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APPENDIX I

Summary of pivotal studies demonstrating benefit of levetiracetam in the treatment of epilepsy

Authors and year	Total number of patients/number given levetiracetam	Dose (mg/day)	Impact of levetiracetam on seizure frequency	Significant adverse events
Ben-Menachem and Falter, 2000[1]	286/181	3000	Significant benefit of LEV vs placebo both as add on ($p<0.001$) and as subsequent monotherapy	Incidence of adverse events similar in placebo and treatment groups
Betts et al., 2000[2]	119/80	2000 or 4000	Significant benefit of LEV vs placebo at 2000mg per day ($p<0.05$)	Somnolence, asthenia
Cereghino et al., 2000[3]	294/199	1000 or 3000	Significant benefit of LEV vs placebo (50% responder rate $p<0.01$)	Somnolence, asthenia, infection eg rhinitis
Shorvon et al., 2000[4]	324/212	1000 or 2000	Significant benefit of LEV vs placebo	No difference in adverse events vs placebo. Main side effects somnolence, asthenia
Ferrendelli et al, 2003[5]	78/78 (Patients older than 65 years)	1000 to 3000	Sub-set analysis of patients who participated in the open label KEEPER trial (total 1030 patients). 50% responder rate of 76.9%	Somnolence, asthenia. Medication well tolerated in older people
Cochrane review[6] (meta analysis of 11 trials, including the above)	1861/1565	1000 to 4000	Significant benefit of LEV vs placebo at every dose. Improved cognitive outcomes in adults	Somnolence, infection

References:

1. Ben-Menachem E and Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group. Epilepsia 2000; 41:1276-83
2. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 2000;9: 80-87
3. Cereghino JJ, Biton V, Abou-Khalil B, Dreifus F, Gauer LJ, Leppik I. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000; 55:236-242
4. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. Epilepsia 2000; 41:1179-86
5. Ferrendelli JA, French J, Leppik I, Morrell MJ, Herveuval A, Han J, Magnus L. Use of levetiracetam in a population of patients aged 65 years and older: subset analysis of the KEEPER trial. Epilepsy Behav. 2003 4: 702-9
6. Mbizvo G, Dixon P, Hutton J, Marson A. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. 2012; https://doi.org/10.1002/14651858.CD001901.pub2

APPENDIX II: Tabulated list of adverse reactions of levetiracetam – https://www.medicines.org.uk/emc/product/2293/smpc#gref (3.12.22)

Adverse reaction	Frequency of adverse reaction			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations	Nasopharyngitis			Infection
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated
Eye disorders			Diplopia, vision blurred	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders				Electrocardiogram QT prolonged
Respiratory, thoracic and mediastinal disorders		Cough		
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis
Renal and Urinary Disorders				Acute Kidney injury
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
General disorders and administration site conditions		Asthenia/fatigue		
Injury, poisoning and procedural complications			Injury	

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the above table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). * especially in Japanese populations

Information regarding paediatric population – copied verbatim from https://www.medicines.org.uk/emc/product/2293/smpc#gref (3.12.22)

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However, subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

APPENDIX III. Systematic review – complete details

Methodology

We summarized the evidence from recent meta-analyses comparing the effectiveness and safety of antiseizure medications (phenobarbital, phenytoin, carbamazepine, valproic acid, lamotrigine, lacosamide, levetiracetam, topiramate, oxcarbazepine, zonisamide, gabapentin) in adults and children with epilepsy.

PICO Question

EPI3. In adults and children with epilepsy, which antiseizure medications are effective and safe?

Population (P): Adults and children with epilepsy
Intervention (I): phenobarbital, phenytoin, carbamazepine, valproic acid, lamotrigine, lacosamide, levetiracetam, topiramate, oxcarbazepine, zonisamide, gabapentin
Comparator (C): head-to-head comparison
Outcomes (O):

List critical outcomes:

- **Critical outcome 1:** seizure recurrence
- **Critical outcome 2:** adverse effects

List important outcomes:

- **Important outcome 1:** Mortality
- **Important outcome 2:** Quality of life

Search strategy

Existing systematic reviews were identified by conducting searches in the following bibliographic databases:

- PubMed
- Embase
- Cochrane Register of Studies (CRS Web)
- ClinicalTrials.gov
- The World Health Organization International Clinical Trials Registry Platform (ICTRP)

Databases were searched for systematic reviews reporting on efficacy and safety of antiseizure medications. The term antiseizure medications (ASM) has been adopted and will replace the term antiepileptic drug in this guideline given the drugs considered are expected to prevent seizures rather than to prevent the development of epilepsy [1]. For the purpose of the systematic search, both anti-seizure medication and anti-epileptic drugs were used to prevent missing any data due to lexicon. Search strings were structured to take into account general and drug-specific terms, either as MeSH terms or keywords, including the combination of the following:

(i) Epilepsy OR epileptic OR epilep* OR seizure OR seizures;

(ii) Anticonvulsants OR antiepileptic* OR antiseizure OR ((phenobarbital OR phenobarb*) OR phenytoin OR carbamazepine OR (valproic acid OR valproate OR valpr*) OR lamotrigine OR levetiracetam OR topiramate OR zonisamide OR gabapentin OR oxcarbazepine;

(iii) (Efficacy OR effectiveness OR seizure recurrence OR seizure prevention) OR (adverse events OR Drug-Related Side Effects and Adverse Reactions OR adverse e* OR tolerability) OR (Mortality OR death OR survival) OR (Quality of life OR Life Quality OR Health-Related Quality Of Life OR Health Related Quality Of Life).

Restrictions were applied to include only studies on (i) humans, (ii) children, adolescents and adults (6 years or older), (iii) published in English language, and to exclude prophylactic treatment after traumatic brain injury (*Type of studies*). We restricted results to systematic reviews and meta-analyses, including network meta-analysis as the highest level of evidence[2]. The period of the searches covered from 1 January 2000 until 22 April 2022.

Data collection and analysis

Records retrieved from the bibliographic databases were assessed for eligibility by examining titles and abstracts, based on the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant based on their titles and abstracts were retrieved, examined and checked against inclusion criteria. Data from eligible studies were extracted into pre-defined templates that include the general characteristics of the study, population, intervention, comparator, and outcomes.

Three reviewers (MR, AH, AS) independently assessed the eligibility of the studies identified and extracted data from study reports. Discrepancies between the reviewers were resolved through consensus. The search strategy and results reporting the databases searched, the strategy used to search each database, the total number of citations retrieved from each database, and the reasons for excluding some publications after reviewing the full text have been carefully documented. The flow of articles throughout the search and up to the final cohort of included studies is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage.

Selection and coding of identified records

Mendeley was used for the management of references and for the selection of studies based on titles and abstracts, and was used to store the references and pdfs of the included studies for the final stages of the project. Data extraction was conducted by three authors (MR, AH, AS), with disagreements resolved by consensus. Data regarding population, comorbidities, type of ASM, sample size, mean age and gender distribution were extracted.

Quality assessment

The quality of the included systematic reviews was assessed with the **AMSTAR quality appraisal tool 2**. Three independent researchers (MR, AH, AS) applied the AMSTAR-2 checklist to the included studies, and any disagreements were resolved by consensus.

The certainty of the evidence was assessed using **GRADE** (Grading of Recommendations, Assessment, Development and Evaluations), and using **CiNeMA** approach in case of network meta-analysis, based on the GRADE framework. When available, we extracted the original assessments from the meta-analysis and network meta-analysis. GRADE assessment was based on:

- **Risk of bias (RoB):** We extracted the RoB ratings from the individual studies included in the meta-analyses (when available). We adjudicated RoB depending on the percentage of trials rated at low, high, and unclear risk of bias, weight of studies, sample size and number of studies available.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics I^2, which indicates the percentage of heterogeneity between effect sizes, and its 95% confidence interval (95% CI). When the 95% CI of the I^2 is not reported, we computed it and used it in our judgements. We judged inconsistency as serious when I^2 was over 75%.
- **Indirectness**: adjudicated depending on how indirect the reviewed evidence was in terms of population, intervention/comparator, and outcomes.
- **Imprecision**: The width of confidence intervals is included in our judgements, as well as the number of events and sample size. The optimal information size is estimated by taking into account the control group event rate, the relative risk reduction and a standard power calculation (α 0.05 and β 0.20).
- **Other considerations**: For this item we explored publication bias. We rated it as serious if there was evidence for publication bias in the meta-analyses, based on statistical tests. However, we did not downgrade the evidence if a meta-analysis did not investigate it.

For network meta-analysis (NMA), quality of evidence followed CINeMA (Certainty in Network Meta-Analysis) framework[3], which includes the assessment of within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence (inconsistency). We downgraded evidence by one level in case of serious limitation, and two levels if very serious. Whenever available, we referred to the quality of evidence rating in the original NMA.

Analysis of subgroups or subsets

As optimal ASM choice depends on seizure semiology, we a priori defined to report the outcomes separately for focal onset seizures (focal seizures with/without awareness, focal to bilateral tonic clonic) and generalized onset seizures (with or without other generalized seizure types such as myoclonus or absence seizures).

