National Institute for Health and Care Excellence

FINAL

Epilepsies in children, young adults and adults: diagnosis and management

[11] Evidence review: Antiseizure medication for prolonged seizures: monotherapy

NICE guideline NG217

Evidence reviews underpinning recommendations 7.3.1 – 7.3.4 in the NICE guideline

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1 Anti-seizure medication for prolonged seizures: Monotherapy

1.1 Review question: What Anti-seizure medications (monotherapy) are effective in the treatment of prolonged seizures

1.1.1 Introduction

People with recurrent, prolonged or continuous seizures require urgent intervention to limit their risk of neurological harm and death. Adherence to standard management protocols, including early intervention is important to improve outcomes of from prolonged seizures in adults and children. Such protocols need to be individualised and built upon the best evidence to guide the most effective and timely interventions in both community and hospital settings.

This review presents the clinical and cost-effectiveness evidence on the management of prolonged seizures using antiseizure medication.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: children, young people and adults with prolonged seizures Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
Interventions	Brivaracetam Carbamazepine Chloral hydrate (trichlophos) Clobazam Clonazepam Diazepam Fenfluramine Levetiracetam Lorazepam Midazolam Nitrazepam Oxygen Paraldehyde Phenytoin Steroids / adrenocorticotropic hormone (ACTH) Topiramate Valproate (sodium valproate / valproic acid) Vigabatrin
Comparisons	Drug vs placebo/no treatment One drug vs another drug
Outcomes	• mortality (including SUDEP) • time to seizure cessation, within 24 hours after drug administration, 24 to 72

	hours, greater than 72 hours 1 week
	• time to event seizure cessation
	• quality of life (QOLIE-31, QOLIE-AD-48)
	• length of hospital stay
	• adverse events
	  ○ respiratory depression
	  ○ hypotension
	  ○ frequency of endotracheal intubation
	  ○ ICU admission
	  ○ neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance
	• healthcare resource use

Study design	RCTs Systematic reviews of RCTs

1.1.3 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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

No relevant clinical studies examining monotherapy for prolonged seizures were identified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Economic evidence

1.1.5.1 Included studies

No health economic studies were included.

1.1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.6 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.1.7 Unit costs

Please see unit costs presented in Evidence Review 09: ASMs Monotherapy and Add on Therapies for status epilepticus and Evidence Review 10: ASMs Monotherapy and Add on Therapies for repetitive or cluster seizures.

1.1.8 Evidence statements

- None.

1.1.8.1 Economic

- No relevant economic evaluations were identified.

1.2 Committee's discussion of the evidence

The summarised discussion of this evidence can be found in evidence review 09. The committee agreed it was important for the recommendations to distinguish between convulsive and non-convulsive prolonged seizures to ensure emergency management plans are developed accordingly.

1.2.1 Recommendations supported by this evidence review

This evidence review supports recommendations 7.3.1 – 7.3.4 in the NICE guideline.

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Appendices

Appendix A Review protocols

A.1 Review protocol for [add key area, for example, unplanned hospital admission]

ID	Field	Content
0.	PROSPERO registration number	CRD42019155841
1.	Review title	What AEDs (monotherapy) are effective in the treatment of prolonged seizures?
2.	Review question	What AEDs (monotherapy) are effective in the treatment of prolonged seizures?
3.	Objective	Some people with epilepsy can have prolonged seizures. In this review we aim to determine if there is evidence to support the usage of specific medications to acutely abort prolonged seizures and the impact this may have on overall seizure control/the epilepsy as a whole.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches:

		• Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Prolonged seizures are serious medical events and as such considered medical emergencies. They require medication as soon as possible.
6.	Population	Inclusion: children, young people and adults with acute repetitive seizures or clusters over a number of hours or days Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention/Exposure/Test	Brivaracetam Carbamazepine Chloral hydrate (trichlophos) Clobazam Clonazepam Diazepam Fenfluramine Levetiracetam Lorazepam Midazolam Nitrazepam Oxygen Paraldehyde Phenytoin Steroids / adrenocorticotropic hormone (ACTH) Topiramate

