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[Intervention Review]

Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data

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ABSTRACT

Background

This is an updated version of the original Cochrane Review published in 2017.

Epilepsy is a common neurological condition with a worldwide prevalence of around 1%. Approximately 60% to 70% of people with epilepsy will achieve a longer-term remission from seizures, and most achieve that remission shortly after starting antiepileptic drug treatment. Most people with epilepsy are treated with a single antiepileptic drug (monotherapy) and current guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom for adults and children recommend carbamazepine or lamotrigine as first-line treatment for focal onset seizures and sodium valproate for generalised onset seizures; however, a range of other antiepileptic drug (AED) treatments are available, and evidence is needed regarding their comparative effectiveness in order to inform treatment choices.

Objectives

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 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.

PLAIN LANGUAGE SUMMARY

Antiepileptic drug monotherapy (single drug treatment) for epilepsy

Background

Epilepsy is a common neurological disorder in which abnormal electrical discharges from the brain cause recurrent seizures. We studied two types of epileptic seizures in this review: focal seizures that start in one area of the brain, and generalised onset tonic-clonic seizures that start in both cerebral hemispheres simultaneously.

For around 70% of people with epilepsy, seizures can be controlled and, for the majority, seizures are controlled with a single antiepileptic drug. Currently in the UK, National Institute for Health and Care Excellence (NICE) guidelines for adults and children recommend carbamazepine or lamotrigine as the first treatment options to try for individuals with newly diagnosed focal seizures and sodium valproate for individuals with newly diagnosed generalised tonic-clonic seizures; however, a range of other antiepileptic drug treatments are available.

The choice of the first antiepileptic drug for an individual with newly diagnosed seizures is of great importance and should be made taking into account high-quality evidence of how effective the drugs are at controlling seizures and whether they are associated with side effects. It is also important that drugs appropriate for different seizure types are compared to each other.

Review methods

The antiepileptic drugs of interest to this review were carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate, and lacosamide. In this review, we evaluated the evidence from 89 randomised controlled clinical trials comparing two or more of the drugs of interest based on how effective the drugs were at controlling seizures (i.e. whether people had recurrence of seizures or had long periods of freedom from seizures (remission)) and how tolerable any related side effects of the drugs were. We were able to combine data for 14,789 people from 39 of the 89 trials; for the remaining 7251 people from 50 trials, data were not available to use in this review. No data were available from people receiving eslicarbazepine acetate.

We performed two types of analysis in this review; firstly, we combined data available where pairs of drugs had been compared directly in clinical trials and, secondly, we performed an analysis to combine all information from the clinical trials across the 'network' of 11 drugs. This analysis allowed us to compare drugs in the network that had not previously been compared to each other in clinical trials.

Key results

Our 'network' analysis showed that, for people with focal seizures and for people with generalised seizures, the oldest drugs (phenobarbitone and phenytoin) were better options in terms of seizure control than the other drugs but that these older drugs were the worst in terms of long-term retention (stopping the treatment) compared to the newer drugs such as lamotrigine and levetiracetam. Sodium valproate was the best option of all the drugs for achieving control and remission of generalised tonic-clonic seizures.

The most commonly reported side effects across all drugs were drowsiness or fatigue, headache or migraine, gastrointestinal disturbances (stomach upsets), dizziness or faintness, and rash or skin disorders.

Quality of the evidence

This review provides high-quality evidence for individuals with focal seizures and moderate- to high-quality evidence for individuals with generalised tonic-clonic seizures, as less information was available for some of the drugs of interest for people with this seizure type.

Conclusions

The results of this review support the NICE guidelines that carbamazepine and lamotrigine are suitable first treatment options for individuals with focal onset seizures, and also show that levetiracetam would be a suitable first treatment. Results of this review also support the use of sodium valproate as the first treatment for individuals with generalised tonic-clonic seizures and show that lamotrigine and levetiracetam would be suitable alternative first treatments, particularly for those who are pregnant or considering becoming pregnant, for whom sodium valproate may not be an appropriate treatment option.

How up-to-date is this review?

The evidence is current to April 2021.