Results

List of systematic reviews and/or studies identified by the search process

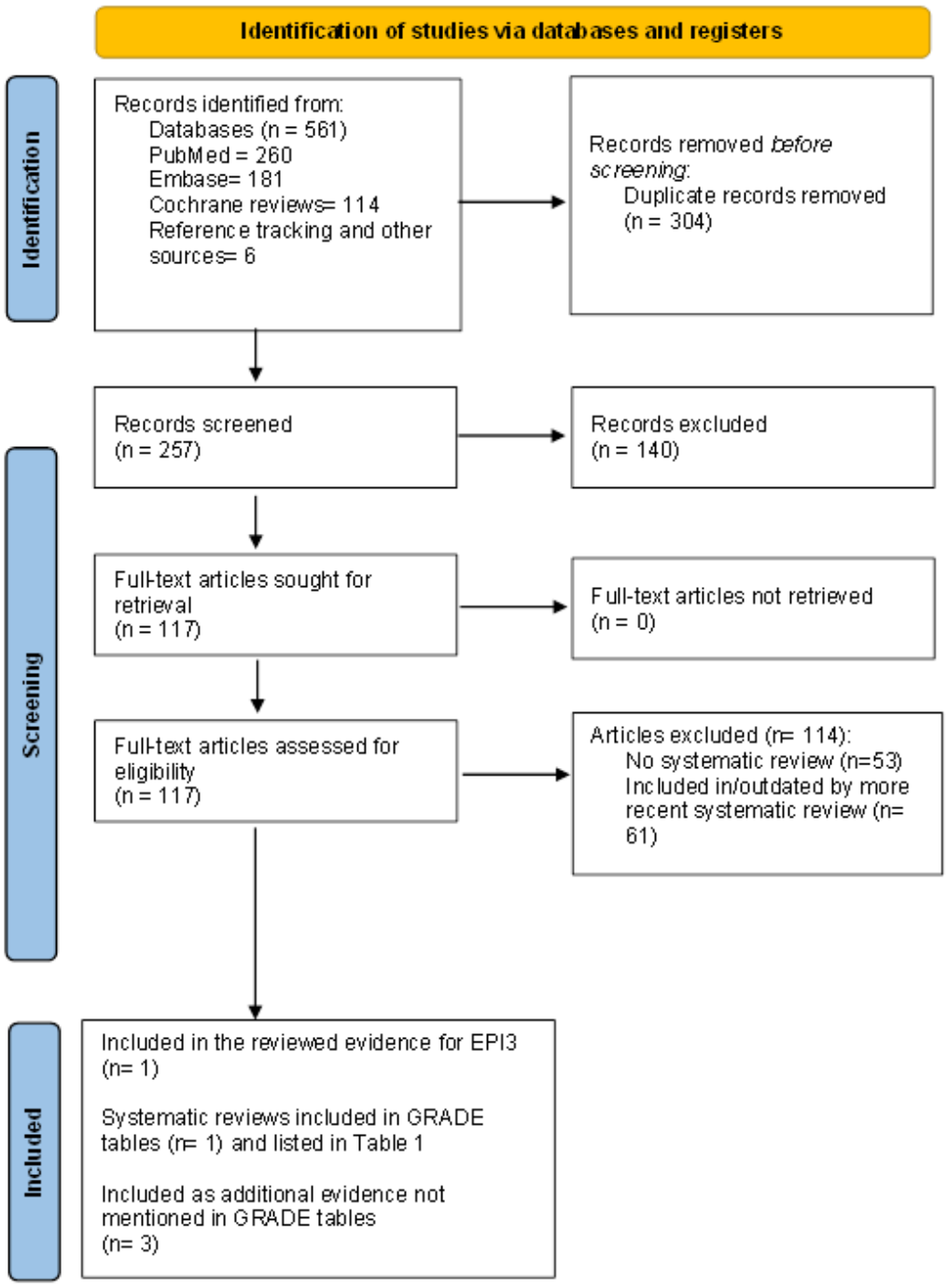


Figure 1: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only

INCLUDED IN GRADE TABLES/FOOTNOTES

Nevitt, S.J., Sudell, M., Cividini, S., Marson, A.G., Tudur Smith, C., 2022. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst. Rev. 2022. doi:10.1002/14651858.CD011412.pub4

EXCLUDED FROM GRADE TABLES/FOOTNOTES

Kanner, A.M., Ashman, E., Gloss, D., Harden, C., Bourgeois, B., Bautista, J.F., Abou-Khalil, B., Burakgazi-Dalkilic, E., Park, E.L., Stern, J., Hirtz, D., Nespeca, M., Gidal, B., Faught, E., French, J., 2018. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology 91, 74–81. doi:10.1212/WNL.0000000000005755

Leone, M.A., Giussani, G., Nevitt, S.J., Marson, A.G., Beghi, E., 2021. Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure. Cochrane Database Syst. Rev. 2021. doi:10.1002/14651858.CD007144.pub3

Kanner, A.M., Bicchi, M.M., 2022. Antiseizure Medications for Adults with Epilepsy: A Review. JAMA - J. Am. Med. Assoc. 327, 1269–1281. doi:10.1001/jama.2022.3880
(narrative review, but included as supporting evidence given the focus on antiseizure medication in adults and children)

Table 1: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
1	**Antiseizure medications** (phenobarbital, phenytoin, carbamazepine, valproic acid, lamotrigine, lacosamide, levetiracetam, topiramate, oxcarbazepine, zonisamide, gabapentin) **vs each other in adults and children with epilepsy.**	Seizure recurrence (time to)	Nevitt et al., 2022	Most recent high-quality network meta-analysis available on antiepileptic drug monotherapy for epilepsy, covering time to remission and lack of efficacy
		Adverse events (time to)	Nevitt et al., 2022	Most recent high-quality network meta-analysis available on antiepileptic drug monotherapy for epilepsy, covering adverse events
		Mortality	NA	NA
		Quality of life	NA	NA

Narrative description of studies that contributed to GRADE analysis[1]

Nevitt et al., 2020: To compare the time to treatment failure, remission and first seizure of 12 AEDs (carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate, lacosamide) currently used as monotherapy in children and adults with focal onset seizures (simple focal, complex focal or secondary generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus). Search methods For the latest update, we searched the following databases on 12 April 2021: the Cochrane Register of Studies (CRS Web), which includes PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Epilepsy Group Specialised Register and MEDLINE (Ovid, 1946 to April 09, 2021). We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators and experts in the field. Selection criteria We included randomised controlled trials of a monotherapy design in adults or children with focal onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types). Data collection and analysis This was an individual participant data (IPD) and network meta-analysis (NMA) review. Our primary outcome was 'time to treatment failure', and our secondary outcomes were 'time to achieve 12-month remission', 'time to achieve six-month remission', and 'time to first seizure post-randomisation'. We performed frequentist NMA to combine direct evidence with indirect evidence across the treatment network of 12 drugs. We investigated inconsistency between direct 'pairwise' estimates and NMA results via node splitting. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and we assessed the certainty of the evidence using the CiNeMA approach, based on the GRADE framework. We have also provided a narrative summary of the most commonly reported adverse events. Main results IPD were provided for at least one outcome of this review for 14,789 out of a total of 22,049 eligible participants (67% of total data) from 39 out of the 89 eligible trials (43% of total trials). We could not include IPD from the remaining 50 trials in analysis for a variety of reasons, such as being unable to contact an author or sponsor to request data, data being lost or no longer available, cost and resources required to prepare data being prohibitive, or local authority or country-specific restrictions. No IPD were available from a single trial of eslicarbazepine acetate, so this AED could not be included in the NMA. Network meta-analysis showed high-certainty evidence that for our primary outcome, ‘time to treatment failure’, for individuals with focal seizures; lamotrigine performs better than most other treatments in terms of treatment failure for any reason and due to adverse events, including the other first-line treatment carbamazepine; HRs (95% CIs) for treatment failure for any reason for lamotrigine versus: levetiracetam 1.01 (0.88 to 1.20), zonisamide 1.18 (0.96 to 1.44), lacosamide 1.19 (0.90 to 1.58), carbamazepine 1.26 (1.10 to 1.44), oxcarbazepine 1.30 (1.02 to 1.66), sodium valproate 1.35 (1.09 to 1.69), phenytoin 1.44 (1.11 to 1.85), topiramate 1.50 (1.23 to 1.81), gabapentin 1.53 (1.26 to 1.85), phenobarbitone 1.97 (1.45 to 2.67). No significant difference between lamotrigine and levetiracetam was shown for any treatment failure outcome, and both AEDs seemed to perform better than all other AEDs. For people with generalised onset seizures, evidence was more limited and of moderate certainty; no other treatment performed better than first-line treatment sodium valproate, but there were no differences between sodium valproate, lamotrigine or levetiracetam in terms of treatment failure; HRs (95% CIs) for treatment failure for any reason for sodium valproate versus: lamotrigine 1.06 (0.81 to 1.37), levetiracetam 1.13 (0.89 to 1.42), gabapentin 1.13 (0.61 to 2.11), phenytoin 1.17 (0.80 to 1.73), oxcarbazepine 1.24 (0.72 to 2.14), topiramate 1.37 (1.06 to 1.77), carbamazepine 1.52 (1.18 to 1.96), phenobarbitone 2.13 (1.20 to 3.79), lacosamide 2.64 (1.14 to 6.09). Network meta-analysis also showed high-certainty evidence that for secondary remission outcomes, few notable differences were shown for either seizure type; for individuals with focal seizures, carbamazepine performed better than gabapentin (12-month remission) and sodium valproate (six-month remission). No differences between lamotrigine and any AED were shown for individuals with focal seizures,
or between sodium valproate and other AEDs for individuals with generalised onset seizures. Network meta-analysis also showed high- to moderate-certainty evidence that, for ‘time to first seizure,’ in general, the earliest licensed treatments (phenytoin and phenobarbitone) performed

[1]Please note that this section includes the abstracts as taken directly from the publications.

better than the other treatments for individuals with focal seizures; phenobarbitone performed better than both first-line treatments carbamazepine and lamotrigine. There were no notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide) for either seizure type.
Generally, direct evidence (where available) and network meta-analysis estimates were numerically similar and consistent with confidence intervals of effect sizes overlapping. There was no important indication of inconsistency between direct and network meta-analysis results. The most commonly reported adverse events across all drugs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders; however, reporting of adverse events was highly variable across AEDs and across studies. Authors' conclusions High-certainty evidence demonstrates that for people with focal onset seizures, current first-line treatment options carbamazepine and lamotrigine, as well as newer drug levetiracetam, show the best profile in terms of treatment failure and seizure control as first-line treatments. For people with generalised tonic-clonic seizures (with or without other seizure types), current first-line treatment sodium valproate has the best profile compared to all other treatments, but lamotrigine and levetiracetam would be the most suitable alternative first-line treatments, particularly for those for whom sodium valproate may not be an appropriate treatment option. Further evidence from
randomised controlled trials recruiting individuals with generalised tonic-clonic seizures (with or without other seizure types) is needed.

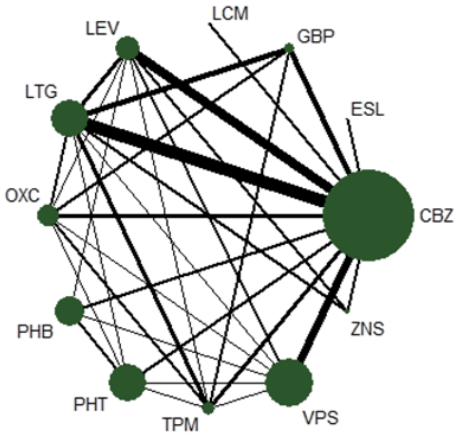
Grading the Evidence and Summary of findings

The certainty of the evidence for network meta-analyses was calculated with the CINeMA (Certainty in Network Meta-Analysis) framework[3]. Significant differences are displayed in **bold** in estimates and importance column.

Table 1
ASM monotherapy in focal onset epilepsy – time to remission

Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with carbamazepine as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 4

Geometry of the network displayed in figure.