		Valproate (sodium valproate / valproic acid) Vigabatrin
8.	Comparator/Reference standard/Confounding factors	Drug vs placebo/no treatment One drug vs another drug
9.	Types of study to be included	RCTs Systematic reviews of RCTs Non-randomised studies will be excluded as it is anticipated there will be sufficient RCTs evidence
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
11.	Context	There is no definitive clinical definition of prolonged seizures. For the purpose of this review prolonged seizures are defined as those that occur longer than a person's usual seizure length up to 5 min. At 5 mins and greater seizures are defined as status epilepticus.
12.	Primary outcomes (critical outcomes)	• mortality (including SUDEP) • time to seizure cessation, within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours 1 week • time to event seizure cessation • quality of life (QOLIE-31, QOLIE-AD-48) • length of hospital stay • adverse events – respiratory depression – hypotension – frequency of endotracheal intubation – ICU admission – neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance

		• healthcare resource use
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was 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/ • Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.	
17.	Analysis of sub-groups	In the presence of heterogeneity, sub-group analysis will be conducted: 1) according to the risk of bias of individual studies 2) by age (older people/adults/children) 3) study location (UK, US, Europe and rest of the world) 4) route of administration 5) drug dose	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	September 2019	
22.	Anticipated completion date	To be determined	

<table>
<tr><td rowspan="7">23.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact Angela Cooper
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Angela.cooper@rcplondon.ac.uk
5b Named contact e-mail
epilepsies@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:
Gill Ritchie, Guideline Lead
Angela Cooper, Senior Research Fellow
Rafina Yarde, Systematic reviewer</td></tr>
</table>

		Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	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.
28.	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/documents.
29.	Other registration details	
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol if there is one.]
31.	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.
32.	Keywords	Epilepsy, prolonged seizures, anti-epileptic drugs
33.	Details of existing review	

	of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[121] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following reviews:

- What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What antiepileptic drugs (monotherapy) are effective in the treatment of status epilepticus?
- What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?
- What AEDs (monotherapy) are effective in the treatment of prolonged seizures?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[121]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 2: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 5 of 12 CENTRAL to 2021 Issue 5 of 12	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5

7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Anticonvulsants/
28.	exp Acetazolamide/
29.	exp Carbamazepine/
30.	exp Chloral hydrate/
31.	exp Clomethiazole/
32.	exp Clonazepam/
33.	exp Clorazepate Dipotassium/
34.	exp Diazepam/
35.	exp Ethosuximide/
36.	exp Levetiracetam/
37.	exp Lorazepam/
38.	exp Mephenytoin/
39.	exp Mephobarbital/
40.	exp Midazolam/
41.	exp Methazolamide/
42.	exp Nitrazepam/
43.	exp Paraldehyde/
44.	exp Pentobarbital/
45.	exp Phenobarbital/
46.	exp Phenytoin/
47.	exp Primidone/
48.	exp Propofol/
49.	exp Temazepam/
50.	exp Thiopental/
51.	exp Topiramate/
52.	exp Trimethadione/
53.	exp Valproic Acid/

54.	exp Vigabatrin/
55.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
56.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
57.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
58.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
59.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
60.	hyperbaric oxygen.ti,ab.
61.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
62.	*Adrenal Cortex Hormones/ or *adrenocorticotropic hormone/ or *cosyntropin/
63.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
64.	or/27-63
65.	randomized controlled trial.pt.
66.	controlled clinical trial.pt.
67.	randomi#ed.ti,ab.
68.	placebo.ab.
69.	randomly.ti,ab.
70.	Clinical Trials as topic.sh.
71.	trial.ti.
72.	or/65-71
73.	Meta-Analysis/

74.	exp Meta-Analysis as Topic/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(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.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	26 and 64
85.	84 and (72 or 83)

Embase (Ovid) search terms

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp Anticonvulsants/
26.	exp Acetazolamide/
27.	exp Carbamazepine/
28.	exp Chloral hydrate/
29.	exp Clomethiazole/
30.	exp Clonazepam/