Summary of findings 1. Summary of findings - Time to treatment failure for individuals with focal seizures (reference carbamazepine)

Antiepileptic drug monotherapy for epilepsy: time to treatment failure for participants with focal seizures (reference carbamazepine)

Patient or population: adults and children with focal seizures

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: phenobarbitone, phenytoin, sodium valproate, lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide

Comparison: carbamazepine

Outcome	Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[g]
				Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)[b]			
Any reason	Phenobarbone	Carbamazepine	520 (4 studies)	1.55 (1.16 to 2.07); I^2 = 68%	1.56 (1.18 to 2.07)	18.5%	⊕⊕⊕⊕ **HIGH** d,e,f	Carbamazepine better than phenobarbitone
Adverse events			520 (4 studies)	1.52 (1.06 to 2.19); I^2 = 73%	1.99 (1.21 to 3.27)	31.7%	⊕⊕⊕⊕ **HIGH** d,e,f	
Lack of efficacy			388 (3 studies)	1.86 (1.26 to 2.75); I^2 = 0%	1.88 (1.25 to 2.81)	37.2%	⊕⊕⊕⊕ **HIGH** d,e	
Any reason	Phenytoin	Carbamazepine	428 (3 studies)	1.19 (0.87 to 1.61); I^2 = 0%	1.14 (0.90 to 1.44)	24.4%	⊕⊕⊕⊕ **HIGH** d,e	No difference between drugs for any outcome
Adverse events			428 (3 studies)	0.83 (0.56 to 1.24); I^2 = 0%	1.00 (0.66 to 1.53)	35.3%	⊕⊕⊕⊕ **HIGH** d,e	
Lack of efficacy			428 (3 studies)	1.12 (0.76 to 1.64); I^2 = 0%	1.14 (0.78 to 1.68)	33.2%	⊕⊕⊕⊕ **HIGH** d,e	
Any reason	Sodium valproate	Carbamazepine	814 (5 studies)	1.02 (0.80 to 1.29); I^2 = 0%	1.08 (0.88 to 1.31)	23.8%	⊕⊕⊕⊕ **HIGH** d,e	No difference between drugs for any outcome

Adverse events			570 (3 studies)	0.94 (0.70 to 1.26); I^2 = 0%	0.88 (0.59 to 1.29)	40.3%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			814 (5 studies)	1.04 (0.82 to 1.33); I^2 = 0%	1.16 (0.88 to 1.52)	52.9%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Lamotrigine	Carbamazepine	2203 (9 studies)	0.75 (0.65 to 0.88); I^2 = 0%	0.79 (0.69 to 0.91)	27.7%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than carbamazepine for treatment failures for any reason and due to adverse events
Adverse events			2203 (9 studies)	0.57 (0.47 to 0.70); I^2 = 0%	0.56 (0.44 to 0.73)	32.9%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			2098 (8 studies)	1.00 (0.72 to 1.39); I^2 = 0%	1.02 (0.78 to 1.33)	17.7%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Oxcarbazepine	Carbamazepine	599 (2 studies)	1.10 (0.85 to 1.43); I^2 = 66%	1.03 (0.82 to 1.30)	0.4%	⊕⊕⊕⊕ **HIGH** **d,e,f**	No difference between drugs for any outcome
Adverse events			599 (2 studies)	1.01 (0.73 to 1.38); I^2 = 0%	0.75 (0.46 to 1.22)	18.4%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			599 (2 studies)	1.17 (0.76 to 1.81); I^2 = 0%	1.14 (0.73 to 1.77)	0.0%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Topiramate	Carbamazepine	976 (2 studies)	1.23 (1.03 to 1.48); I^2 = 0%	1.19 (0.99 to 1.43)	24.2%	⊕⊕⊕⊕ **HIGH** **d,e**	No difference between drugs for any outcome
Adverse events			976 (2 studies)	1.10 (0.88 to 1.39); I^2 = 0%	0.99 (0.69 to 1.43)	29.6%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			976 (2 studies)	1.48 (1.08 to 2.03); I^2 = 0%	1.32 (0.95 to 1.83)	21.9%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Gabapentin	Carbamazepine	681 (2 studies)	1.22 (1.02 to 1.45); I^2 = 0%	1.21 (1.01 to 1.45)	26.6%	⊕⊕⊕⊕ **HIGH** **d,e**	Carbamazepine better for treatment failures for any reason and lack of efficacy Gabapentin better for treatment failures
Adverse events			681 (2 studies)	0.68 (0.53 to 0.89); I^2 = 88%	0.58 (0.37 to 0.91)	1.7%	⊕⊕⊕⊕ **HIGH** **d,e,f**	
Lack of efficacy			681 (2 studies)	2.05 (1.59 to 2.66); I^2 = 0%	2.07 (1.56 to 2.75)	30.5%	⊕⊕⊕⊕ **HIGH** **d,e**	