Outcome: time to remission (12-month seizure-free status)

Population: adults and children with focal onset epilepsy (n=11911)
Intervention: Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Sodium valproate, Topiramate, Zonisamide

Comparator: carbamazepine

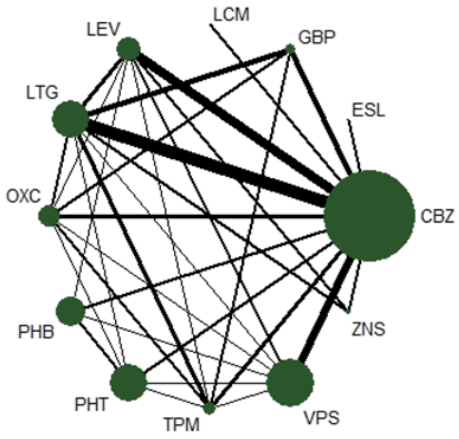
Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (4,5)		
Levetiracetam	Carbamazepine	3	1567	1.09 (0.92 to 1.29); I2 = 0%	1.08 (0.94 to 1.24)	22.30%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Gabapentin	Carbamazepine	1	666	**1.32 (1.09 to 1.60); I2 = NA**	**1.29 (1.06 to 1.57)**	20.40%	⨁⨁⨁⨁ HIGH	CRITICAL	**Carbamazepine better than gabapentin**

Lacosamide	Carbamazepine	1	806	1.00 (0.83 to 1.19); I2 = NA	1.00 (0.81 to 1.22)	100.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Lamotrigine	Carbamazepine	2	907	1.08 (0.91 to 1.28); I2 = 0%	1.06 (0.93 to 1.22)	18.40%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Oxcarbazepine	Carbamazepine	2	591	0.97 (0.78 to 1.20); I2 = 0%	0.95 (0.78 to 1.15)	17.80%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Phenobarbitone	Carbamazepine	4	525	1.00 (0.73 to 1.35); I2 = 42%	1.03 (0.77 to 1.38)	16.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Phenytoin	Carbamazepine	3	430	1.03 (0.78 to 1.37); I2 = 0%	1.04 (0.84 to 1.29)	21.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Sodium valproate	Carbamazepine	5	816	1.06 (0.86 to 1.30); I2 = 30%	1.08 (0.91 to 1.29)	17.70%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Topiramate	Carbamazepine	2	962	1.20 (1.00 to 1.44); I2 = 0%	1.13 (0.94 to 1.36)	21.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Zonisamide	Carbamazepine	1	582	1.05 (0.85 to 1.30); I2 = NA	1.10 (0.94 to 1.29)	18.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference

1. Order of drugs in the table: alphabetical.
2. HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. Certainty of evidence: several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence

Grade Table 2: ASM monotherapy in focal onset epilepsy – time to remission
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with lamotrigine as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 5

Geometry of the network displayed in figure.



Outcome: time to remission (12-month seizure-free status)

Population: adults and children with focal onset epilepsy (n=11911)
Intervention: Gabapentin, Lacosamide, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Sodium valproate, Topiramate, Zonisamide

Comparator: lamotrigine

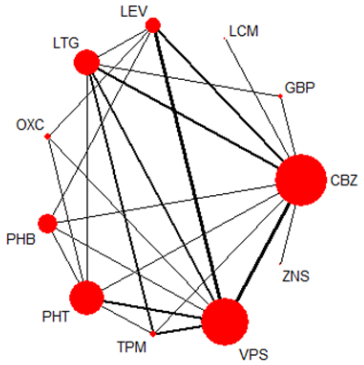
Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (4,5)		
Levetiracetam	Lamotrigine	2	902	1.02 (0.86 to 1.20); I2 = 0%	1.01 (0.87 to 1.18)	23.60%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Carbamazepine	Lamotrigine	2	907	0.92 (0.78 to 1.09); I2 = 0%	0.94 (0.82 to 1.08)	18.40%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference

Gabapentin	Lamotrigine	1	660	1.21 (1.00 to 1.47); I2 = NA	1.21 (0.99 to 1.48)	19.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Lacosamide	Lamotrigine	no direct evidence	no direct evidence	No direct evidence	0.94 (0.73 to 1.20)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Oxcarbazepine	Lamotrigine	1	511	0.87 (0.69 to 1.01); I2 = NA	0.89 (0.72 to 1.10)	15.60%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Phenobarbitone	Lamotrigine	no direct evidence	no direct evidence	No direct evidence	0.97 (0.71 to 1.33)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Phenytoin	Lamotrigine	no direct evidence	no direct evidence	No direct evidence	0.98 (0.76 to 1.25)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Sodium valproate	Lamotrigine	3	267	1.35 (0.68 to 2.67); I2 = 0%	1.02 (0.83 to 1.25)	4.10%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Topiramate	Lamotrigine	2	683	1.12 (0.92 to 1.36); I2 = 0%	1.06 (0.88 to 1.29)	19.50%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Zonisamide	Lamotrigine	1	658	1.07 (0.88 to 1.29); I2 = NA	1.04 (0.87 to 1.23)	24.70%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference

1. Order of drugs in the table: alphabetical.
2. HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. Certainty of evidence: several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence

Grade Table 3: ASM monotherapy in generalized onset epilepsy – time to remission
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with sodium valproate as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 6

Geometry of the network displayed in figure.



Outcome: time to remission (12-month seizure-free status)

Population: adults and children with generalized onset epilepsy
Intervention: Gabapentin, Lacosamide, Lamotrigine, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Topiramate, Zonisamide

Comparator: Sodium valproate

Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (4,5)		
Levetiracetam	Sodium valproate	2	1032	1.10 (0.59 to 2.04); I2: 55%	0.99 (0.82 to 1.20)	53.20%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Carbamazepine	Sodium valproate	4	412	1.01 (0.72 to 1.43); I2 = 0%	1.01 (0.83 to 1.22)	40.40%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Phenobarbitone	Sodium valproate	2	98	1.15 (0.53 to 2.49); I2 =42%	1.32 (0.88 to 2.00)	12.40%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Phenytoin	Sodium	4	269	0.87 (0.55 to	0.96 (0.75	36.10%	⨁⨁⨁⨁	CRITICAL	No difference

	valproate			1.40); I2 = 0%	to 1.28)		HIGH		
Lamotrigine	Sodium valproate	3	555	1.27 (0.64 to 2.50); I2 = 0%	1.19 (0.95 to 1.50)	12.40%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Oxcarbazepine	Sodium valproate	No direct evidence	No direct evidence	No direct evidence	1.27 (0.85 to 1.90)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Topiramate	Sodium valproate	2	585	1.86 (0.94 to 3.71); I2 = 0%	1.08 (0.87 to 1.34)	4.30%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Gabapentin	Sodium valproate	No direct evidence	No direct evidence	No direct evidence	1.30 (0.82 to 2.07)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Lacosamide	Sodium valproate	No direct evidence	No direct evidence	No direct evidence	1.05 (0.56 to 1.94)	0.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference

1. Order of drugs in the table: alphabetical.
2. **Interpretation of results** HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. **Explanations for certainty of evidence:** several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence

Grade Table 4: ASM monotherapy in focal onset epilepsy – time to adverse events
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with carbamazepine as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 1

Outcome: time to adverse events
Population: adults and children with focal onset epilepsy (n=11911)
Intervention: Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Sodium valproate, Topiramate, Zonisamide
Comparator: carbamazepine

Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (4,5)		
Levetiracetam	Carbamazepine	3	1567	**0.60 (0.47 to 0.77); I2 = 35%**	**0.65 (0.47 to 0.90)**	28.80%	⊕⊕⊕⊕ HIGH	CRITICAL	**Levetiracetam better**
Gabapentin	Carbamazepine	2	681	**0.68 (0.53 to 0.89); I2 = 88%**	**0.58 (0.37 to 0.91)**	1.70%	⊕⊕⊕⊕ HIGH (7)	CRITICAL	**Gabapentin better**
Lacosamide	Carbamazepine	1	807	1.22 (0.84 to 1.79); I2 = NA	1.24 (0.65 to 2.37)	100.00%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Lamotrigine	Carbamazepine	9	2203	**0.57 (0.47 to 0.70); I2 = 0%**	**0.56 (0.44 to 0.73)**	32.90%	⊕⊕⊕⊕ HIGH	CRITICAL	**Lamotrigine better**
Oxcarbazepine	Carbamazepine	2	599	1.01 (0.73 to 1.38); I2 = 0%	0.75 (0.46 to 1.22)	18.40%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Phenobarbitone	Carbamazepine	4	520	**1.52 (1.06 to 2.19); I2 = 73%**	**1.99 (1.21 to 3.27)**	31.70%	⊕⊕⊕⊕ HIGH (7)	CRITICAL	**Carbamazepine better**
Phenytoin	Carbamazepine	3	428	0.83 (0.56 to 1.24); I2 = 0%	1.00 (0.66 to 1.53)	35.30%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Sodium	Carbamazepine	3	570	0.94 (0.70 to 1.26); I2	0.88 (0.59 to 1.29)	40.30%	⊕⊕⊕⊕	CRITICAL	No difference

valproate				= 0%			HIGH		
Topiramate	Carbamazepine	2	976	1.10 (0.88 to 1.39); I2 = 0%	0.99 (0.69 to 1.43)	29.60%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference
Zonisamide	Carbamazepine	1	583	0.96 (0.59 to 1.55); I2 = NA	0.70 (0.43 to 1.13)	17.90%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference

1. Order of drugs in the table: alphabetical.
2. **Interpretation of results** HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. **Explanations for certainty of evidence:** several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence
7. Large amount of heterogeneity present in pairwise meta-analysis (direct evidence), with heterogeneity likely due to difference in trial designs (e.g. age of participants). Numerical results from direct evidence and NMA were similar, therefore any heterogeneity was judged as not impacting results.

