Review protocol for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks?

Table 9: Review protocol for effectiveness of antiseizure therapies in the management of tonic or atonic seizures/drop attacks

Field	Content
PROSPERO registration number	CRD42020166880
Review title	Effectiveness of antiseizure therapies for tonic or atonic seizures/drop attacks
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks? Note: The review question has been amended to include the term “drop attacks” as both tonic or atonic seizures can be described (and often are in the literature) as such.
Objective	The objective of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have tonic or atonic seizures/drop attacks. This review will determine the effectiveness of drugs given alone (monotherapy) or as add-ons (combination therapy).
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare

Field	Content
	Searches will be restricted by: • Date: No limit • English language studies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Epilepsy with tonic or atonic seizures/ drop attacks
Population	Inclusion: People with confirmed epilepsy with tonic or atonic seizures/drop attacks. Exclusion: • Newborn babies (under 28 days) with acute symptomatic seizures • People with cardiogenic drop attacks • People with syncopal drop attacks.
Intervention	The following antiseizure therapies and their combinations will be considered: • Brivaracetam • Ethosuximide • Felbamate • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Perampanel • Rufinamide • Sodium Valproate • Topiramate • Zonisamide

Field	Content
Comparator	• 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 people with epilepsy with different seizure types) will be excluded, unless subgroup analysis for epilepsy with tonic or atonic seizures/drop attacks has been reported. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias. • Corpus callostomy
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)
	• Adverse effects, as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse events)
	  ○ Injuries due to drop attacks
	  ○ Treatment cessation due to adverse event (dichotomous outcome only)
	  ○ Mortality
	• Frequency of drop attacks

Secondary outcomes (im-	• Health-related quality of life (validated tools only)

Field	Content
portant outcomes)	Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/searchresults
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria. Duplicate screening will not be undertaken for this review question. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and will include: study setting; design; aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of intervention and controls; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. 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 reasons for its exclusion. All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data synthesis Where possible pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm and <1% events in the other. Risk difference will be used for outcomes

Field	Content
	with zero events in both arms. Mean differences or standardised mean differences will be presented for continuous outcomes. Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • by age (older people (>65 years old/adults (> 25 to 65 years old)/young people (>11 to 25 years old)/ infants and children (0 to 11 years old)) • study location Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. Minimal important differences (MIDs): • Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes • For risk ratios: 0.8 and 1.25 For continuous outcomes: • For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm. • For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. • For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. • For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.

Field	Content			
	Validity • The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/			
Analysis of sub-groups (stratification)	Stratification If data is available, results will be presented separately by: • Those with and without learning difficulties/disabilities • Part or not part of underlying epilepsy syndrome (this is, if drop attacks occur as part of another syndrome or in isolation)			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	30th April 2020			
Anticipated completion date	2nd June 2021			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑

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

Field	Content
	https://www.nice.org.uk/guidance/indevelopment/gid-ng10112
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166880
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Epilepsy; tonic seizures; atonic seizures; drop attacks
Details of existing review of same topic by same authors	Not applicable
Additional information	Not applicable
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: The Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; ROBIS: risk of bias in systematic reviews; RR: risk ratio; SD: standard deviation