31.	exp Clorazepate Dipotassium/
32.	exp Diazepam/
33.	exp Ethosuximide/
34.	exp Lorazepam/
35.	exp Mephenytoin/
36.	exp Mephobarbital/
37.	exp Midazolam/
38.	exp Methazolamide/
39.	exp Nitrazepam/
40.	exp Paraldehyde/
41.	exp Pentobarbital/
42.	exp Phenobarbital/
43.	exp Phenytoin/
44.	exp Primidone/
45.	exp Propofol/
46.	exp Temazepam/
47.	exp Thiopental/
48.	exp Topiramate/
49.	exp Trimethadione/
50.	exp Valproic Acid/
51.	exp Vigabatrin/
52.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
53.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
54.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
55.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.

56.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
57.	hyperbaric oxygen.ti,ab.
58.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
59.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
60.	*corticosteroid/ or *tetracosactide/
61.	or/25-60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	systematic review/
73.	meta-analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(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.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	24 and 61
84.	83 and (71 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] explode all trees
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] explode all trees
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Anticonvulsants] explode all trees
#8.	MeSH descriptor: [Acetazolamide] explode all trees

#9.	MeSH descriptor: [Carbamazepine] explode all trees
#10.	MeSH descriptor: [Chloral Hydrate] explode all trees
#11.	MeSH descriptor: [Chlormethiazole] explode all trees
#12.	MeSH descriptor: [Clonazepam] explode all trees
#13.	MeSH descriptor: [Clorazepate Dipotassium] explode all trees
#14.	MeSH descriptor: [Diazepam] explode all trees
#15.	MeSH descriptor: [Ethosuximide] explode all trees
#16.	MeSH descriptor: [Lorazepam] explode all trees
#17.	MeSH descriptor: [Mephenytoin] explode all trees
#18.	MeSH descriptor: [Mephobarbital] explode all trees
#19.	MeSH descriptor: [Midazolam] explode all trees
#20.	MeSH descriptor: [Methazolamide] explode all trees
#21.	MeSH descriptor: [Nitrazepam] explode all trees
#22.	MeSH descriptor: [Paraldehyde] explode all trees
#23.	MeSH descriptor: [Pentobarbital] explode all trees
#24.	MeSH descriptor: [Phenobarbital] explode all trees
#25.	MeSH descriptor: [Phenytoin] explode all trees
#26.	MeSH descriptor: [Primidone] explode all trees
#27.	MeSH descriptor: [Propofol] explode all trees
#28.	MeSH descriptor: [Temazepam] explode all trees
#29.	MeSH descriptor: [Thiopental] explode all trees
#30.	MeSH descriptor: [Topiramate] explode all trees
#31.	MeSH descriptor: [Trimethadione] explode all trees
#32.	MeSH descriptor: [Valproic Acid] explode all trees
#33.	MeSH descriptor: [Vigabatrin] explode all trees
#34.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline):ti,ab
#35.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*):ti,ab
#36.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide):ti,ab
#37.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa

	or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide):ti,ab
#38.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate):ti,ab
#39.	hyperbaric oxygen:ti,ab
#40.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids):ti,ab
#41.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin):ti,ab
#42.	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#43.	MeSH descriptor: [Adrenocorticotropic Hormone] explode all trees
#44.	MeSH descriptor: [Cosyntropin] explode all trees
#45.	(or #7-#44)
#46.	#6 and #45

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner

	syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.