Grade Table 5: ASM monotherapy in focal onset epilepsy – time to adverse events
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with lamotrigine as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 2

Outcome: time to adverse events

Population: adults and children with focal onset epilepsy (n=11911)
Intervention: Gabapentin, Lacosamide, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Sodium valproate, Topiramate, Zonisamide

Comparator: lamotrigine

Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (GRADE) (4,5)		
Levetiracetam	Lamotrigine	2	902	0.84 (0.60 to 1.19); I2 =32%	1.16 (0.81 to 1.66)	14.6%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Carbamazepine	Lamotrigine	9	2203	**1.75 (1.43 to 2.14); I2 =0**	**1.77 (1.37 to 2.28)**	32.9%	⨁⨁⨁⨁ HIGH (7)	CRITICAL	**Lamotrigine better**
Gabapentin	Lamotrigine	1	676	1.50 (1.09 to 2.08); I2 =NA	1.02 (0.63 to 1.65)	21.1%	⨁⨁⨁⨁ HIGH	CRITICAL	No difference
Lacosamide	Lamotrigine	no direct evidence	no direct evidence	**no direct evidence**	**2.21 (1.10 to 4.41)**	0.0%	⨁⨁⨁⨀ MODERATE	CRITICAL	**Lamotrigine probably better**
Oxcarbazepine	Lamotrigine	1	521	**1.37 (1.05 to 1.81); I2 =NA**	**1.30 (1.02 to 1.66)**	17.1%	⨁⨁⨁⨁ HIGH	CRITICAL	**Lamotrigine better**
Phenobarbitone	Lamotrigine	no direct evidenc	no direct evidence	**no direct evidence**	**3.52 (2.04 to 6.09)**	0.0%	⨁⨁⨁⨀ MODERAT	CRITICAL	**Lamotrigine probably better**

		e					E		
Phenytoin	Lamotrigine	1	90	**0.89 (0.33 to 2.37); I2 =NA**	**1.78 (1.13 to 2.81)**	4.4%	⊕⊕⊕⊕ HIGH	CRITICAL	**Lamotrigine better**
Sodium valproate	Lamotrigine	3	267	**3.53 (1.28 to 9.71); I2 =0%**	**1.55 (1.02 to 2.38)**	4.3%	⊕⊕⊕⊕ HIGH	CRITICAL	**Lamotrigine better**
Topiramate	Lamotrigine	2	699	**2.20 (1.63 to 2.99); I2 =0%**	**1.75 (1.17 to 2.62)**	17.6%	⊕⊕⊕⊕ HIGH (7)	CRITICAL	**Lamotrigine better**
Zonisamide	Lamotrigine	1	658	0.90 (0.57 to 1.41); I2 =NA	1.24 (0.75 to 2.03)	20.3%	⊕⊕⊕⊕ HIGH	CRITICAL	No difference

1. Order of drugs in the table: alphabetical.
2. **Interpretation of results** HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. **Explanations for certainty of evidence:** several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence
7. Wide confidence intervals in NMA estimates led to down-grading of evidence.

Grade Table 6: ASM monotherapy in generalized onset epilepsy – time to adverse events
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis with sodium valproate as main comparator
Reference List: Nevitt et al., 2021 – From summary of findings table 3

Outcome: time to adverse events

Population: adults and children with generalized onset epilepsy (n=11911)
Intervention: Gabapentin, Lacosamide, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Lamotrigine, Topiramate, Zonisamide

Comparator: sodium valproate

Quality assessment				Summary of findings				Importance	Interpretation (6)
				Direct evidence	Network meta-analysis				
Intervention (1)	Comparator	No of studies	Participants	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (GRADE) (4,5)		
Levetiracetam	Sodium valproate	2	1032	0.79 (0.19 to 3.39); I2 =0%	1.21 (0.66 to 2.21)	14.7%	⨁⨁⨁⨁ HIGH (7)	CRITICAL	No difference
Carbamazepine	Sodium valproate	2	117	**0.74 (0.18 to 2.98); I2 =0%**	**1.96 (1.13 to 3.39)**	52.9%	⨁⨁⨁⨁ HIGH (7)	CRITICAL	**Sodium valproate better**
Phenobarbitone	Sodium valproate	2	94	0.26 (0.06 to 1.05); I2 =28%	2.14 (0.82 to 5.57)	4.1%	⨁⨁⨁⊖ MODERATE (7)	CRITICAL	Sodium valproate possibly better
Phenytoin	Sodium valproate	4	326	0.37 (0.06 to 2.13); I2 =0%	1.56 (0.75 to 3.24)	13.8%	⨁⨁⨁⨁ HIGH (7)	CRITICAL	No difference
Lamotrigine	Sodium valproate	3	560	1.88 (0.68 to 5.21); I2	0.86 (0.50 to 1.48)	20.3%	⨁⨁⨁⨁ HIGH (7)	CRITICAL	No difference

				=0%					
Oxcarbazepine	Sodium valproate	no direct evidence	no direct evidence	no direct evidence	1.00 (0.33 to 3.02)	0.0%	⊕⊕⊕⊖ MODERATE (7)	CRITICAL	Probably no difference
Topiramate	Sodium valproate	2	588	1.53 (0.59 to 3.97); I2 =54%	1.42 (0.82 to 2.46)	10.8%	⊕⊕⊕⊕ HIGH (7)	CRITICAL	No difference
Gabapentin	Sodium valproate	no direct evidence	no direct evidence	no direct evidence	0.66 (0.21 to 2.08)	0.0%	⊕⊕⊕⊕ HIGH (7)	CRITICAL	No difference
Lacosamide	Sodium valproate	no direct evidence	no direct evidence	no direct evidence	8.61 (1.29 to 57.5)	0.0%	⊕⊕⊖⊖ LOW (8)	CRITICAL	Probably better

1. Order of drugs in the table: alphabetical.
2. **Interpretation of results** HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-eLect analyses (pairwise and network meta-analysis). Heterogeneity (I2) presented for pairwise meta-analysis only
3. Direct evidence represents the proportion of the network estimate contributed by direct evidence
4. **Explanations for certainty of evidence:** several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD showed similar numerical results and no changes to conclusions. Therefore, any risks of bias within the trials was judged not to influence the overall results (no downgrade of certainty of evidence).
5. No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
6. Interpretation of network meta-analysis results took into account direct evidence for the comparison and certainty of the evidence
7. Wide confidence intervals in NMA estimates led to down-grading of evidence.
8. Very wide confidence intervals in NMA estimates led to down-grading twice the level of evidence.

Grade Table 7: ASM monotherapy in focal or generalized onset epilepsy – mortality
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis
Reference List: //

Outcome: mortality

Population: adults and children with focal or generalized onset epilepsy
Intervention: Gabapentin, Lacosamide, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Lamotrigine, Topiramate, Zonisamide, Sodium valproate

Comparator: any antiepileptic drug

Quality assessment								Summary of findings				Importance
								Direct evidence	Network meta-analysis			
No of studies	Participants	Design	Risk of bias	Inconsistency (5)	Indirectness	Imprecision	Other considerations	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (GRADE) (4)	
0	0	no evidence available					none				Not estimable	IMPORTANT

Grade Table 8: ASM monotherapy in focal or generalized onset epilepsy – quality of life
Author(s): Michele Romoli, Asma Hallab, Arjune Sen
Methods: Network-meta-analysis
Reference List: //

Outcome: quality of life

Population: adults and children with focal or generalized onset epilepsy
Intervention: Gabapentin, Lacosamide, Carbamazepine, Levetiracetam, Oxcarbazepine, Phenobarbitone, Phenytoin, Lamotrigine, Topiramate, Zonisamide, Sodiu valproate

Comparator: any antiepileptic drug

Quality assessment								Summary of findings				Importance
								Direct evidence	Network meta-analysis			
No of studies	Participants	Design	Risk of bias	Inconsistency (5)	Indirectness	Imprecision	Other considerations	Estimate HR (95%CI) (2)	Estimate HR (95%CI) (2)	Direct evidence (3)	Certainty of the evidence (GRADE) (4)	
0	0	no evidence available					none				Not estimable	IMPORTANT

Subgroup analysis

Regarding seizure semiology, results from the NMA reaching final stages of the systematic review[4] are reported according to focal or generalized onset. Regarding age, no data were found specifically for children or adults. Sensitivity analysis results adjusted for age returned estimates similar to those displayed in main results[4]. Age range for NMA was 1-95 years old, with 4/39 studies providing individual-patient data for NMA including people aged 15 or lower, and 35/39 studies including people older than 15 years.

Additional evidence not mentioned in GRADE tables

Kanner et al., 2020; Epilepsy affects approximately 65 million people worldwide. Persistent seizures are associated with a 20% to 40% risk of bodily injuries (eg, fractures, burns, concussions) over 12-month follow-up. The primary goal of epilepsy treatment is to eliminate seizures while minimizing adverse effects of antiseizure drugs (ASDs). OBSERVATIONS An epileptic seizure is defined as a sudden occurrence of transient signs and symptoms caused by abnormal and excessive or synchronous neuronal activity in the brain. Focal and generalized epilepsy are the 2 most frequent types of epilepsy; diagnosis is based on the type of seizures. There are 26 US Food and Drug Administration–approved medications for epilepsy, of which 24 have similar antiseizure efficacy for focal epilepsy and 9 have similar efficacy for generalized epilepsy. The decision to initiate an ASD should be individualized, but should be strongly considered after 2 unprovoked seizures or after 1 unprovoked seizure that occurred during sleep and/or in the presence of epileptiform activity on an electroencephalogram and/or in the presence of a structural lesion on the brain magnetic resonance imaging. The ASDs must be selected based on the seizure and epilepsy types, the epilepsy syndrome, and the adverse effects associated with the drug. For focal epilepsy, oxcarbazepine and lamotrigine are first-line therapy, while levetiracetam can be also considered if there is no history of psychiatric disorder. For generalized epilepsy, the selection of the ASD is based on the type of epilepsy syndrome and the patient's sex, age, and psychiatric history. Seizure freedom is achieved in approximately 60%to 70% of all patients. A total of 25%to 50% of patients also experience neurologic, psychiatric, cognitive, or medical disorders, such as mood, anxiety, and attention deficit disorders and migraines. For these patients, selecting an ASD should consider the presence of these disorders and concomitant use of medications to treat them. ASDs with cytochrome P450 enzyme-inducing properties (eg, carbamazepine, phenytoin) may worsen comorbid coronary and cerebrovascular disease by causing hyperlipidemia and accelerating the metabolism of concomitant drugs used for their treatment. They can also facilitate the development of osteopenia and osteoporosis. CONCLUSIONS AND RELEVANCE Epilepsy affects approximately 65 million people worldwide and is associated with increased rates of bodily injuries and mortality when not optimally treated. For focal and generalized epilepsy, selection of ASDs should consider the seizure and epilepsy types and epilepsy syndrome, as well as the patient's age and sex, comorbidities, and potential drug interactions.