								due to adverse events
Any reason	Levetiracetam	Carbamazepine	1567 (3 studies)	0.85 (0.71 to 1.01); I^2 = 50%	0.80 (0.69 to 0.93)	15.8%	⊕⊕⊕⊕ **HIGH** **d,e,f**	Leviracetam better than carbamazepine for treatment failures for any reason and due to adverse events
Adverse events			1567 (3 studies)	0.60 (0.47 to 0.77); I^2 = 35%	0.65 (0.47 to 0.90)	28.8%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			1567 (3 studies)	1.44 (0.98 to 2.12); I^2 = 0%	1.07 (0.78 to 1.45)	23.0%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Zonisamide	Carbamazepine	583 (1 study)	1.08 (0.81 to 1.44); I^2 = NA	0.93 (0.77 to 1.14)	15.7%	⊕⊕⊕⊕ **HIGH** **d,e**	No difference between drugs for any outcome
Adverse events			583 (1 study)	0.96 (0.59 to 1.55); I^2 = NA	0.70 (0.43 to 1.13)	17.9%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			583 (1 study)	1.07 (0.60 to 1.92); I^2 = NA	1.23 (0.86 to 1.77)	10.3%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Lacosamide	Carbamazepine	807 (1 study)	0.94 (0.75 to 1.19); I^2 = NA	0.95 (0.74 to 1.22)	100.0%	⊕⊕⊕⊕ **HIGH** **d,e**	No difference between drugs for any outcome
Adverse events			807 (1 study)	1.22 (0.84 to 1.79); I^2 = NA	1.24 (0.65 to 2.37)	100.0%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			807 (1 study)	0.79 (0.49 to 1.26); I^2 = NA	0.79 (0.47 to 1.33)	100.0%	⊕⊕⊕⊕ **HIGH** **d,e**	

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).
[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only
[c]Proportion of the network estimate contributed by direct evidence

[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence).

[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)

[f]Large amount of heterogeneity present in pairwise meta-analysis (direct evidence); heterogeneity likely due to difference in trial designs (e.g. age of participants). Despite heterogeneity, numerical results from direct evidence and from NMA were similar, therefore, we judged that any heterogeneity present in pairwise meta-analysis had not influenced the overall results (no downgrade of certainty of evidence).

[g]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

Summary of findings 2. Summary of findings - Time to treatment failure for individuals with focal seizures (reference lamotrigine)

Antiepileptic drug monotherapy for epilepsy: time to treatment failure for participants with focal seizures (reference lamotrigine)

Patient or population: adults and children with focal seizures

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: carbamazepine, phenobarbitone, phenytoin, sodium valproate, oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide

Comparison: lamotrigine

Outcome	Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[g]
				Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)[b]			
Any reason	Carbamazepine	Lamotrigine	2203 (9 studies)	1.33 (1.14 to 1.54); I^2 = 0%	1.26 (1.10 to 1.44)	27.7%	⊕⊕⊕⊕ **HIGH** [d,e]	Lamotrigine better than carbamazepine for treatment failures for any reason and due to adverse events
Adverse events			2203 (9 studies)	1.75 (1.43 to 2.14); I^2 = 0%	1.77 (1.37 to 2.28)	32.9%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			2098 (8 studies)	0.68 (0.49 to 0.94); I^2 = 0%	0.98 (0.75 to 1.29)	17.7%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Phenobarbitone	Lamotrigine	No direct evidence	No direct evidence	1.97 (1.45 to 2.67)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	Lamotrigine probably better than phenobarbitone
Adverse events			No direct evidence	No direct evidence	3.52 (2.04 to 6.09)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	