50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/

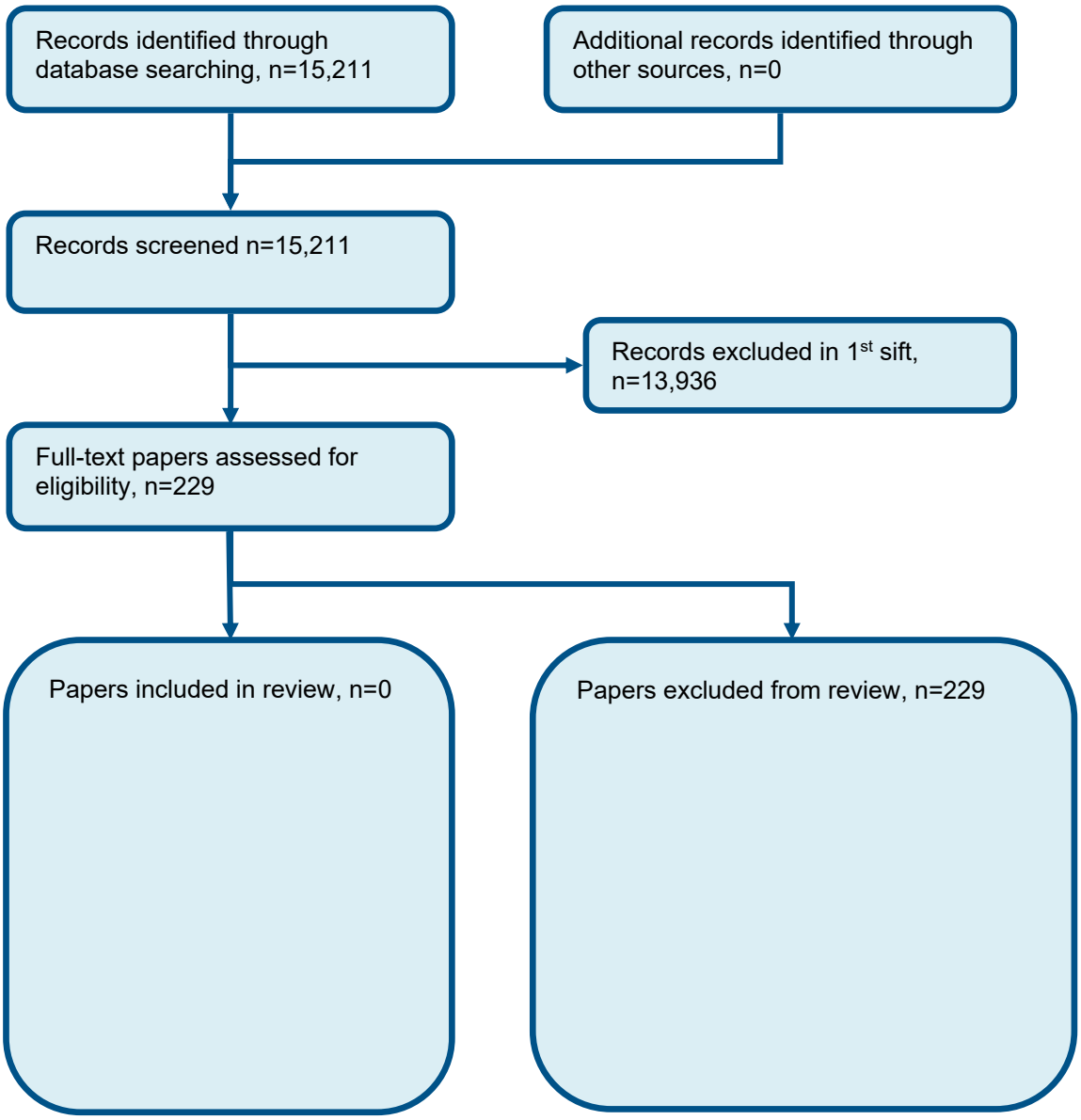
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of monotherapy for prolonged seizures



Appendix D Effectiveness evidence

No evidence was identified.