Leone et al., 2021: There is considerable disagreement about the risk of recurrence following a first unprovoked epileptic seizure. A decision about whether to start antiepileptic drug treatment following a first seizure should be informed by information on the size of any reduction in risk of future seizures, the impact on long-term seizure remission, and the risk of adverse effects.
Objectives To review the probability of seizure recurrence, seizure remission, mortality, and adverse effects of antiepileptic drug (AED) treatment given immediately after the first seizure compared to controls (placebo, deferred treatment, or no treatment) in children and adults. Search methods For the latest

update, we searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to May 24, 2019) on 28 May 2019. There were no language restrictions. The Cochrane Register of Studies includes the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised or quasi-randomised, controlled trials from Embase, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP). Selection criteria Randomised controlled trials (RCTs) and quasi-RCTs that could be blinded or unblinded. People of any age with a first unprovoked seizure of any type. Included studies compared participants receiving immediate antiepileptic treatment versus those receiving deferred treatment, those assigned to placebo, and those untreated. Data collection and analysis Two review authors independently assessed the studies identified by the search strategy for inclusion in the review and extracted data. The certainty of the evidence for the outcomes was classified in four categories according to the GRADE approach. Dichotomous outcomes were expressed as Risk Ratios (RR) with 95% confidence intervals (CI). Time-to-event outcomes were expressed as Hazard Ratios (HR) with 95% CI. Only one trial used a double-blind design, and the two largest studies were unblinded. Most of the recurrences were generalized tonic-clonic seizures, a major type of seizures that is easily recognised, which should reduce the risk of outcome reporting bias. Main results After exclusion of irrelevant papers, six studies (eleven reports) were selected for inclusion. Individual participant data were available from the two largest studies for meta-analysis. Selection bias and attrition bias could not be excluded within the four smaller studies, but the two largest studies reported attrition rates and adequate methods of randomisation and allocation concealment. Only one small trial used a double-blind design and the other trials were unblinded; however, most of the recurrences were generalised tonic-clonic seizures, a type of seizure that is easily recognisable. Compared to controls, participants randomised to immediate treatment had a lower probability of relapse at one year (RR 0.49, 95% CI 0.42 to 0.58; 6 studies, 1634 participants; high-certainty evidence), at five years (RR 0.78; 95% CI 0.68 to 0.89; 2 studies, 1212 participants; high certainty evidence) and a higher probability of an immediate five-year remission (RR 1.25; 95% CI 1.02 to 1.54; 2 studies, 1212 participants; high-certainty evidence). However, there was no difference between immediate treatment and control in terms of five-year remission at any time (RR 1.02, 95% CI 0.87 to 1.21; 2 studies, 1212 participants; high-certainty evidence). Antiepileptic drugs did not affect overall mortality after a first seizure (RR 1.16; 95% CI 0.69 to 1.95; 2 studies, 1212 participants; high-certainty evidence). Compared to deferred treatment, treatment of the first seizure was associated with a significantly higher risk of adverse events (RR 1.49, 95% CI 1.23 to 1.79; 2 studies, 1212 participants; moderate-certainty evidence). We assessed the certainty of the evidence as moderate to low for the association of higher risk of adverse events when treatment of the first seizure was compared to no treatment or placebo, (RR 14.50, 95% CI 1.93 to 108.76; 1 study; 118 participants) and (RR 4.91, 95% CI 1.10 to 21.93; 1 study, 228 participants) respectively. Authors' conclusions Treatment of the first unprovoked seizure reduces the risk of a subsequent seizure but does not affect the proportion of patients in remission in the long term. Antiepileptic drugs are associated with adverse events, and there is no evidence that they reduce mortality. In light of this review, the decision to start antiepileptic drug treatment following a first unprovoked seizure should be individualised and based on patient preference, clinical, legal, and sociocultural factors.

Brigo et al., 2021: Background: This is an updated version of the Cochrane Review previously published in 2019. Absence seizures (AS) are brief epileptic seizures which present in childhood and adolescence. Depending on clinical features and electroencephalogram (EEG) findings they are divided into typical, atypical absences, and absences with special features. Typical absences are characterised by sudden loss of awareness and an EEG typically shows generalised spike wave discharges at three cycles per second. Ethosuximide, valproate and lamotrigine are currently used to treat absence seizures. This review aims to determine the best choice of antiepileptic drug for children and adolescents with AS.
Objectives: To review the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures (AS), when compared with placebo or each other.
Search methods: For the latest update we searched the Cochrane Register of Studies (CRS Web, 22 September 2020) and MEDLINE (Ovid, 1946 to September 21, 2020). CRS Web includes randomised or quasi-randomised, controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized

Registers of Cochrane Review Groups including Epilepsy. No language restrictions were imposed. In addition, we contacted Sanofi Winthrop, Glaxo Wellcome (now GlaxoSmithKline) and Parke Davis (now Pfizer), manufacturers of sodium valproate, lamotrigine and ethosuximide respectively.
Selection criteria: Randomised parallel group monotherapy or add-on trials which include a comparison of any of the following in children or adolescents with AS: ethosuximide, sodium valproate, lamotrigine, or placebo.
Data collection and analysis: Outcome measures were: 1. proportion of individuals seizure free at one, three, six, 12 and 18 months post randomisation; 2. individuals with a 50% or greater reduction in seizure frequency; 3. normalisation of EEG and/or negative hyperventilation test; and 4. adverse effects. Data were independently extracted by two review authors. Results are presented as risk ratios (RR) with 95% confidence intervals (95% CIs). We used GRADE quality assessment criteria to evaluate the certainty of evidence for the outcomes derived from all included studies.
Main results: On the basis of our selection criteria, we included no new studies in the present review. Eight small trials (total number of participants: 691) were included from the earlier review. Six of them were of poor methodological quality (unclear or high risk of bias) and seven recruited less than 50 participants. There are no placebo-controlled trials for ethosuximide or valproate, and hence, no evidence from randomised controlled trials (RCTs) to support a specific effect on AS for either of these two drugs. Due to the differing methodologies used in the trials comparing ethosuximide, lamotrigine and valproate, we thought it inappropriate to undertake a meta-analysis. One large randomised, parallel double-blind controlled trial comparing ethosuximide, lamotrigine and sodium valproate in 453 children with newly diagnosed childhood absence epilepsy found that at 12 months, seizure freedom was higher in patients taking ethosuximide (70/154, 45%) than in patients taking lamotrigine (31/146, 21%; $P < 0.001$), with no difference between valproate (64/146, 44%) and ethosuximide (70/154, 45%; $P > 0.05$). In this study, the frequency of treatment failures due to intolerable adverse events was significantly different among the treatment groups, with the largest proportion of adverse events in the valproic acid group (48/146, 33%) compared to the ethosuximide (38/154, 25%) and the lamotrigine (29/146, 20%) groups ($P < 0.037$). Overall, this large study demonstrates the superior effectiveness of ethosuximide and valproic acid compared to lamotrigine as initial monotherapy aimed to control seizures without intolerable adverse effects in children with childhood absence epilepsy. This study provided high certainty of the evidence for outcomes for which data were available. However, the certainty of the evidence provided by the other included studies was low, primarily due to risk of bias and imprecise results because of the small sample sizes. Hence, conclusions regarding the efficacy of ethosuximide, valproic acid and lamotrigine derive mostly from this single study.
Authors' conclusions: Since the last version of this review was published, we have found no new studies. Hence, the conclusions remain the same as the previous update. With regards to both efficacy and tolerability, ethosuximide represents the optimal initial empirical monotherapy for children and adolescents with AS. However, if absence and generalised tonic-clonic seizures coexist, valproate should be preferred, as ethosuximide is probably inefficacious on tonic-clonic seizures.

From Evidence to Recommendations

Table 3: Summary of findings table

Table	Population	Outcome	Intervention	Comparator	Estimate HR (95%CI)	Certainty of the Evidence
1	**Focal onset seizure**	**time to remission**	Gabapentin	Carbamazepine	**1.29 (1.06 to 1.57)**	⨁⨁⨁⨁ HIGH
			Lacosamide	Carbamazepine	1.00 (0.81 to 1.22)	⨁⨁⨁⨁ HIGH
			Lamotrigine	Carbamazepine	1.06 (0.93 to 1.22)	⨁⨁⨁⨁ HIGH
			Levetiracetam	Carbamazepine	1.08 (0.94 to 1.24)	⨁⨁⨁⨁ HIGH
			Oxcarbazepine	Carbamazepine	0.95 (0.78 to 1.15)	⨁⨁⨁⨁ HIGH
			Phenobarbitone	Carbamazepine	1.03 (0.77 to 1.38)	⨁⨁⨁⨁ HIGH
			Phenytoin	Carbamazepine	1.04 (0.84 to 1.29)	⨁⨁⨁⨁ HIGH
			Sodium valproate	Carbamazepine	1.08 (0.91 to 1.29)	⨁⨁⨁⨁ HIGH
			Topiramate	Carbamazepine	1.13 (0.94 to 1.36)	⨁⨁⨁⨁ HIGH
			Zonisamide	Carbamazepine	1.10 (0.94 to 1.29)	⨁⨁⨁⨁ HIGH
2	**Focal onset seizure**	**time to remission**	Carbamazepine	Lamotrigine	0.94 (0.82 to 1.08)	⨁⨁⨁⨁ HIGH
			Gabapentin	Lamotrigine	1.21 (0.99 to 1.48)	⨁⨁⨁⨁ HIGH
			Lacosamide	Lamotrigine	0.94 (0.73 to 1.20)	⨁⨁⨁⨁ HIGH
			Levetiracetam	Lamotrigine	1.01 (0.87 to 1.18)	⨁⨁⨁⨁ HIGH
			Oxcarbazepine	Lamotrigine	0.89 (0.72 to 1.10)	⨁⨁⨁⨁ HIGH
			Phenobarbitone	Lamotrigine	0.97 (0.71 to 1.33)	⨁⨁⨁⨁ HIGH
			Phenytoin	Lamotrigine	0.98 (0.76 to 1.25)	⨁⨁⨁⨁ HIGH
			Sodium valproate	Lamotrigine	1.02 (0.83 to 1.25)	⨁⨁⨁⨁ HIGH
			Topiramate	Lamotrigine	1.06 (0.88 to 1.29)	⨁⨁⨁⨁ HIGH
			Zonisamide	Lamotrigine	1.04 (0.87 to 1.23)	⨁⨁⨁⨁ HIGH
3	**Generalized onset seizure**	**time to remission**	Carbamazepine	Sodium valproate	1.01 (0.83 to 1.22)	⨁⨁⨁⨁ HIGH
			Phenobarbitone	Sodium valproate	1.32 (0.88 to 2.00)	⨁⨁⨁⨁ HIGH
			Phenytoin	Sodium valproate	0.96 (0.75 to 1.28)	⨁⨁⨁⨁ HIGH
			Lamotrigine	Sodium	1.19 (0.95 to 1.50)	⨁⨁⨁⨁ HIGH