Lack of efficacy			No direct evidence	No direct evidence	1.85 (1.14 to 2.98)	0.0%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Phenytoin	Lamotrigine	90 (1 study)	0.82 (0.40 to 1.65); I^2 = NA	1.44 (1.11 to 1.85)	3.9%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than phenytoin for treatment failures for any reason and due to adverse events
Adverse events			90 (1 study)	0.89 (0.33 to 2.37); I^2 = NA	1.78 (1.13 to 2.81)	4.4%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			No direct evidence	No direct evidence	1.12 (0.71 to 1.78)	0.0%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Sodium valproate	Lamotrigine	267 (3 studies)	2.37 (1.32 to 4.27); I^2 = 0%	1.35 (1.09 to 1.69)	5.1%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than sodium valproate for treatment failures for any reason and due to adverse events
Adverse events			267 (3 studies)	3.53 (1.28 to 9.71); I^2 = 0%	1.55 (1.02 to 2.38)	4.3%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			267 (3 studies)	1.77 (0.77 to 4.05); I^2 = 0%	1.14 (0.80 to 1.62)	2.3%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Oxcarbazepine	Lamotrigine	521 (1 study)	1.37 (1.05 to 1.81); I^2 = NA	1.30 (1.02 to 1.66)	17.1%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than oxcarbazepine for treatment failures for any reason
Adverse events			521 (1 study)	1.91 (1.33 to 2.73); I^2 = NA	1.33 (0.80 to 2.20)	15.3%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			521 (1 study)	1.21 (0.79 to 1.85); I^2 = NA	1.12 (0.71 to 1.76)	20.6%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Topiramate	Lamotrigine	699 (2 studies)	1.62 (1.30 to 2.02); I^2 = 0%	1.50 (1.23 to 1.81)	17.4%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than topiramate for treatment failures for any reason and due to adverse events
Adverse events			699 (2 studies)	2.20 (1.63 to 2.99); I^2 = 0%	1.75 (1.17 to 2.62)	17.6%	⊕⊕⊕⊕ **HIGH** **d,e**	
Lack of efficacy			699 (2 studies)	1.49 (1.07 to 2.08); I^2 = 0%	1.30 (0.92 to 1.85)	22.8%	⊕⊕⊕⊕ **HIGH** **d,e**	
Any reason	Gabapentin	Lamotrigine	676 (1 study)	1.64 (1.32 to 2.04); I^2 = NA	1.53 (1.26 to 1.85)	17.8%	⊕⊕⊕⊕ **HIGH** **d,e**	Lamotrigine better than gabapentin for treatment failures for any reason and due

Adverse events			676 (1 study)	1.50 (1.09 to 2.08); I^2 = NA	1.02 (0.63 to 1.65)	21.1%	⊕⊕⊕⊕ **HIGH** [d,e]	to lack of efficacy
Lack of efficacy			676 (1 study)	2.30 (1.70 to 3.11); I^2 = NA	2.04 (1.48 to 2.80)	18.0%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Levetiracetam	Lamotrigine	902 (2 studies)	0.87 (0.71 to 1.07); I^2 = 0%	1.01 (0.86 to 1.20)	23.3%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs for any outcome
Adverse events			902 (2 studies)	0.84 (0.60 to 1.19); I^2 = 32%	1.16 (0.81 to 1.66)	14.6%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			902 (2 studies)	0.83 (0.57 to 1.21); I^2 = 3%	1.05 (0.76 to 1.46)	30.9%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Zonisamide	Lamotrigine	658 (1 study)	1.01 (0.80 to 1.28); I^2 = NA	1.18 (0.96 to 1.44)	25.0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs for any outcome
Adverse events			658 (1 study)	0.90 (0.57 to 1.41); I^2 = NA	1.24 (0.75 to 2.03)	20.3%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			658 (1 study)	1.12 (0.78 to 1.59); I^2 = NA	1.22 (0.86 to 1.72)	22.2%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Lacosamide	Lamotrigine	No direct evidence	No direct evidence	1.19 (0.90 to 1.58)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	Lamotrigine probably better than lacosamide for treatment failures due to adverse events
Adverse events			No direct evidence	No direct evidence	2.21 (1.10 to 4.41)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	
Lack of efficacy			No direct evidence	No direct evidence	0.78 (0.44 to 1.40)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).

