18.8%)	RR 0.82 (0.16 to 4.2)	34 fewer per 1000 (from 157 fewer to 600 more)	⊕OOO VERY LOW	IMPORTANT
EEG spike index - left (better indicated by lower values)												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	13	16	-	MD 14.4 higher (0.55 to 28.25 higher)	⊕⊕OO LOW	IMPORTANT
EEG spike index - right (better indicated by lower values)												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	16	-	MD 15.3 higher (4.57 to 26.03	⊕OOO VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OXC	No treat-ment	Relative (95% CI)	Absolute	Quality	Importance
										higher)		
Full scale intelligence quotient (6 months) (better indicated by higher values)												
1 (Kwon 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	13	16	-	MD 13.8 lower (23.78 to 3.82 lower)	⊕⊕OO LOW	IMPORTANT

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *2 Confidence interval crosses both MIDs (0.8 and 1.25)*
3 *3 95% CI crosses 1 MID (+/-0.5 x control group SD for mean reduction in spike index - left = +/- 10)*
4 *4 95% CI crosses 1 MID (+/-0.5 x control group SD for mean difference in full-scale intelligence quotient - left = +/- 9.3)*
5

6 **Table 16: Clinical evidence profile. Comparison 5: clonazepam versus valporate**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CZP	VPA	Relative (95% CI)	Absolute	Quality	Importance
Disappearance of RD on EEG (follow-up mean 4 weeks)												
1 (Mitsudome 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/20 (75%)	1/10 (10%)	RR 7.5 (1.15 to 48.98)	650 more per 1000 (from 15	⊕OOO VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CZP	VPA	Relative (95% CI)	Absolute	Quality	Importance
										more to 1000 more)		

1 [1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 [2] *Confidence interval crosses 1 MID (0.8 or 1.25)*

3 **Table 17: Clinical evidence profile. Comparison 6: clonazepam versus carbamazepine**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CZP	CBZ	Relative (95% CI)	Absolute	Quality	Importance
Disappearance of RD on EEG (follow-up mean 4 weeks)												
1 (Mitsudome 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/20 (75%)	0/10 (0%)	POR 18.17 (4.09 to 80.86)	750 more per 1000 (from 530 more to 970 more)	⊕⊕OO LOW	IMPORTANT

4 [1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
5

Table 18: Clinical evidence profile. Comparison 7: valporate versus carbamazepine

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VPA	CBZ	Relative (95% CI)	Absolute	Quality	Importance
Disappearance of RD in EEG (follow-up mean 4 weeks)												
1 (Mitsudome 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/10 (10%)	0/10 (0%)	POR 7.39 (0.15 to 372.38)	100 more per 1000 (140 fewer to 340 more)	⊕OOO VERY LOW	IMPORTANT

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Confidence intervals cross both MIDs (0.8 and 1.25)*

Table 19: Clinical evidence profile. Comparison 8: sulthiame versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	STM	Placebo	Relative (95% CI)	Absolute	Qual-ity	Importance
Treatment failure (follow-up mean 6 months)												
1 (Rating 2000)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/31 (19.4%)	25/35 (71.4%)	RR 0.27 (0.13 to 0.57)	521 fewer per 1000 (from 307 fewer to 621 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
EEG: specific pathology - Awake EEG (follow-up mean 6 months)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	STM	Placebo	Relative (95% CI)	Absolute	Qual-ity	Importance
1 (Rating 2000)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/25 (40%)	5/10 (50%)	RR 0.8 (0.37 to 1.75)	100 fewer per 1000 (from 315 fewer to 375 more)	⊕⊕OO LOW	IMPORTANT
EEG: normal - Awake EEG (follow-up mean 6 months)												
1 (Rating 2000)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/25 (44%)	2/10 (20%)	RR 2.2 (0.59 to 8.2)	240 more per 1000 (from 82 fewer to 1000 more)	⊕⊕OO LOW	IMPORTANT
EEG: specific pathology - Sleep EEG (follow-up mean 6 months)												
1 (Rating 2000)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/25 (40%)	6/10 (60%)	RR 0.67 (0.33 to 1.34)	198 fewer per 1000 (from 402 fewer to 204 more)	⊕⊕OO LOW	IMPORTANT
EEG: normal - Sleep EEG (follow-up mean 6 months)												
1 (Rating 2000)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/25 (40%)	1/10 (10%)	RR 4 (0.59 to 27.29)	300 more per 1000 (from 41 fewer to 1000 more)	⊕⊕OO LOW	IMPORTANT