				valproate		
			Oxcarbazepine	Sodium valproate	1.27 (0.85 to 1.90)	⊕⊕⊕⊕ HIGH
			Topiramate	Sodium valproate	1.08 (0.87 to 1.34)	⊕⊕⊕⊕ HIGH
			Gabapentin	Sodium valproate	1.30 (0.82 to 2.07)	⊕⊕⊕⊕ HIGH
			Levetiracetam	Sodium valproate	0.99 (0.82 to 1.20)	⊕⊕⊕⊕ HIGH
			Lacosamide	Sodium valproate	1.05 (0.56 to 1.94)	⊕⊕⊕⊕ HIGH
4	**Focal onset seizure**	**time to adverse events**	Gabapentin	Carbamazepine	**0.58 (0.37 to 0.91)**	⊕⊕⊕⊕ HIGH
			Lacosamide	Carbamazepine	1.24 (0.65 to 2.37)	⊕⊕⊕⊕ HIGH
			Lamotrigine	Carbamazepine	**0.56 (0.44 to 0.73)**	⊕⊕⊕⊕ HIGH
			Levetiracetam	Carbamazepine	**0.65 (0.47 to 0.90)**	⊕⊕⊕⊕ HIGH
			Oxcarbazepine	Carbamazepine	0.75 (0.46 to 1.22)	⊕⊕⊕⊕ HIGH
			Phenobarbitone	Carbamazepine	**1.99 (1.21 to 3.27)**	⊕⊕⊕⊕ HIGH
			Phenytoin	Carbamazepine	1.00 (0.66 to 1.53)	⊕⊕⊕⊕ HIGH
			Sodium valproate	Carbamazepine	0.88 (0.59 to 1.29)	⊕⊕⊕⊕ HIGH
			Topiramate	Carbamazepine	0.99 (0.69 to 1.43)	⊕⊕⊕⊕ HIGH
			Zonisamide	Carbamazepine	0.70 (0.43 to 1.13)	⊕⊕⊕⊕ HIGH
5	**Focal onset seizure**	**time to adverse events**	Carbamazepine	Lamotrigine	**1.77 (1.37 to 2.28)**	⊕⊕⊕⊕ HIGH
			Gabapentin	Lamotrigine	1.02 (0.63 to 1.65)	⊕⊕⊕⊕ HIGH
			Lacosamide	Lamotrigine	**2.21 (1.10 to 4.41)**	⊕⊕⊕⊖ MODERATE
			Levetiracetam	Lamotrigine	1.16 (0.81 to 1.66)	⊕⊕⊕⊕ HIGH
			Oxcarbazepine	Lamotrigine	**1.30 (1.02 to 1.66)**	⊕⊕⊕⊕ HIGH
			Phenobarbitone	Lamotrigine	**3.52 (2.04 to 6.09)**	⊕⊕⊕⊖ MODERATE
			Phenytoin	Lamotrigine	**1.78 (1.13 to 2.81)**	⊕⊕⊕⊕ HIGH
			Sodium valproate	Lamotrigine	**1.55 (1.02 to 2.38)**	⊕⊕⊕⊕ HIGH
			Topiramate	Lamotrigine	**1.75 (1.17 to 2.62)**	⊕⊕⊕⊕ HIGH
			Zonisamide	Lamotrigine	1.24 (0.75 to 2.03)	⊕⊕⊕⊕ HIGH
6	**Generalized onset**	**time to adverse**	Carbamazepine	Sodium valproate	**1.96 (1.13 to 3.39)**	⊕⊕⊕⊕ HIGH

seizure	**events**	Phenobarbitone	Sodium valproate	2.14 (0.82 to 5.57)	⨁⨁⨁⊖ MODERATE
		Phenytoin	Sodium valproate	1.56 (0.75 to 3.24)	⨁⨁⨁⨁ HIGH
		Lamotrigine	Sodium valproate	0.86 (0.50 to 1.48)	⨁⨁⨁⨁ HIGH
		Oxcarbazepine	Sodium valproate	1.00 (0.33 to 3.02)	⨁⨁⨁⊖ MODERATE
		Topiramate	Sodium valproate	1.42 (0.82 to 2.46)	⨁⨁⨁⨁ HIGH
		Gabapentin	Sodium valproate	0.66 (0.21 to 2.08)	⨁⨁⨁⨁ HIGH
		Levetiracetam	Sodium valproate	1.21 (0.66 to 2.21)	⨁⨁⨁⨁ HIGH
		Lacosamide	Sodium valproate	**8.61 (1.29 to 57.5)**	⨁⨁⊖⊖ LOW

Narrative summary of the evidence base	All antiseizure medications (ASMs) taken into account (carbamazepine, lamotrigine, oxcarbazepine, topiramate, gabapentin, sodium valproate, levetiracetam, lacosamide, zonisamide, phenytoin, phenobarbitone) are widely considered effective in controlling seizures. No systematic review of RCTs comparing these ASMs with placebo was found. It is considered unethical to conduct RCTs comparing standard ASMs, especially as monotherapy, with placebo in established epilepsy as epilepsy should be treated to decrease morbidity and premature mortality. Network meta-analysis found high-certainty evidence suggesting that, for focal onset seizures, carbamazepine performs better than gabapentin in terms of seizure remission (HR 1.29, 95%CI 1.06 to 1.57), and that carbamazepine has similar performance to other ASMs, including levetiracetam and lamotrigine. In focal onset epilepsy, levetiracetam and lamotrigine perform significantly better than carbamazepine in terms of adverse events (HR 0.56, 95%CI 0.44 to 0.73 for lamotrigine vs carbamazepine, HR 0.65, 95%CI 0.47 to 0.90 for levetiracetam vs carbamazepine). There is high certainty that, in generalized-onset seizures, valproic acid has an advantage over carbamazepine in terms of adverse events (HR 1.96, 95%CI 1.13 to 3.39). Given the teratogenic risks associated with sodium valproate if prescribed to women and girls who are able to have children, lamotrigine or levetiracetam should be used as first-line treatment in this population. Phenytoin despite being used as a first line drug, has a problematic pharmacokinetic profile. Levetiracetam and lamotrigine have similar efficacy and adverse event profile compared to sodium valproate in generalized onset seizures. All ASMs are associated with adverse effects. Phenobarbital is considered to be associated with a higher risk of short and long term tolerability problems. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.
Summary of the quality of evidence	For critical outcomes, the quality of evidence was HIGH or MODERATE For important outcomes, no estimates could be provided due to lack of data.
Balance of benefits versus harms	The balance of benefits versus harms is in favor of treatment of children and adults with focal onset epilepsy, with lamotrigine and levetiracetam being the ASMs with the most convenient risk/benefit profile. The balance of benefits versus harms is in favour of treatment of children and adults with generalized onset epilepsy.

Values and preferences including any variability and human rights issues	Epilepsy should be treated as treatment decreases morbidity and premature mortality and improves the quality of life of people with epilepsy.
Costs and resource use and any other relevant feasibility issues	Carbamazepine, lamotrigine, phenobarbital, phenytoin, and sodium valproate are included in the WHO list of essential medicines. Given the results of the current systematic review, it might be reasonable to discuss the inclusion of levetiracetam on the essential medicines list. Phenobarbital is commonly used as a first line drug in LMICs as it is much cheaper than other ASMs. Phenobarbital, being a controlled substance, means strict regulations in many countries can affect its accessibility.
Final recommendation(s)	Monotherapy with any of the standard ASMs (carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with generalized-onset epilepsy. Given the acquisition costs, phenobarbital should be offered as a first option if availability can be assured. Sodium valproate should be avoided in women of childbearing potential due to teratogenic risk. Considering risks and benefits of each ASM, it might be proposed to consider the following medications: - First line medications for generalized epilepsy: levetiracetam or lamotrigine or valproic acid for boys and men, girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children, women who are unable to have children. In women of child bearing potential, lamotrigine and levetiracetam are the first line options for generalized epilepsy If the first tried monotherapy does not suit, one of the alternative first line treatments should then be tried - Second line medications: lacosamide, phenobarbital - Third line medications: topiramate, phenytoin, carbamazepine, zonisamide. Clinicians should be aware that the following antiseizure medications may exacerbate seizures in people with absence or myoclonic seizures (generalized-onset): carbamazepine, gabapentin, lamotrigine (myoclonus), oxcarbazepine, phenytoin. Given the efficacy and tolerability profile and being mindful of potential long term side effects, if available, lamotrigine or levetiracetam should be offered as first line options in focal onset seizures. Considering risks an benefit of each ASM, it might be proposed to consider the following medications: - First line medications for focal onset epilepsy: levetiracetam or lamotrigine If the first tried monotherapy does not suit, the other first line treatment should then be tried

	- Second line medications: carbamazepine, lacosamide As this guideline is intended for use in non-specialist settings, add-on treatments are not considered in the current recommendation and a referral to a specialist should be made when monotherapy is unsuccessful.
Any additional remarks	Regulatory issues are a barrier to the access to antiseizure medications in some settings and needs to be addressed. Levetiracetam status among essential medicines may be revised on the basis of efficacy and tolerability emerging from this systematic review, also taking into account potential impact on costs.
Main research gaps	The current systematic review did not provide estimates according to patient subgroups, particularly regarding etiology and age. Therefore, further research focusing on efficacy and tolerability of antiseizure medications may further refine estimates for seizure prevention and adverse event occurrence.

Table 4: Evidence to decision table

*Please note * indicates evidence from overarching qualitative review.*

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognised priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Epilepsy affects approximately 50 million people worldwide. Seizures are associated with 40% risk of bodily injuries over 12-month follow-up. The primary goal of epilepsy treatment is to eliminate seizures while minimizing adverse effects of antiseizure medications[5]. All antiseizure medications (ASMs) taken into account (carbamazepine, lamotrigine, oxcarbazepine, topiramate, gabapentin, sodium valproate, levetiracetam, lacosamide, zonisamide, phenytoin, phenobarbitone) are widely considered effective in controlling seizures. It is considered unethical to conduct RCTs comparing standard ASMs, especially as monotherapy, with placebo in established epilepsy as epilepsy should be treated to decrease morbidity and premature mortality. It is necessary to investigate seizure	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			control, adverse events, quality of life and mortality with different ASMS to allow people with epilepsys and their clinicians to make individualized choices about the most appropriate ASM.	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know	• **Seizure remission:** Network meta-analysis found high-certainty evidence suggesting that, for focal onset seizures, carbamazepine performs better than gabapentin in terms of seizure remission (HR 1.29, 95%CI 1.06 to 1.57), and that carbamazepine has similar performance to other ASMs, including levetiracetam and lamotrigine. There is high certainty that, in generalized-onset seizures, valproic acid has an advantage over carbamazepine in terms of adverse events (HR 1.96, 95%CI 1.13 to 3.39).	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ Don't know	• **Adverse events**: In focal onset epilepsy, levetiracetam and lamotrigine perform significantly better than carbamazepine in terms of adverse events (HR 0.56, 95%CI 0.44 to 0.73 for lamotrigine vs carbamazepine, HR 0.65, 95%CI 0.47 to 0.90 for levetiracetam vs carbamazepine). • **Mortality and quality of life**: no estimate could be provided.	Phenytoin despite being used as a first line drug, has a problematic pharmacokinetic profile. Levetiracetam and lamotrigine have similar efficacy and adverse event profile compared to sodium valproate in generalized onset seizures. All ASMs are associated with potential adverse effects. Phenobarbital associates with a higher risk of short and long term tolerability problems. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of	☐ Very low	**Seizure recurrence**: The certainty was	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects	☒ Low ☒ Moderate ☒ High ☐ No included studies	moderate to high depending on the type of intervention. **Adverse events:** The certainty was low to high depending on the type of intervention.	
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called 'utility values'.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ No important uncertainty or variability	• With regards to their epilepsy, people with epilepsy list seizure control and being able to work as being of highest priority (https://epilepsyresearch.org.uk/shape-network-the-findings-so-far/).	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgments regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	• The balance of benefits versus harms is in favour of treatment of children and adults with focal onset epilepsy, with lamotrigine and levetiracetam being the ASMs with the most convenient risk/benefit profile.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which <u>fewer</u> resources are required? • How large is the difference in each item of resource use for which <u>more</u> resources are	☐ Large costs ☐ Moderate costs ☐ Negligible costs	We have no systematically collected evidence regarding this question. However, the desirable effects of drug tailoring may lead to a decrease in drug discontinuation, higher rates of seizure control and therefore to optimal	Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy. Avoiding valproate in women of childbearing