[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only

[c]Proportion of the network estimate contributed by direct evidence

[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence).

[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)

[f]Wide confidence intervals around the NMA treatment-effect estimate (downgraded once for imprecision)

[g]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

Summary of findings 3. Summary of findings - Time to treatment failure for individuals with generalised seizures (reference sodium valproate)

Antiepileptic drug monotherapy for epilepsy: time to treatment failure for participants with generalised seizures (reference sodium valproate)

Patient or population: adults and children with generalised tonic-clonic seizures with or without other seizure types

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: carbamazepine, phenobarbitone, phenytoin, oxcarbazepine, lamotrigine, topiramate, gabapentin, levetiracetam and lacosamide

Comparison: sodium valproate

Outcome	Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[h]
				Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)[b]			
Any reason	Carbamazepine	Sodium valproate	405 (4 studies)	1.26 (0.73 to 2.20); I^2 = 7%	1.52 (1.18 to 1.96)	23.3%	⊕⊕⊕⊕ **HIGH** [d,e]	Sodium valproate better than carbamazepine for treatment failures for any reason and due to adverse events
Adverse events			117 (2 studies)	0.74 (0.18 to 2.98); I^2 = 0%	1.96 (1.13 to 3.39)	52.9%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			405 (4 studies)	1.31 (0.71 to 2.42); I^2 = 0%	0.97 (0.63 to 1.49)	51.3%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Phenobarbitone	Sodium valproate	94 (2 studies)	0.56 (0.20 to 1.54); I^2 = 0%	2.13 (1.20 to 3.79)	19.7%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	Sodium valproate is probably better than phenobarbitone

Adverse events			94 (2 studies)	0.26 (0.06 to 1.05); I^2 = 28%	2.14 (0.82 to 5.57)	4.1%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	for treatment failures for any reason
Lack of efficacy			94 (2 studies)	0.88 (0.25 to 3.07); I^2 = 0%	1.57 (0.71 to 3.50)	25.8%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	
Any reason	Phenytoin	Sodium valproate	326 (4 studies)	0.65 (0.26 to 1.63); I^2 = 22%	1.17 (0.80 to 1.73)	10.4%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs for any outcome
Adverse events			326 (4 studies)	0.37 (0.06 to 2.13); I^2 = 0%	1.56 (0.75 to 3.24)	13.8%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			326 (4 studies)	0.49 (0.15 to 1.55); I^2 = 0%	0.60 (0.27 to 1.34)	26.8%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Lamotrigine	Sodium valproate	560 (3 studies)	1.91 (0.93 to 3.90); I^2 = 0%	1.06 (0.81 to 1.37)	15.9%	⊕⊕⊕⊕ **HIGH** [d,e]	Sodium valproate better than lamotrigine for treatment failures due to lack of efficacy
Adverse events			560 (3 studies)	1.88 (0.68 to 5.21); I^2 = 0%	0.86 (0.50 to 1.48)	20.3%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			560 (3 studies)	1.98 (0.60 to 6.49); I^2 = 0%	1.85 (1.11 to 3.11)	14.1%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Oxcarbazepine	Sodium valproate	No direct evidence	No direct evidence	1.24 (0.72 to 2.14)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	Probably no difference between drugs for any outcome
Adverse events			No direct evidence	No direct evidence	1.00 (0.33 to 3.02)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	
Lack of efficacy			No direct evidence	No direct evidence	1.51 (0.50 to 4.54)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	
Any reason	Topiramate	Sodium valproate	588 (2 studies)	1.81 (0.91 to 3.60); I^2 = 36%	1.37 (1.06 to 1.77)	11.0%	⊕⊕⊕⊕ **HIGH** [d,e]	Sodium valproate better than topiramate for treatment failures for any reason and due to lack of efficacy
Adverse events			588 (2 studies)	1.53 (0.59 to 3.97); I^2 = 54%	1.42 (0.82 to 2.46)	10.8%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			588 (2 studies)	4.81 (1.14 to 20.3); I^2 = 0%	1.78 (1.10 to 2.87)	34.6%	⊕⊕⊕⊕ **HIGH** [d,e]	