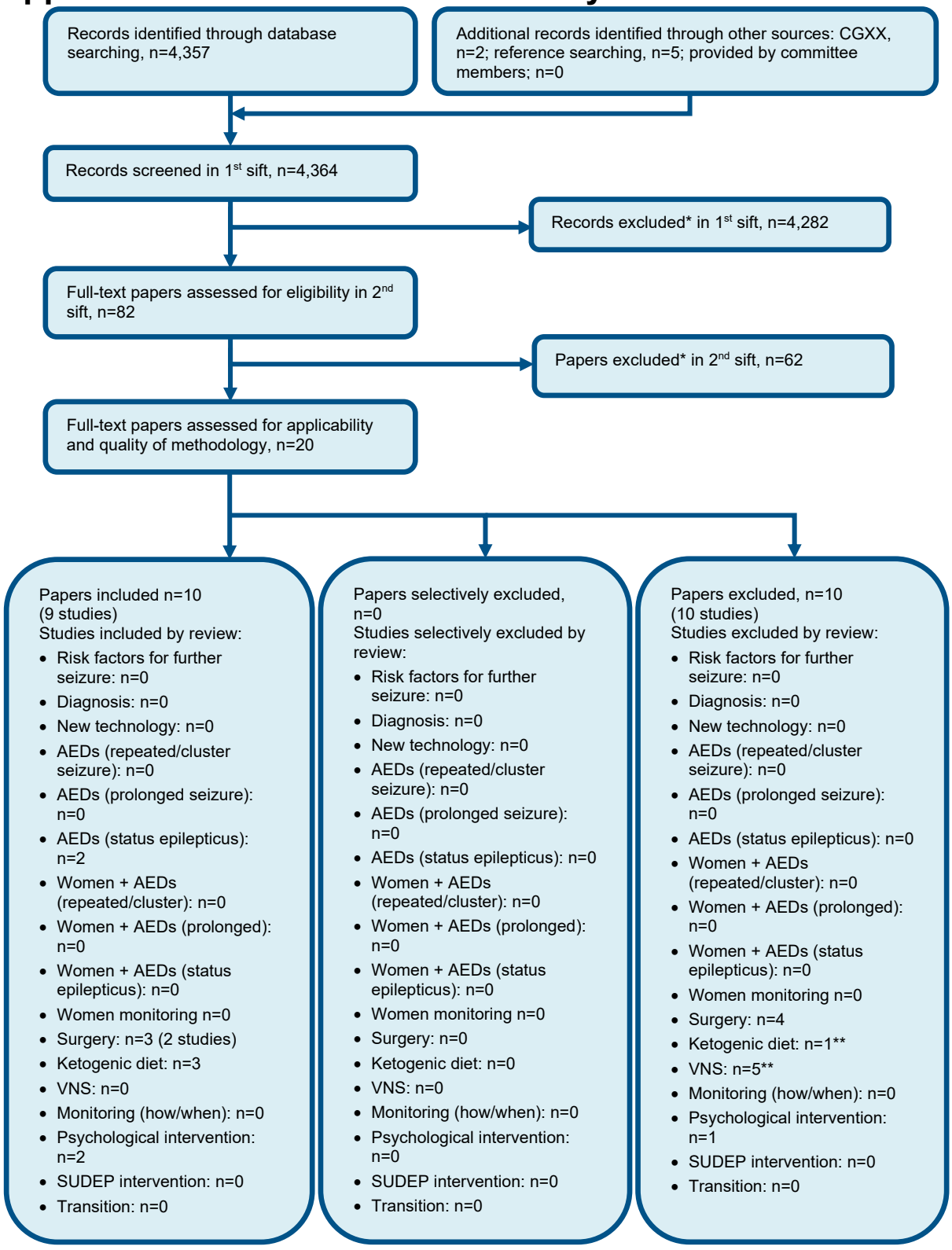
Appendix E Forest plots

No evidence was identified.

Appendix F GRADE tables

No evidence was identified.

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the

Appendix H Economic evidence tables

None

Appendix I Health economic model

No original economic modelling was undertaken.