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	required? • How large an investment of resources would the option require or save?	and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	compliance, with savings related to reduction of costs due, for example, to injuries.	potential can prevent fetal malformations and reduce the costs for healthcare in these cases. Please refer to EPI4 questions for the use of antiseizure medications in women of childbearing potential.
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ No included studies		Please see the previous section for consideration of resource requirement costs.
Cost effectiveness	Does the cost-effectiveness of the intervention favor the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• Judgments regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☒ No included studies		Carbamazepine, lamotrigine, phenobarbital, phenytoin, and sodium valproate are included in the WHO list of essential medicines. Phenobarbital is commonly used as a first line drug in LMICs as it is much cheaper than other ASMs. Phenobarbital, being a controlled substance, faces strict regulations in many countries which affects its accessibility. As per the arguments made in the previous section, ASMs indicated (carbamazepine, levetiracetam, lamotrigine, valproate) may have a favorable profile. Based on the results of this network meta-analysis it would be reasonable to consider levetiracetam being added to the WHO list of essential medicines.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favor of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the	☒ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	ASMs should be available to all who need them. Treatment with ASM with higher efficacy and higher tolerability should be promoted, as this would in turn result in reduction of health inequities. Optimal seizure control with medications having no or little adverse events would help people with epilepsy to reach seizure control , improve quality of life and enable better social engagement	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	need, and will it be subject to periodic review?			
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	Availability of ASMs is a critical 'pinch-point' to be targeted in low-income and middle-income countries[6]. Actions to mitigate the cost in light of country per-capita income would be needed.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socio-culturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favor of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socio-culturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do	☐ No ☐ Probably no ☒ Probably yes		We did not search evidence for this specific question, but we believe that seizure prevention and mitigation of adverse event can be considered critical actions in

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	patients/beneficiaries value different non-health outcomes? • Is the intervention socio-culturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socio-economic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ Yes ☐ Varies ☐ Don't know		favour of human rights principles.

Summary of judgments

Table 5: Summary of judgments for seizure remission: *This provides a snapshot of the evidence to decision table.*

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	- **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	- **Moderate**	- Large
Undesirable effects	- Don't know	- Varies		- Large	- Moderate	- **Small**	- Trivial
Certainty of the evidence	- No included studies			- Very low	- **Low**	- **Moderate**	- **High**
Values				- Important uncertainty or variability	- Possibly important uncertain-ty or variability	- Probably no important uncertainty or variability	- **No impor-tant uncertain-ty or variabi-lity**
Balance of effects	- Don't know	- Varies	- Favours no interven-tion	- Probably favours no intervention	- Does not favour either	- **Probably favours interven-tion**	- Favours interven-tion
Resources required	- Don't know	- **Varies**	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	- **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effective-ness	- **Don't know**	- Varies	- Favours no interven-tion	- Probably favours no intervention	- Does not favour either	- Probably favours interventio n	- Favours interven-tion
Equity, equality and non-discrimina-tion	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	- Probably increased	- Increased
Feasibility	- Don't know	- Varies		- No	- Probably No	- **Probably Yes**	- Yes

Human rights and socio-cultural acceptability	- Don’t know	- Varies		- No	- Probably No	- **Probably Yes**	- Yes

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Glossary

ASM: antiseizure medications, a term preferred to the previously adopted antiepileptic drugs in relation to the actual potential of these medication class, which focuses on preventing seizures rather than being disease-modifying.

Appendix IV: Summary of data relating to levetiracetam in status epilepticus

Comparison of Phenytoin/Fosphenytoin , Valproate and Levetiracetam in adults with established status epilepticus				
Outcome	**Phenytoin vs Levetiracetam**	**Levetiracetam Vs Fosphenytoin**	**Valproate Vs Phenytoin**	**Levetiracetam Vs Valproate**
Seizure cessation within 60 min	1 study (1) RR 1.058 (0.664 to 1.685) No difference	1 study (2) RR 0.96 (0.67 to 1.38) No difference	1 study (3) RR 1.05 (0.89 to 1.23) No difference	1 study (2) RR 0.977 (0.690 to 1.383) No difference
Summary of quality of evidence	Low	Moderate	Very low	Moderate
Death	1 study RR 1.000 (0.154 to 6.470) No difference	1 study RR 2.30 (0.68 to 9.06) No difference	1 study RR 1.00 (0.27 to 3.78) No difference	1 study RR 5.07 (0.64 to 41.10) No difference
Summary of quality of evidence	Very low	Low	Very low	Low
Respiratory depression	1 study RR 1.50 (0.49 to 4.59) No difference	1 study RR 1.14 (0.68 to 1.91) No difference	1 study Very few events, RR not estimable[a]	1 study RR 1.372 (0.780 to 2.360) No difference
Summary of quality of evidence	Very low	Moderate	Very low	Moderate
Cardiovascular adverse effects	Not reported	1 study RR 0.526 (0.090 to 3.060) Favours Levetiracetam	1 study RR not estimable[b]	1 study RR not estimable[d]
Summary of quality of evidence	NA	Low	Very low	Low
Seizure freedom for 24 hours	1 study RR 0.940 (0.391 to 2.256) No difference	Not reported	1 study RR 1.118 (0.874 to 1.430) No difference	Not reported
Summary of quality of evidence	Very low	NA	Very low	NA
Any other adverse events reported	2/22 had adverse drug reactions in phenytoin arm but type not clarified	Nil	Nil	Nil

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3 Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure 2007; 16: 527–532

Comparison of Levetiracetam , Phenytoin/Fosphenytoin and Valproate in established status epilepticus in children			
Outcome	**Levetiracetam Vs Phenytoin**	**Levetiracetam Vs Fosphenytoin**	**Levetiracetam Vs Valproate**
Seizure cessation within 60 min	4 studies RR 1.03 (0.92 to 1.15) No difference	4 studies RR 1.07 (0.96 to 1.19) No difference	2 studies RR 1.01 (0.83 to 1.23) No difference
Summary of quality of evidence	Moderate	Moderate	High
Death	Not reported	4 studies RR 2.51 (0.10 to 60.71) No difference	2 studies RR 0.56 (0.07 to 4.30) No difference
Summary of quality of evidence	NA	Low	Low
Respiratory depression	4 studies RR 0.88 (0.65 to 1.20) No difference	3 studies RR 0.29 (0.15 to 0.56) Favors Levetiracetam	2 studies RR 0.67 (0.37 to 1.47) No difference
Summary of quality of evidence	Low	Moderate	Moderate
Cardiovascular adverse effects	4 studies RR 0.48 (0.18 to 1.32) No difference	3 studies RR 0.25 (0.04 to 1.50) No difference	2 studies RR 0.12 (0.01 to 2.21) No difference
Summary of quality of evidence	Moderate	Moderate	Low
Seizure freedom for 24 hours	1 study RR 1.175 (0.954 to 1.448) No difference	3 studies RR 0.61 (0.31 to 1.22) No difference	Not reported
Summary of quality of evidence	Moderate	Very Low	NA
Any other adverse events reported	Extravasation- Dalziel 2019- 2/72 in Phenytoin arm, 1/70 in Levetiracetam arm Lyttle 2019-0/152 in Levetiracetam arm, 4/134 in Phenytoin arm.	Nil	Nil

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Appendix V: mhGAP process note

mhGAP Guideline Update: Notes on process for identifying level of evidence review required v2_0 (13/12/2021)

This document is intended to provide guidance to focal points on the level of evidence review required as part of the evidence retrieval process for the mhGAP guideline update process. As a general rule, the update process should be informed by existing high quality systematic reviews.
The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714.

Three main categories of evidence review are proposed in this document:

1) Existing relevant, up to date, high quality systematic review(s) provide the evidence required. **An existing systematic review is sufficient to prepare the evidence summaries**. It may be possible to include more than one systematic review for the same PICO, as different reviews may match different outcomes of a PICO. However, if more than one systematic review is available for the same PICO outcome, one review should be selected, based on quality, relevance, search comprehensiveness and date of last update. The selection process should be transparently reported, with justification of choices.
2) Existing high quality systematic reviews are either out of date or do not fully address the PICO, though it is considered that the review can be updated to meet these requirements. **An update of an existing systematic review is required before the evidence summaries can be prepared**. The update process may require addition of new studies published after the review, or inclusion of outcomes not covered by the existing reviews.
3) Existing systematic reviews are either not of sufficiently high quality or cannot be updated to fully address the PICO. **A new systematic review is required before the evidence summaries can be prepared**