[1] *Confidence interval crosses both MIDs (0.8 and 1.25)*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

Clinical studies

Table 20: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Akter, N., Rahman, M. M., Akhter, S., Fatema, K., A Randomized Controlled Trial of Phenobarbital and Levetiracetam in Childhood Epilepsy, Mymensingh Medical Journal: MMJ, 27, 776-784, 2018	Population does not meet the inclusion criteria: no specific reference to participants with CECTS
Ambrosetto, G., Tassinari, C. A., Antiepileptic drug treatment of benign childhood epilepsy with rolandic spikes: is it necessary?, Epilepsia, 31, 802-5, 1990	Study design does not meet inclusion criteria - retrospective case control study
Anderson, M., Choonara, I., A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period, Archives of Disease in Childhood, 95, 731-738, 2010	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Andrade, R., García-Espinosa, A., Machado-Rojas, A., García-González, M. E., Trápaga-Quincoses, O., Morales-Chacón, L. M., A prospective, open, controlled and randomised study of clobazam versus carbamazepine in patients with frequent episodes of Rolandic epilepsy, Revista de neurologia, 49, 581-586, 2009	Publication not in English
Anonymous,, Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Canadian Study Group for Childhood Epilepsy, Epilepsia, 39, 952-9, 1998	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Arya, R., Giridharan, N., Anand, V., Garg, S. K., Clobazam monotherapy for focal or generalized seizures, Cochrane Database of Systematic Reviews, 2018	Systematic review, relevant studies which meet the protocol inclusion criteria are already included
Arya, R., Glauser, T. A., Pharmacotherapy of focal epilepsy in children: A systematic review of approved agents, CNS Drugs, 27, 273-286, 2013	Systematic review. No relevant data could be extracted for inclusion. References checked for inclusion
Asadi-Pooya, A. A., Forouzesh, M., Eidi, H., Mirzaghafour, S. E., Levetiracetam versus carbamazepine in treatment of rolandic epilepsy, Epilepsy and Behavior, 94, 1-8, 2019	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Ay, Y., Gokben, S., Serdaroglu, G., Polat, M., Tosun, A., Tekgul, H., Solak, U., Kesikci, H., Neuropsychologic Impairment in Children With Rolandic Epilepsy, Pediatric Neurology, 41, 359-363, 2009	Study design does not meet the inclusion criteria - prospective case control study
Banu, S. H., Jahan, M., Koli, U. K., Ferdousi, S., Khan, N. Z., Neville, B., Side effects of phenobarbital and carbamazepine in childhood epilepsy: Randomised controlled trial, British Medical Jour-	Population does not meet the inclusion criteria: No specific reference to participants with CECTS

Study	Reason for Exclusion
nal, 334, 1207-1210, 2007	
Barik, K. L., Paul, U. K., Bhattacharyya, A. K., Adhikary, A., Agarwal, G., Rana, K. S., New onset paediatric epilepsy in 1-5 years age group children--approach to management in a tertiary care centre with newer anti-epileptic levetiracetam, Journal of the Indian Medical Association, 112, 100-2, 2014	Population does not meet the inclusion criteria: no specific reference to participants with CECTS
Basnec, A., Skarpa, D., BarisiÄ‡, N., Jurin, M., MuciÄ-PuciÄ, B., The risk of second seizure in children with benign childhood epilepsy with centrotemporal spikes without treatment--a prospective study, Acta medica Croatica, 59, 59â€• 62, 2005	Publication not in English
Bast, T., Völp, A., Wolf, C., Rating, D., The influence of sulthiame on EEG in children with benign childhood epilepsy with centrotemporal spikes (BECTS), Epilepsia, 44, 215â€• 220, 2003	Secondary publication from the included study, Rating 2000. The paper does not report any additional, relevant outcomes
Bawden, H. N., Camfield, C. S., Camfield, P. R., Cunningham, C., Darwish, H., Dooley, J. M., Gordon, K., Ronen, G., Stewart, J., van Mastrigt, R., The cognitive and behavioural effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy, Epilepsy Research, 33, 133-43, 1999	Population does not meet the inclusion criteria: No specific reference to participants with CECTS
Berg, I., Butler, A., Ellis, M., Foster, J., Psychiatric aspects of epilepsy in childhood treated with carbamazepine phenytoin or sodium valproate: A random trial, Developmental Medicine and Child Neurology, 35, 149-157, 1993	Population do not meet the inclusion criteria: No specific reference to participants with CECTS
Bonfert, M., Armbruster, S., Bastian, B., Heinen, F., Efficacy of levetiracetam in the treatment of children with BECTS: a prospective, open-label pilot trial prior to a controlled, randomised, double-blind German multicentre study (HEAD study), Epilepsia, 47 Suppl 3, 133, Abstract no: p510, 2006	Conference abstract
Borggraefe, I., Bonfert, M., Bast, T., Neubauer, B. A., Schotten, K. J., Massmann, K., Noachtar, S., Tuxhorn, I., May, T. W., Heinen, F., A double-blinded, randomized, head-to-head trial of levetiracetam vs. sulthiame in benign epilepsy with centrotemporal spikes, Epilepsy Currents, 1), 67, 2013	Conference abstract
Borggraefe, I., Bonfert, M., Gerstl, L., Heinen, F., Neubauer, B., A double-blinded, randomized evaluation of neuropsychological and behavioral changes in children with benign epilepsy with centrotemporal spikes treated either with levetiracetam or sulthiame, Epilepsy Currents, 1), 278, 2015	Conference abstract
Borggrafe, I., Bonfert, M., Bast, T., Neubauer, B. A., Schotten, K. J., Masmann, K., Noachtar, S., Tuxhorn, I., May, T. W., Heinen, F., A double-blinded, randomized, head-to-head trial of levetiracetam versus sulthiame in benign epilepsy with centrotemporal spikes, Neuropediatrics. Con-	Conference abstract