Appendix J Excluded studies

J.1 Clinical studies

Table 4: Studies excluded from the clinical review

Reference	Exclusion reason
Abou-Khalil 2013[1]	Comparison does not match protocol: autoinjector placebo
Ag Sguder 2016[2]	Incorrect study design retrospective cohort
Agarwal 2007[3]	Incorrect population
Ahmad 2006[4]	Incorrect population
Alldredge 2001[5]	Incorrect population
Amiri-Nikpour 2018[6]	Incorrect population
Amouian 2014[7]	Non-English language publication (Arabic)
Appleton 1995[8]	Incorrect population
Appleton 2004[9]	NMA; incorrect population
Arya 2015[10]	NMA; incorrect population
Ashrafi 2010[11]	Incorrect population
Banta- Banzali 2012[12]	Conference abstract
Bauerschmidt 2017[13]	Incorrect study design; non-systematic review
Bayrlee 2015[14]	Incorrect study design; non-systematic review
Baysun 2005[15]	Incorrect population
Bebin 1994[16]	Conference abstract
Beghi 2018[17]	Incorrect study design; health economic study
Bergin 2008[18]	Incorrect study design; non-systematic review
Bhattacharyya 2006[19]	Study analysed according to seizure number not patient data
Bleck 2013[20]	Incorrect study design; study protocol of unpublished study
Brigo 2012[30]	Systematic review; incorrect population
Brigo 2013[25]	Systematic review; incorrect population
Brigo 2015[28]	Incorrect population
Brigo 2015[29]	Systematic review; incorrect population
Brigo 2016[21]	Systematic review; incorrect population
Brigo 2016[22]	Systematic review; incorrect population
Brigo 2017[23]	Systematic review; incorrect population
Brigo 2018[24]	Systematic review; incorrect population
Brigo 2018[27]	Systematic review; incorrect population
Brigo 2019[26]	Systematic review; incorrect population
Cereghino 2002 [31]	Incorrect population
Cereghino, 1998[32]	Incorrect population

Reference	Exclusion reason
Chakravarthi 2014[34]	Incorrect population
Chakravarthi 2015[33]	Incorrect population
Chamberlain 1997[35]	Incorrect population
Chamberlain 2014[36]	Incorrect population
Chen 2011[37]	Incorrect population
Chitsaz 2013[38]	Incorrect population
Collins 2003[39]	Incorrect population
Dalziel 2017[41]	Incorrect population
Dalziel 2019[40]	Incorrect population
de 2010[43]	Incorrect study design; longitudinal cross over
de Assis 2012[42]	Incorrect study design; non-systematic review
DeToledo 2000[44]	Incorrect study design; narrative review
Doshi 2010[45]	Systematic review; incorrect population
Dreifuss 1998[46]	Incorrect population
Fa Yyazi 2012[47]	Incorrect intervention
Fallah 2007[48]	Incorrect population
Farrokh 2019[49]	Systematic review; incorrect population
Fisgin 2002[50]	Incorrect population
Fitzgerald 2003[51]	Incorrect study design; retrospective observational study
Gathwala 2012[52]	Incorrect population
Gilad 2008[53]	Incorrect population
Glauser 2016[54]	Systematic review; incorrect population
Gomes 2018[55]	Systematic review; incorrect population
Gujjar 2017[56]	Incorrect population
Gunawan 2015[57]	Incorrect population
Gunawan 2015[57]	Incorrect population
Hofler 2013[58]	Systematic review of non-randomised studies
Holsti 2010[59]	Incorrect population
Holsti 2010[60]	Incorrect population
Huertas Gonzalez 2019[61]	Non-English language publication (Spanish)
Husain 2015[62]	Unavailable
Isguder 2014[63]	Incorrect study design; retrospective cohort
Jain 2016[64]	Systematic review; incorrect population
Javadzadeh 2012[65]	Incorrect population
Jenkinson 2011[66]	Incorrect study design; non-systematic review
Kapur (ESETT Trial) 2019[67]	Incorrect population
Kellinghaus 2015[68]	Incorrect population
Kellinghaus 2018[69]	Incorrect study design; registry data
Khajeh 2018[70]	Incorrect population
Kinirons 2008[71]	Incorrect study design; literature review
Knake 2008[72]	Incorrect study design; retrospective cohort
Kriel 1991 [74]	Incorrect study design; questionnaire results
Kriel 1999[75]	Incorrect population
Kriel 2009[73]	Incorrect study design; commentary
Ku 2018[76]	Incorrect population