Any reason	Gabapentin	Sodium Valproate	No direct evidence	No direct evidence	1.13 (0.61 to 2.11)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	Sodium valproate better than gabapentin for treatment failures due to lack of efficacy
Adverse events			No direct evidence	No direct evidence	0.66 (0.21 to 2.08)	0.0%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			No direct evidence	No direct evidence	2.76 (1.14 to 6.70)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	
Any reason	Levetiracetam	Sodium valproate	1032 (2 studies)	1.46 (0.63 to 3.38); I^2 = 0%	1.13 (0.89 to 1.42)	17.8%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs for any outcome
Adverse events			1032 (2 studies)	0.79 (0.19 to 3.39); I^2 = 0%	1.21 (0.66 to 2.21)	14.7%	⊕⊕⊕⊕ **HIGH** [d,e]	
Lack of efficacy			1032 (2 studies)	3.02 (0.43 to 21.1); I^2 = 0%	1.25 (0.81 to 1.93)	22.0%	⊕⊕⊕⊕ **HIGH** [d,e]	
Any reason	Lacosamide	Sodium valproate	No direct evidence	No direct evidence	2.64 (1.14 to 6.09)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	Sodium valproate probably better than lacosamide for treatment failures for any reason and may be better than lacosamide for treatment failures due to adverse events
Adverse events			No direct evidence	No direct evidence	8.61 (1.29 to 57.5)	0.0%	⊕⊕⊖⊖ **LOW** [d,e,g]	
Lack of efficacy			No direct evidence	No direct evidence	0.40 (0.07 to 2.26)	0.0%	⊕⊕⊕⊖ **MODERATE** [d,e,f]	

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).
[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only
[c]Proportion of the network estimate contributed by direct evidence

[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence).
[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
[f]Wide confidence intervals around the NMA treatment-effect estimate (downgraded once for imprecision)
[g]Very wide confidence intervals around the NMA treatment-effect estimate (downgraded twice for imprecision)
[h]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

Summary of findings 4. Summary of findings - Time to 12-month remission for individuals with focal seizures (reference carbamazepine)

Antiepileptic drug monotherapy for epilepsy: time to 12-month remission for individuals with focal seizures (reference carbamazepine)

Patient or population: adults and children with focal seizures

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: phenobarbitone, phenytoin, sodium valproate, lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide

Comparison: carbamazepine

Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[f]
			Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)			
Phenobarbitone	Carbamazepine	525 (4 studies)	1.00 (0.73 to 1.35); I^2 = 42%	1.03 (0.77 to 1.38)	16.9%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs
Phenytoin	Carbamazepine	430 (3 studies)	1.03 (0.78 to 1.37); I^2 = 0%	1.04 (0.84 to 1.29)	21.9%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs
Sodium valproate	Carbamazepine	816 (5 studies)	1.06 (0.86 to 1.30); I^2 = 30%	1.08 (0.91 to 1.29)	17.7%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs
Lamotrigine	Carbamazepine	907 (2 studies)	1.08 (0.91 to 1.28); I^2 = 0%	1.06 (0.93 to 1.22)	18.4%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs
Oxcarbazepine	Carbamazepine	591 (2 studies)	0.97 (0.78 to 1.20); I^2 = 0%	0.95 (0.78 to 1.15)	17.8%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs
Topiramate	Carbamazepine	962 (2 studies)	1.20 (1.00 to 1.44); I^2 = 0%	1.13 (0.94 to 1.36)	21.9%	⊕⊕⊕⊕ **HIGH**[d,e]	No difference between drugs