Study	Reason for Exclusion
ference: 39th Annual Meeting of the Society of Neuropediatrics. Innsbruck Austria. Conference Publication:, 44, 2013	
Bourgeois, B., Brown, L. W., Pellock, J. M., Buroker, M., Greiner, M., Garofalo, E. A., Schimschock, J. R., Griesemer, D., Bebin, M. E., Murphy, J. V., Gabapentin (Neurontin) monotherapy in children with benign childhood epilepsy with centrotemporal spikes (BECTS): a 36-week, double-blind, placebo-controlled study, Epilepsia, 39 Suppl 6, 163, 1998	Conference abstract
Braathen, G., Andersson, T., Gylje, H., Melander, H., Naglo, A. S., Noren, L., Persson, A., Rane, A., Sjors, K., Theorell, K., Wigertz, A., Comparison between one and three years of treatment in uncomplicated childhood epilepsy: A prospective study. I. Outcome in different seizure types, Epilepsia, 37, 822-832, 1996	Intervention does not meet inclusion criteria: The study compares 1 to 3 years of treatment, not different treatment types
Callenbach, P. M. C., Bouma, P. A. D., Geerts, A. T., Arts, W. F. M., Stroink, H., Peeters, E. A. J., Van Donselaar, C. A., Peters, A. C. B., Brouwer, O. F., Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood, Seizure, 19, 501-506, 2010	Study design does not meet the inclusion criteria - prospective cohort study
Camfield, P., Booth, F., Buckley, D., Camfield, C., Darwish, H., Dooley, J., Farrell, K., Gordon, K., Hwang, P., Langevin, P., Larbrisseau, A., Lowry, N., Meek, D., Munn, R., Reggin, J., Ronen, G., Sinclair, B., Tibbles, J., Whiting, S., Wilfong, A., Yager, J., Stewart, J., Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy, Epilepsia, 39, 952-959, 1998	Population does not meet the inclusion criteria: No specific reference to participants with CECTS
Chen, Y. J., Kang, W. M., So, W. C. M., Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: A psychometric and neurophysiological study, Epilepsia, 37, 81-86, 1996	Population does not meet the inclusion criteria: No specific reference to participants with CECTS
Clemens, B., Menes, A., Piros, P., Bessenyei, M., Altmann, A., Jerney, J., Kollar, K., Rosdy, B., Rozsavolgyi, M., Steinecker, K., Hollody, K., Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings, Epilepsy Research, 70, 190-9, 2006	Study design does not meet the inclusion criteria - non-randomized, cohort screening study
Connock, M., Frew, E., Evans, B. W., Bryan, S., Cummins, C., Fry-Smith, A., Li Wan Po, A., Sandercock, J., The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review, Health Technology Assessment, 10, iii-118, 2006	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Coppola, G., Franzoni, E., Verrotti, A., Garane, C., Sarajlija, J., Operto, F., Pascotto, A., Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign rolandic seizures in children: an open-label, parallel group study, Epilep-	Conference abstract