Figure 1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

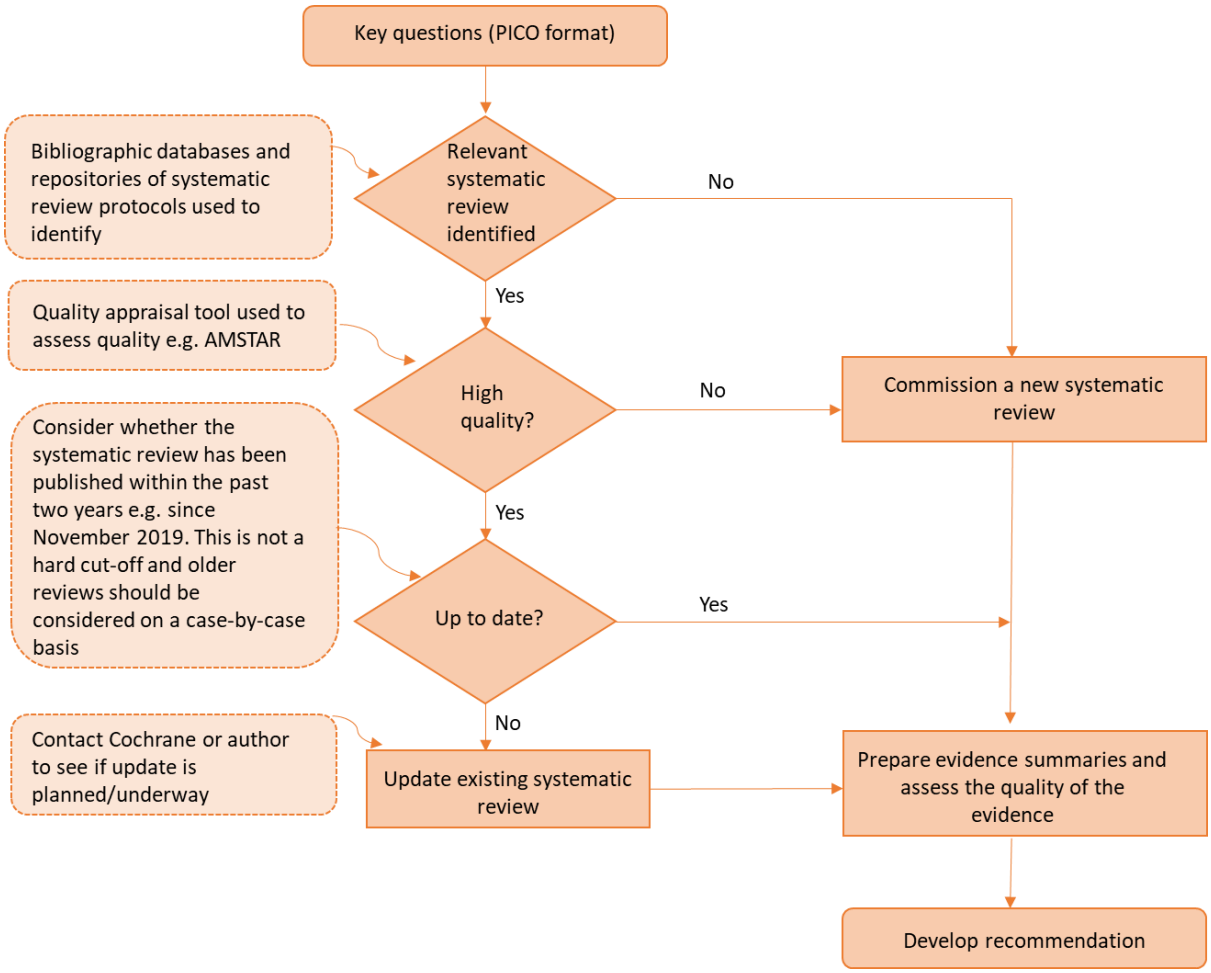

Figure 1: Is a new systematic review needed

All key questions are currently in PICO format as presented in the Appendix of the planning proposal PICOs. Subsequent steps include the following:

1. **Identify and evaluate existing systematic reviews**: Identify one or more systematic review(s) to address each PICO question. Existing systematic reviews will inform the guideline development process, whether or not a new systematic review or an update of an existing review is required, and the evidence review team will detail existing systematic reviews in each case. The method for identifying existing systematic reviews should be fully detailed in the evidence summary and include the following sources:
    a. Search of bibliographic databases, such as PubMed/Medline, EMBASE, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHIL, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus.
    b. Search of repositories of systematic reviews protocols, including PROSPERO, Open Science Framework (OSF), and Cochrane.
2. **Assess if systematic review is up to date:** It is preferred that identified systematic reviews have been published within the past two years e.g. since

April 2020. This is not a hard cut-off and older reviews should be considered on a case-by-case basis, particularly those covering the time period since the last update of the mhGAP guideline in 2012. It is acknowledged that COVID has led to a pausing of many mental health research activities over the past two years, and this may also impact the availability of systematic reviews within the preferred two-year period. For any reviews that fall outside the two-year period, the guideline methodologist will advise on suitability.

3. **Appraise quality of systematic review:** Use the AMSTAR-2 quality appraisal tool to assess the quality of the identified systematic review(s) https://amstar.ca/docs/AMSTAR-2.pdf . This includes consideration of the extent to which the PICO is fully addressed by the systematic review(s) identified.

By following the process outlined in figure 1, and steps 1-3 above, the FP and evidence review team will have sufficient evidence to assess which of the three main categories of evidence review apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

Appendix VI: Search terms used to identify systematic reviews

PubMed

((Epilepsy OR epileptic OR epilep* OR seizure OR seizures) AND (Anticonvulsants OR antiepileptic* OR antiseizure OR ((phenobarbital OR phenobarb*) OR phenytoin OR carbamazepine OR (valproic acid OR valproate OR valpr*) OR lamotrigine OR lacosamide OR levetiracetam OR topiramate))) AND ((Efficacy OR effectiveness OR seizure recurrence OR seizure prevention) OR (adverse events OR Drug-Related Side Effects and Adverse Reactions OR adverse effe* OR tolerability) OR (Mortality OR death OR survival) OR (Quality of life OR Life Quality OR Health-Related Quality Of Life OR Health Related Quality Of Life)) NOT (prophylactic).

Restrictions were applied to include only studies on (i) humans, (ii) children, adolescents and adults (6 years or older), (iii) published in English language, (iv) prophylactic treatment after traumatic brain injury. We restricted results to systematic reviews.

 # Timeframe
2012-2022

Appendix VII: Decision Tree used to evaluate ROB GRADE item

- No data available for risk of bias → serious

- When vast majority (>60%) of trials are low risk → not serious
- When low risk is between 50-60%:
  - High risk <25% → not serious
  - High risk >25% → serious

- When vast majority (>60%) is high risk → very serious
- When high risk is between 50-60%:
  - Low risk <25% → very serious
  - Low risk >25% → serious

- When vast majority is unclear risk (>60%) → serious
- When unclear risk is between 50-60%:
  - High risk <25% → not serious
  - High risk >25% → serious

- If unclear/high/low risk are all < 50%:
  - High risk <25% → not serious
  - High risk >25% → serious

Figure 2: Developed tree for the assessment of the risk of bias item in GRADE

Appendix VIII: Letters of support

International League Against Epilepsy

13 December 2022

Chair of the WHO Essential Medicines Committee,

I am writing as the Vice President of the International League Against Epilepsy (ILAE). The ILAE is a global organization of 129 Chapters in 160 countries and territories comprising over 28,000 professionals working in the field of epileptology.

The ILAE is the world's preeminent professional organization providing education and guidance as well as promoting essential research to improve understanding, diagnosis, prevention, treatment, and care for people with epilepsy.

In my capacity as Vice President and on behalf of the International League Against Epilepsy I am writing to express our full support for the inclusion of oral levetiracetam in the Essential Medicine List (EML) and, in intravenous form, in the EMLc.

Oral Levetiracetam is an effective first line treatment in epilepsy and its addition to the EML would provide treatment option for many of the 50 million people with epilepsy globally for whom the currently available anti-seizure medicines are either ineffective or inappropriate. Intravenous Levetiracetam has been shown to be an effective second line treatment for prolonged seizures and status epilepticus. Status epilepticus is a medical emergency associate with a 20% mortality rate. Its inclusion of intravenous levetiracetam in the EMLc could potentially save many lives each year.

Levetiracetam has specific advantages compared with the anti-seizure medications currently listed in the EML, including few drug-drug interactions, no known long-term side effects, good tolerability in older people and the safest teratogenic profile of all anti-seizure medications.

The profile of Levetiracetam provides treatment options for girls and women of childbearing age that are currently not available with carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate, as there are no known interactions with hormonal contraceptives (or replacement therapy) and levetiracetam is not associated with any increased teratogenicity risk above the background risk of the general population.

The lack of any significant drug-drug interactions with levetiracetam offers greater treatment options for the significant numbers of people with epilepsy who require pharmaceutical treatments for co-morbidities, an increasing issue with the growing numbers of older people with epilepsy in many parts of the world. Additionally levetiracetam as a monotherapy has also been shown to be well tolerated in the elderly and studies demonstrate little or no impact on cognitive function.

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IBE INTERNATIONAL BUREAU FOR EPILEPSY

NGO in Special Consultative Status with the Economic and Social Council of the United Nations and in official relations with WHO

14 December 2022

Esteemed Chair of the WHO Essential Medicines Committee,

I am writing on behalf of the International Bureau for Epilepsy to support the inclusion of **levetiracetam** as an individual medicine in the core list of the EML and EMLc for the treatment of focal onset and generalized onset epilepsy.

The International Bureau for Epilepsy (IBE) is a global organization with nearly 150 chapters in over 100 countries supporting the needs of people with epilepsy, their carers, and their communities as they strive for a world where no person's life is limited by epilepsy.

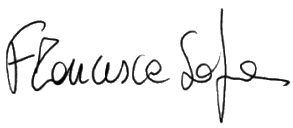
For many years the IBE and our community have been concerned about the lack of safe and effective treatment options for women of childbearing age. It is estimated that over 50 million people have epilepsy worldwide at least one quarter of whom are women of child-bearing age.

All of the anti-seizure medicines currently included in the EML (carbamazepine, lamotrigine, phenobarbital, phenytoin, valproate) pose significant concerns for women of child-bearing age leaving girls and women with limited reproductive health options and forcing many to choose not to have children, to terminate wanted pregnancies or worry throughout pregnancy about the health of their unborn children.

- Carbamazepine, phenytoin and phenobarbital interfere with the oral contraceptive making them less effective
- Oestrogen containing oral contraceptives (and hormone replacement therapy) can lower lamotrigine levels
- Sodium valproate increases the risk of structural anomalies at birth (for example spina bifida, cleft lip, cleft palate, cardiac anomalies) up to around 10% in women taking valproate through pregnancy and there is a 30-40% risk that their offspring will have neurodevelopmental anomalies (autism, learning disabilities).

It is vital, therefore, that women and girls have access to anti-seizure medicines that are effective and minimize these risks. Levetiracetam does not interact with hormonal contraceptives nor with hormone replacement therapies and, to date, has not been associated with any increased teratogenicity risk above the background risk in the general population.

The 12 million women of childbearing age around the world who live with epilepsy have a right to effective reproductive health choices and to be able to access medication to manage their epilepsy during child-bearing age and pregnancy without negatively impacting the healthy development of their unborn child. Including levetiracetam in the EML would be an important step towards achieving this right.



Francesca Sophia PhD
President
International Bureau for Epilepsy

International Bureau for Epilepsy

Founded in 1961
US Charter ID 721834-DNP
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