Reference	Exclusion reason
Lahat 2000[77]	Incorrect population
Lalji 1967[78]	Incorrect study design; non-randomised study
Lambrechtsen 2008[79]	Incorrect study design; retrospective cohort
Langer 2014[80]	Incorrect study design; retrospective cohort
Lee 2005[81]	Incorrect population
Lee 2016[82]	Commentary on discontinued study
Legros 2014[83]	Incorrect population
Leppik 1983[84]	Incorrect intervention
Liu 2012[85]	Systematic review; incorrect population
Lombroso 1989[86]	Incorrect study design; non-randomised study
Lowenstein 1988[91]	Incorrect study design; retrospective and prospective cohort
Lowenstein 1999[90]	Unavailable abstract
Lowenstein 2001[89]	Incorrect study design; protocol
Lowenstein 2003[87]	Unavailable
Lowenstein 2005[88]	Incorrect study design; literature review
Lyttle 2017[92]	Incorrect population
Lyttle 2019[93]	Incorrect population
Mahmoud 2018[94]	Systematic review; incorrect population
Mahmoudian 2004[96]	Incorrect population
Mahmoudian 2006[95]	Incorrect study design; case control study
Malamiri 2012[97]	Incorrect population
Malu 2014[98]	Incorrect population
Masapu 2018[99]	Incorrect population
Mayer 2002[100]	Incorrect study design; retrospective cohort study
McIntyre 2005[101]	Incorrect population
McKee 2015[102]	Incorrect study design; review
McMullan 2010[103]	Systematic review; incorrect population
McTague 2012[104]	Incorrect study design; observational study
McTague 2018[105]	Systematic review; incorrect population
Mehta 2007[106]	Incorrect population
Menon 2013[107]	Incorrect study design; literature review
Misra 2006[112]	Incorrect population
Misra 2012[111]	Incorrect population
Misra 2016[110]	Incorrect population
Misra 2017[109]	Unavailable
Misra 2017[108]	Incorrect population
Mittal 2006[113]	Incorrect population
Momen 2015[114]	Incorrect population
Morales 2015[115]	Incorrect study design; observational study
Mpimbaza 2008[116]	Incorrect population
Muhlhofer 2019[117]	Incorrect study design; observational study
Mundlamuri 2015[118]	Incorrect population
Murdoch 2007[119]	Incorrect population
Murthy 2006[120]	Incorrect study design; literature review
Navarro 2011[122]	Incorrect population

Reference	Exclusion reason
Navarro 2016[123]	Incorrect population
Neligan 2010[124]	Systematic review; incorrect population
Nene 2019[125]	Incorrect population
Newey 2017[126]	Incorrect population
Ngampoopun 2018[127]	Incorrect study design; observational study
Niermeijer 2003[128]	Incorrect study design; narrative review
Otto 1968[129]	Incorrect study design; abstract only
Owusu 2019[130]	Incorrect study design; retrospective cohort
Pang 2005[131]	Incorrect study design; literature review
Papavasiliou 2004[132]	Incorrect study design; case series
Parviainen 2007[133]	Incorrect population
Pinto 2016[134]	Incorrect population
Poplawska 2015[135]	Incorrect study design; narrative review
Portela 2015[136]	Incorrect population
Prabhakar 2013[137]	Systematic review; incorrect population
Prasad 2001[138]	Incorrect study design; retrospective cohort
Prasad 2007[139]	Systematic review; incorrect population
Prasad 2013[141]	Incorrect population
Prasad 2014[140]	Systematic review; incorrect population
Qureshi 2002[142]	Incorrect study design; comparative audit
Rajiv 2019[143]	Systematic review; incorrect population
Rantsch 2011[144]	Incorrect study design; retrospective cohort
Rantsch 2013[145]	Incorrect study design; retrospective cohort
Raspall-Chaure 2006[146]	Systematic review; incorrect population
Reif 2018[147]	Incorrect study design; case report
Remy 1992[148]	Incorrect population
Reznik 2016[149]	Incorrect study design; narrative review
Rosenow 2002[150]	Incorrect study design; narrative review
Rossetti 2004[154]	Incorrect study design; retrospective cohort
Rossetti 2008[152]	Incorrect study design; observational study
Rossetti 2011[153]	Incorrect population
Rossetti 2018[151]	Incorrect study design; narrative review
Ruegg 2003[155]	Incorrect study design; narrative review
Sabers 2013[156]	Incorrect population
Sanchez Fernandez 2014[157]	Incorrect study design; literature review
Sanchez Fernandez 2019[158]	Incorrect study design; economic analysis
Santamarina 2013[159]	Incorrect study design; retrospective cohort
Scott 1999[160]	Incorrect population
Shah 2005 [161]	Incorrect population
Shaner 1985[162]	Incorrect study design; abstract only
Shaner 1988[163]	Incorrect population
Shibata 2016[164]	Incorrect study design; non-randomised study
Shorvon 2011[166]	Incorrect study design; narrative review
Shorvon 2011[167]	Incorrect study design; narrative review
Shorvon 2012[165]	Incorrect study design; narrative review