Study	Reason for Exclusion
sia, 47 Suppl 3, 179â€• 180, 2006	
Cross, J. H., Auvin, S., Patten, A., Giorgi, L., Safety and tolerability of zonisamide in paediatric patients with epilepsy, European Journal of Paediatric Neurology, 18, 747-758, 2014	Systematic review, no data relevant could be extracted for inclusion. References checked for inclusion
Ctri,, Study of effect of treatment versus no treatment on seizures, psychological, behavioral and EEG parameters in children with BECTS type of epilepsy, Http://www.who.int/trialsearch/trial2.aspx? Trialid=ctri/2018/02/012248, 2018	Trial registration
De Goede, C. G., Gupta, R., Antiepileptic drugs versus no treatment or placebo for children with benign epilepsy with centro temporal spikes, Cochrane Database of Systematic Reviews, (4) (no pagination), 2007	Protocol
De Negri, M., Baglietto, M. G., Gaggero, R., Benzodiazepine (BDZ) treatment of benign childhood epilepsy with centrotemporal spikes (BECCT), Brain & Development, 19, 506, 1997	Letter to the editor
De Paola, L., The not so benign idiopathic focal epilepsies of childhood: A second look on the benign childhood epilepsy with centrotemporal spikes (BECTS), Arquivos de Neuro-Psiquiatria, 61, 59-64, 2003	Narrative review
De Silva, M., MacArdle, B., McGowan, M., Hughes, E., Stewart, J., Neville, B. G. R., Johnson, A. L., Reynolds, E. H., Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy, Lancet, 347, 709-713, 1996	Population does not meet the inclusion criteria: No specific reference to participants with CECTS
Deonna, T., Roulet-Perez, E., Cronel-Ohayon, S., Mayor-Dubois, C., Correspondence on "deterioration in cognitive function in children with benign epilepsy of childhood with central temporal spikes treated with sulthiame", Journal of Child Neurology, 25, 127-8, 2010	Letter to the editor
Dulac, O., Lamotrigine in the treatment of childhood epilepsy, Bollettino - Lega Italiana contro l'Epilessia, 37-38, 1994	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Euctr, D. E., HEAD-TO-HEAD evaluation of the antiepileptic drugs Levetiracetam (LEV) vs. Sulthiame (STM) in a German multi-centre, double-blind controlled trial in children with benign epilepsy with centro-temporal spikes - HEAD-STUDIE, Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2005-004468-22-de, 2006	Trial registration
Euctr, G. B., Sleep and learning in children with a benign focal epilepsy of childhood, Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2011-001571-39-gb, 2011	Trial registration
Eun, S. H., Eun, B. L., Lee, J. S., Hwang, Y. S., Kim, K. J., Lee, Y. M., Lee, I. G., Lee, M., Ko, T. S., Kim, J. T., Eom, S., Kim, H. D., Effects of	Population do not meet the inclusion criteria - no specific reference to participants with CECTS

Study	Reason for Exclusion
lamotrigine on cognition and behavior compared to carbamazepine as monotherapy for children with partial epilepsy, Brain and Development, 34, 818-823, 2012	
Eun, S. H., Kim, H. D., Eun, B. L., Lee, I. K., Chung, H. J., Kim, J. S., Kang, H. C., Lee, Y. M., Suh, E. S., Kim, D. W., Eom, S., Lee, J. S., Moon, H. K., Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy, Seizure, 20, 558-563, 2011	Outcome data does not meet the inclusion criteria - despite reference to participants with CECTS no data are reported separately for these participants
Eun, S. H., Kim, H. D., Lee, I. K., Chung, H. J., Eun, B. L., Lee, J. S., Kim, J. S., Kang, H. C., Suh, E. S., Kim, D. W., Eom, S., Moon, H. K., A multicenter comparative trial of low and high dose zonisamide in children with newly diagnosed epilepsy as monotherapy, Epilepsia, 4), 147, 2010	Conference abstract
Eun, S., Kim, H., Lee, I., Chung, H., Eun, B., Lee, J., Kim, J., Kang, H., Suh, E., Kim, D., Eom, S., Moon, H., A multi-center comparative trial of low and highdose zonisamide in children with newly diagnosed epilepsy as monotherapy, Epilepsia, 11), 244, 2009	Conference abstract
Forsythe, I., Butler, R., Berg, I., McGuire, R., Cognitive impairment in new cases of epilepsy randomly associated to carbamazepine, phenytoin and sodium valproate, Developmental Medicine and Child Neurology, 33, 524-534, 1991	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Freydkova, N., Karlov, V., Topamax monotherapy in cases of children's and adolescent's focal epilepsy, Epilepsia, 4), 132, 2009	Conference abstract
Geng, H., Wang, C., Efficacy and safety of oxcarbazepine in the treatment of children with epilepsy: A metaanalysis of randomized controlled trials, Neuropsychiatric Disease and Treatment, 13, 685-695, 2017	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Gerstl, L., Willimsky, E., Remi, C., Noachtar, S., Borggrafe, I., Tacke, M., A Systematic Review of Seizure-Freedom Rates in Patients With Benign Epilepsy of Childhood With Centrotemporal Spikes Receiving Antiepileptic Drugs, Clinical neuropharmacology, 2021	Systematic review. All studies already included in NGA review with the exception of Andrade (2009) which is not available in English.
Gkampeta, A., Fidani, L., Zafeiriou, D., Pavlou, E., Benign epilepsy with centrotemporal spikes: Relationship between type of seizures and response to medication in a Greek population, Journal of Neurosciences in Rural Practice, 6, 545-548, 2015	Study design does not meet the inclusion criteria - participants were not randomised but grouped according to seizure type
Glauser, T. A., Ayala, R., Elterman, R. D., Mitchell, W. G., Van Orman, C. B., Gauer, L. J., Lu, Z., Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures, Neurology, 66, 1654-1660, 2006	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Guerreiro, C., Kalviainen, R., Mattson, R., French, J. A., Perucca, E., Tomson, T., Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion

Study	Reason for Exclusion
for epileptic seizures and syndromes, Epilepsia, 54, 551-563, 2013	
Haigh, D., Forsythe, W. I., The treatment of childhood epilepsy with sodium valproate, Developmental Medicine & Child Neurology, 17, 743-8, 1975	Study design does not meet the inclusion criteria - non-randomised, case series
Halma, E., De Louw, A. J. A., Klinkenberg, S., Aldenkamp, A. P., Ijff, D. M., Majoie, M., Behavioral side-effects of levetiracetam in children with epilepsy: A systematic review, Seizure, 23, 685-691, 2014	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Kanemura, H., Sano, F., Ohyama, T., Sugita, K., Aihara, M., Effect of Levetiracetam Monotherapy in Nonlesional Focal Childhood Epilepsy, Neuropediatrics, 49, 135-141, 2018	Study design does not meet the inclusion criteria - retrospective review of data
Kang, H. C., Eun, B. L., Lee, C. W., Moon, H. K., Kim, J. S., Kim, D. W., Lee, J. S., Chae, K. Y., Cha, B. H., Suh, E. S., et al.,, A multicenter, randomized, open-labeled, clinical study to evaluate the effect on cognitive and behavioral function of topiramate compared with carbamazepine as monotherapy in children with benign rolandic epilepsy, Epilepsia, 47, 138, Abstract no: 2.057, 2006	Conference abstract
Kramer, U., Shahar, E., Zelnik, N., Lerman-Sagie, T., Watemberg, N., Nevo, Y., Ben-Zeev, B., Carbamazepine versus sulthiame in treating benign childhood epilepsy with centrotemporal spikes, Journal of Child Neurology, 17, 914-6, 2002	Study design does not meet the inclusion criteria - non-randomised, case series
Kwok, S. C., Paediatric epilepsy website, Journal of Paediatrics and Child Health, 54, 1268, 2018	Commentary paper
Lagae, L., Buyse, G., Ceulemans, B., Clinical experience with levetiracetam in childhood epilepsy: an add-on and mono-therapy trial, Seizure, 14, 66-71, 2005	Study design does not meet the inclusion criteria - on-randomised cohort study Additionally, the population do not meet the inclusion criteria: No specific reference to participants with CECTS
Lagae, L., Meshram, C., Giorgi, L., Patten, A., Effects of adjunctive zonisamide treatment on weight and body mass index in children with partial epilepsy, Acta Neurologica Scandinavica, 131, 341-346, 2015	Outcomes do not meet the inclusion criteria - data on BMI and weight only. Primary trial checked for inclusion but is not relevant as the population does not meet the inclusion criteria - No specific reference to participants with CECTS
Lenz,R.A., Elterman,R.D., Robieson,W.Z., Vigna,N.V., Saltarelli,M.D., Divalproex Sodium in Children with Partial Seizures: 12-Month Safety Study, Pediatric Neurology, 41, 101-110, 2009	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Lim, K., Kim, H. D., Low-dose topiramate compared with carbamazepine in treating benign rolandic epilepsy, Epilepsia, 45, 322â€• 323, 2004	Conference abstract
Liu, C., Song, M., Wang, J., Nightly oral administration of topiramate for benign childhood epilepsy with centrotemporal spikes, Child's Nervous System, 32, 839-843, 2016	Intervention does not meet the inclusion criteria - compares once nightly with twice daily Topiramate
Liu, M. J., Su, X. J., Md, X. S., Wu, G. F., Zhang, Y. Q., Gao, L., Wang, W., Liao, J. X., Wang, H.,	Study design does not meet the inclusion criteria - retrospective review of current practice in