Reference	Exclusion reason
Silbergleit 2011[170]	Systematic review; incorrect population
Silbergleit 2012[168]	Incorrect population
Silbergleit 2013[169]	Incorrect population
Singh 2009[171]	Incorrect population
Singhi 2002[172]	Incorrect population
Sirven 2003[173]	Incorrect study design; narrative review
Sivakumar 2015[174]	Incorrect study design; retrospective cohort
Skinner 2010[175]	Incorrect study design; case series
Smith 1971[177]	Incorrect study design, case series
Smith 2001[176]	Incorrect study design; narrative review
Sofou 2009[178]	Systematic review; incorrect population
Sorel 1981[179]	Incorrect study design; non-randomised study
Sreenath 2010[180]	Incorrect population
Stecker 1998[181]	Incorrect study design; retrospective and prospective cohort
Strzelczyk 2015[183]	Incorrect population
Strzelczyk 2016[182]	Incorrect population
Strzelczyk 2017[184]	Systematic review; incorrect population
Su 2016[185]	Incorrect population
Sutter 2013[190]	Incorrect study design; cohort study
Sutter 2014[189]	Incorrect study design; cohort study
Sutter 2015[188]	Incorrect study design; narrative review
Sutter 2017[186]	Incorrect study design; cohort study
Sutter 2018[187]	Systematic review; incorrect population
Talukdar 2009 [191]	Incorrect population
Tan 2010[192]	Incorrect population
Tanabe 2011[193]	Incorrect population
Tasker 2014[194]	Incorrect study design; narrative review
Thakker 2013[195]	Incorrect population
Thomson 2005[196]	Incorrect study design; literature review of cohort studies
Tonekaboni 2012[197]	Incorrect population
Towne 1999[198]	Incorrect study design; non-randomised stuy
Treiman 1985[199]	Incorrect study design; abstract only
Treiman 1991[200]	Unavailable abstract
Treiman 1998[201]	Incorrect population
Trinka 2009[202]	Unavailable
Trinka 2009[204]	Incorrect study design; narrative review
Trinka 2011[203]	Incorrect study design; narrative review
Trinka 2014[207]	Systematic review; incorrect population
Trinka 2015[205]	Incorrect study design; narrative review
Trinka 2016[206]	Incorrect study design; narrative review
Trinka 2017[208]	Incorrect study design; narrative review
Tripathi 2010 [209]	Incorrect population
Uges 2009[210]	Incorrect population
Uppal 2018[211]	Incorrect population
Vasquez 2019[212]	Incorrect study design, narrative review

Reference	Exclusion reason
Vohra 2015[213]	Incorrect population
Vossler 2019[214]	Incorrect study design; commentary
Walker 2003[216]	Incorrect study design; narrative review
Walker 2005[215]	Incorrect study design; guide
Welch 2015[217]	Incorrect population
Wheless 2008[220]	Incorrect study design; narrative review
Wheless 2010[218]	Incorrect study design, narrative review
Wheless 2019[219]	Incorrect population
Wilkes 2013[222]	Incorrect study design; narrative review
Wilkes 2014[221]	Systematic review; incorrect population
Willems 2019[223]	Systematic review; incorrect population
Won 2019[224]	Incorrect study design; retrospective cohort
Wongjirattikarn 2019[225]	Incorrect population
Yasiry 2014[226]	Systematic review; incorrect population
Zelano 2012[227]	Systematic review; incorrect population
Zhang 2019[228]	Systematic review; incorrect comparisons
Zhao 2016[229]	NMA; incorrect population

J.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 5: Studies excluded from the health economic review

Reference	Reason for exclusion
None	