Study	Reason for Exclusion
Mai, J. N., Gao, J. Y., Shu, X. M., Huang, S. P., Zhang, L., Zou, L. P., Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children, Medicine, 96, e5623, 2017	Study design does not meet the inclusion criteria - prospective cohort
Maheshwari, M. C., Sodium valproate in the treatment of childhood epilepsies, Indian Pediatrics, 21, 439-46, 1984	Narrative review
Messenheimer, J., Efficacy and safety of lamotrigine in pediatric patients, Journal of Child Neurology, 17, 2S34-2S42, 2002	Narrative review
Messenheimer,J.A., Giorgi,L., Risner,M.E., The tolerability of lamotrigine in children, Drug Safety, 22, 303-312, 2000	Narrative review
Milburn-McNulty, P., Powell, G., Sills, G. J., Marson, A. G., Sulthiame monotherapy for epilepsy, Cochrane Database of Systematic Reviews, CD010062, 2014	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Mitsudome, A., Ohu, M., Yasumoto, S., Ogawa, A., Rhythmic slow activity in benign childhood epilepsy with centrotemporal spikes, Clinical Electroencephalography, 28, 44-8, 1997	Study design does not meet the inclusion criteria - prospective cohort of four participants
Miura, H., Minagawa, K., Kaneko, T., Sudo, Y., Sodium valproate as a single drug in the treatment of childhood epilepsy: A prospective study of plasma levels and seizure control, Brain and Development, 3, 196, 1981	Conference abstract
Miura, H., Minagawa, K., Kaneko, T., Sudo, Y., Carbamazepine as a single drug in the treatment of childhood epilepsy: A prospective study of plasma levels and seizure control, Brain and Development, 2, 272, 1980	Conference abstract
Morris, G. L., Gabapentin, Epilepsia, 40, S63-S70, 1999	Narrative review
Nct,, HEAD-Study Optimizing the Treatment of Children With BECTS, Https://clinicaltrials.gov/show/nct00471744, 2007	Trial registration
Nct,, Electroclinical Effect of Diazepam and Steroid in Patients With Benign Childhood Epilepsy With Centrotemporal Spikes, Https://clinicaltrials.gov/show/nct03490487, 2018	Trial registration.
O'Donohoe, N. V., Use of antiepileptic drugs in childhood epilepsy, Archives of Disease in Childhood, 66, 1173-1175, 1991	Narrative review
Ormrod, D., McClellan, K., Topiramate: A review of its use in childhood epilepsy, Paediatric Drugs, 3, 293-319, 2001	Narrative review
Rai, A., Aggarwal, A., Mittal, H., Sharma, S., Comparative efficacy and safety of intravenous valproate and phenytoin in children, Pediatric Neurology, 45, 300-304, 2011	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Rating, D., Wolf, Ch, Sulthiame vs placebo in the treatment of benign epilepsy with centrotemporal spikes ("Rolandic" Epilepsy), Epilepsia, 40 Suppl 2, 163, 1999	Conference abstract
Rosati, A., De Masi, S., Guerrini, R., Antiepileptic	Narrative review

Study	Reason for Exclusion
Drug Treatment in Children with Epilepsy, CNS Drugs, 29, 847-863, 2015	
Rosati, A., Ilvento, L., Lucenteforte, E., Pugi, A., Crescioli, G., McGreevy, K. S., Virgili, G., Mugelli, A., De Masi, S., Guerrini, R., Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis, Epilepsia, 59, 297-314, 2018	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Rufo-Campos, M., Casas-Fernandez, C., Martinez-Bermejo, A., Long-term use of oxcarbazepine oral suspension in childhood epilepsy: Open-label study, Journal of Child Neurology, 21, 480-485, 2006	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Sankar, R., Update on the pharmacologic management of common pediatric epilepsy syndromes, No To Hattatsu, 48 (Supplement 1), S210, 2016	Publication not in English
Schlumberger, E., Chavez, F., Palacios, L., Rey, E., Pajot, N., Dulac, O., Lamotrigine in treatment of 120 children with epilepsy, Epilepsia, 35, 359-67, 1994	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Tacke, M., EEG changes in rolandic epilepsy under treatment with Levetiracetam and Sulthiame, European Journal of Paediatric Neurology, 21 (Supplement 1), e97, 2017	Conference abstract
Tacke, M., Gerstl, L., Heinen, F., Heukaeufer, I., Bonfert, M., Bast, T., Cornell, S., Neubauer, B. A., Borggraefe, I., Effect of anticonvulsive treatment on neuropsychological performance in children with BECTS, European journal of paediatric neurology: EJPN, 20, 874-879, 2016	Outcome data not extractable for analysis
Tacke, M., Rupp, N., Gerstl, L., Heinen, F., Vill, K., Bonfert, M., Neubauer, B. A., Bast, T., Borggraefe, I., Baumeister, F. A. M., Baethmann, M., Schreiber-Gollwitzer, B., Bentele, K., Blank, C., Held, J., Blank, H. M., Liebrich, K., Bode, H., Braun, J., Bosch, F., Wagner, R., Brandl, U., Wetzel, K., Brockmann, K., Schlockwerder, C., Dahlem, P., Baudler, I., Ernst, J. P., Mayer, H., Feldmann, E., Pattber-Wolff, A., Fiedler, A., Sonnleitner, S., Gerigk, M., Hess, S., Feiereis, T., Hikel, C., Hoffmann, H. G., Rickeshenrich, A., Kieslich, M., Dewitz, R., Baz Bartels, M., Klepper, J., Kleuker, S., Kluger, G., Kirsch, A., Koch, H., Meerpohl, U., Koch, W., Korinthenberg, R., Stehle-Renner, B., Krois, I., Wegener, A., Kuhne, H., Weiss, C., Kurlemann, G., Elkemann, U., Mandl, M., Friedl, A., Mause, U., Muller, M., Navratil, P., Iken, U., Opp, J., Walter, J., Penzien, J., Prietsch, V., Siegrist, B., Quattlander, A., Rating, D., Reuner, G., Schara, U., Shamdeen, M. G., Struchholz, H., prinz, A., Wendker-Magrabi, H., Stephani, U., Muhle, H., Carlsson, G., Strassburg, H. M., Ottensmeier, H., Topke, B., Tatsek, K., Trollmann, R., Poida-Herzing, E., Tuschen-Hofstatter, E., Menschig, M., Waltz, S., Pickartz, A., Weber, G., Gehnen, T., Wien, F. U., Antemann, J., Wolff, M., Serra, E., Polster, T., Freitag,	Outcomes do not meet the inclusion criteria - secondary publication from the included study, Broggraefe 2013

Study	Reason for Exclusion
H., Sonmez, O., Rheinhardt, K., Traus, M., chroder, A., Hoovey, S., Navratil, C., Benign epilepsy with centrotemporal spikes: Correlating spike frequency and neuropsychology, Acta Neurologica Scandinavica, 138, 475-481, 2018	
Takahashi, K., Saito, M., Kyo, K., Gomibuchi, K., Niijima, S., Tada, H., Honda, T., Sato, Y., Takahashi, H., Ohtsuka, C., The effects of clonazepam on rolandic discharge of benign epilepsy of children with centro-temporal EEG foci, Japanese Journal of Psychiatry & Neurology, 45, 468-70, 1991	Study design does not meet the inclusion criteria - non-randomised follow up study
Tan, H. J., Singh, J., Gupta, R., de Goede, C., Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes, Cochrane Database of Systematic Reviews, 2014 (9) (no pagination), 2014	Systematic review, relevant studies which meet the protocol inclusion criteria are already included in the NGA review
Trudeau, V. L., Kilgore, M. B., Poulter, C. J., DuMetz, M. K., Gillem, C. H., Hes, M. S., Koto, E. M., Garofalo, E. A., A multicenter, open-label extension study of gabapentin (Neurontin) monotherapy in pediatric patients with benign epilepsy with centrotemporal spikes (BECTS), Epilepsia, 37 Suppl 5, 111, 1996	Conference abstract
Van Sweden, B., VPA syrup in childhood epilepsy. Results of an international clinical multicentre trial, Acta Neurologica Belgica, 88, 152-62, 1988	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Verdru, P., Epilepsy in children: The evidence for new antiepileptic drugs, Acta Neurologica Scandinavica, 112, 17-20, 2005	Narrative review
Verity, C. M., Hosking, G., Easter, D. J., A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy, ESSAI COMPARATIF DU VALPROATE DE SODIUM ET DE LA CARBAMAZEPINE SUR L'EPILEPSIE DE L'ENFANT, DANS PLUSIEURS CENTRES, Developmental Medicine and Child Neurology, 37, 97-108, 1995	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Verrotti, A., D'Egidio, C., Agostinelli, S., Parisi, P., Chiarelli, F., Coppola, G., Cognitive and linguistic abnormalities in benign childhood epilepsy with centrotemporal spikes, Acta Paediatrica, International Journal of Paediatrics, 100, 768-772, 2011	Study design does not meet the inclusion criteria - non-randomised follow up study
Wang, Y. Y., Wang, M. G., Yao, D., Huang, X. X., Zhang, T., Deng, X., Comparison of impact on seizure frequency and epileptiform discharges of children with epilepsy from topiramate and phenobarbital, European Review for Medical and Pharmacological Sciences, 20, 993-997, 2016	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Weijenberg, A., Brouwer, O. F., Callenbach, P. M. C., Levetiracetam Monotherapy in Children with Epilepsy: A Systematic Review, CNS Drugs, 29, 371-382, 2015	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Weijenberg, A., Offringa, M., Brouwer, O. F., Callenbach, P. M. C., RCTs with new antiepileptic drugs in children: A systematic review of mono-	Systematic review, no relevant data could be extracted for inclusion. References checked for

Study	Reason for Exclusion
therapy studies and their methodology, Epilepsy Research, 91, 1-9, 2010	inclusion
Wheless, J. W., Use of topiramate in childhood generalized seizure disorders, Journal of Child Neurology, 15, S7-S13, 2000	Narrative review
Wheless, J. W., Neto, W., Wang, S., Topiramate, carbamazepine, and valproate monotherapy: Double-blind comparison in children with newly diagnosed epilepsy, Journal of Child Neurology, 19, 135-141, 2004	Population do not meet the inclusion criteria - no specific reference to participants with CECTS
Yamawaki, H., Seki, T., Suzuki, N., Single-drug therapy with valproic acid in childhood epilepsy, Folia Psychiatrica et Neurologica Japonica, 36, 320, 1982	Study design does not meet the inclusion criteria - non-randomised case series
Yasuhara, A., Matsuoka, O., Tamai, H., Suzuki, Y., Imai, K., Woo, M., Hattori, H., Mimaki, T., Nagai, T., Sugimoto, T., Murata, R., Okada, S., Prospective study of benign childhood epilepsy with centrotemporal spikes: Preliminary study, Japanese Journal of Psychiatry and Neurology, 48, 375-377, 1994	Study design does not meet the inclusion criteria - non-randomised cohort
Yi, Z. M., Wen, C., Cai, T., Xu, L., Zhong, X. L., Zhan, S. Y., Zhai, S. D., Levetiracetam for epilepsy: An evidence map of efficacy, safety and economic profiles, Neuropsychiatric Disease and Treatment, 15, 1-19, 2019	Systematic review of systematic reviews and trials. No relevant data could be extracted for inclusion. References checked for inclusion
Zhou, S., Zhan, Q., Wu, X., Effect of levetiracetam on cognitive function and clonic seizure frequency in children with epilepsy, Current molecular medicine., 29, 2019	Population do not meet the inclusion criteria - no specific reference to participants with CECTS

Economic studies

No economic evidence was identified for this review. See supplementary material X for further information.

Appendix L – Research recommendations

Research recommendations for review question: What antiseizure medications (monotherapy or add-on) are effective in the treatment of self-limited epilepsy with centrotemporal spikes?

No research recommendations were made for this review question.