Gabapentin	Carbamazepine	666 (1 study)	1.32 (1.09 to 1.60); I^2 = NA	1.29 (1.06 to 1.57)	20.4%	⊕⊕⊕⊕ **HIGH** [d,e]	Carbamazepine better than gabapentin
Levetiracetam	Carbamazepine	1567 (3 studies)	1.09 (0.92 to 1.29); I^2 = 0%	1.08 (0.94 to 1.24)	22.3%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Zonisamide	Carbamazepine	582 (1 study)	1.05 (0.85 to 1.30); I^2 = NA	1.10 (0.94 to 1.29)	18.9%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Lacosamide	Carbamazepine	806 (1 study)	1.00 (0.83 to 1.19); I^2 = NA	1.00 (0.81 to 1.22)	100.0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).
[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only
[c]Proportion of the network estimate contributed by direct evidence
[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence).
[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
[f]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

Summary of findings 5. Summary of findings - Time to 12-month remission for individuals with focal seizures (reference lamotrigine)

Antiepileptic drug monotherapy for epilepsy: time to 12-month remission for individuals with focal seizures (reference lamotrigine)

Patient or population: adults and children with focal seizures

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: carbamazepine, phenobarbital, phenytoin, sodium valproate, oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide

Comparison: lamotrigine

Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Proportion of direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[f]
			Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)[b]			
Carbamazepine	Lamotrigine	907 (2 studies)	0.92 (0.78 to 1.09); I^2 = 0%	0.94 (0.82 to 1.08)	18.4%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Phenobarbitone	Lamotrigine	No direct evidence	No direct evidence	0.97 (0.71 to 1.33)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Phenytoin	Lamotrigine	No direct evidence	No direct evidence	0.98 (0.76 to 1.25)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Sodium valproate	Lamotrigine	267 (3 studies)	1.35 (0.68 to 2.67); I^2 = 0%	1.02 (0.83 to 1.25)	4.1%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Oxcarbazepine	Lamotrigine	511 (1 study)	0.87 (0.69 to 1.01); I^2 = NA	0.89 (0.72 to 1.10)	15.6%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Topiramate	Lamotrigine	683 (2 studies)	1.12 (0.92 to 1.36); I^2 = 0%	1.06 (0.88 to 1.29)	19.5%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Gabapentin	Lamotrigine	660 (1 study)	1.21 (1.00 to 1.47); I^2 = NA	1.21 (0.99 to 1.48)	19.9%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Levetiracetam	Lamotrigine	902 (2 studies)	1.02 (0.86 to 1.20); I^2 = 0%	1.01 (0.87 to 1.18)	23.6%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Zonisamide	Lamotrigine	658 (1 study)	1.07 (0.88 to 1.29); I^2 = NA	1.04 (0.87 to 1.23)	24.7%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Lacosamide	Lamotrigine	No direct evidence	No direct evidence	0.94 (0.73 to 1.20)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).
[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only
[c]Proportion of the network estimate contributed by direct evidence
[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence).
[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
[f]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

Summary of findings 6. Summary of findings - Time to 12-month remission for individuals with generalised seizures (reference sodium valproate)

Antiepileptic drug monotherapy for epilepsy: time to 12-month remission for individuals with generalised seizures (reference sodium valproate)

Patient or population: adults and children with generalised seizures*

Settings: outpatients globally, followed up in RCTs for up to 12 years

Intervention: carbamazepine, phenobarbitone, phenytoin, lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam and lacosamide

Comparison: sodium valproate

Intervention (experimental treatment)[a]	Comparison (reference treatment)	No of participants (studies) with direct evidence	Relative effect sizes		Proportion of direct evidence (%)[c]	Certainty of the evidence (GRADE)	Interpretation[g]
			Direct evidence HR (95% CI)[b]; I^2 (%)	Network meta-analysis HR (95% CI)[b]			
Carbamazepine	Sodium valproate	412 (4 studies)	1.01 (0.72 to 1.43); I^2 = 0%	1.01 (0.83 to 1.22)	40.4%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Phenobarbitone	Sodium valproate	98 (2 studies)	1.15 (0.53 to 2.49); I^2 = 42%	1.32 (0.88 to 2.00)	12.4%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Phenytoin	Sodium valproate	269 (4 studies)	0.87 (0.55 to 1.40); I^2 = 0%	0.96 (0.75 to 1.28)	36.1%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Lamotrigine	Sodium valproate	555 (3 studies)	1.27 (0.64 to 2.50); I^2 = 0%	1.19 (0.95 to 1.50)	12.4%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs

Oxcarbazepine	Sodium valproate	No direct evidence	No direct evidence	1.27 (0.85 to 1.90)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Topiramate	Sodium valproate	585 (2 studies)	1.86 (0.94 to 3.71); I^2 = 0%	1.08 (0.87 to 1.34)	4.3%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Gabapentin	Sodium valproate	No direct evidence	No direct evidence	1.30 (0.82 to 2.07)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs
Levetiracetam	Sodium valproate	1032 (2 studies)	1.10 (0.59 to 2.04); I^2: 55%	0.99 (0.82 to 1.20)	53.2%	⊕⊕⊕⊕ **HIGH** [d,e,f]	No difference between drugs
Lacosamide	Sodium valproate	No direct evidence	No direct evidence	1.05 (0.56 to 1.94)	0%	⊕⊕⊕⊕ **HIGH** [d,e]	No difference between drugs

Abbreviations: CI: confidence interval; **HR:** hazard ratio; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Order of drugs in the table: drugs were ordered approximately by the date they were licensed as a monotherapy treatment (oldest first).
[b]HR < 1 indicates an advantage to the experimental treatment; HRs and 95% CIs were calculated from fixed-effect analyses (pairwise and network meta-analysis). Heterogeneity (I^2) presented for pairwise meta-analysis only
[c]Proportion of the network estimate contributed by direct evidence
[d]Several trials contributing direct evidence or contributing to NMA were at high risk of bias for at least one domain; we performed numerous sensitivity analyses excluding studies at high risk of bias or studies with inconsistencies within IPD provided to us. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore, we judged that any risks of bias within the trials had not influenced the overall results (no downgrade of certainty of evidence)
[e]No indication of important inconsistency (incoherence) between direct evidence and NMA results (no downgrade of certainty of evidence)
[f]Large amount of heterogeneity present in pairwise meta-analysis (direct evidence); heterogeneity likely due to difference in trial designs (e.g. age of participants). Despite heterogeneity, numerical results from direct evidence and from NMA were similar, therefore we judged that any heterogeneity present in pairwise meta-analysis had not influenced the overall results (no downgrade of certainty of evidence).
[g]Interpretation of network meta-analysis results taking into account direct evidence for the comparison and certainty of the evidence

BACKGROUND

This is an updated version of the original Cochrane Review published in 2017 (Nevitt 2017a).

Description of the condition

Epilepsy is a common neurological condition in which recurrent, unprovoked seizures occur due to abnormal electrical discharges in the brain, with an estimated incidence of 33 to 57 per 100,000 person-years worldwide (Annegers 1999; Hirtz 2007; MacDonald 2000; Olafsson 2005; Sander 1996), affecting over 50 million people worldwide and accounting for approximately 1% of the global burden of disease (WHO 1994; WHO 2021). The lifetime risk of epilepsy onset is estimated to be 1300 to 4000 per 100,000 person years (Hauser 1993; Juul-Jenson 1983), and the lifetime prevalence could be as large as 70 million people world-wide (Ngugi 2010). It is believed that with effective drug treatment, up to 70% of individuals with active epilepsy have the potential to become seizure-free and go into long-term remission shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), and that around 70% of individuals can achieve seizure freedom using a single AED as monotherapy (Cockerell 1995). The remaining 30% of individuals experience refractory or drug-resistant seizures, which often require treatment with combinations of AEDs or alternative treatments such as epilepsy surgery (Kwan 2000).

Epilepsy is not a single condition but is, in fact, a heterogeneous group of conditions ranging from those with a purely genetic cause to those that are symptomatic of a brain injury (e.g. stroke) or other abnormality (e.g. tumour). We also recognise a range of differing seizure types, and epilepsy syndromes that have been classified by the International League Against Epilepsy (ILAE), a classification that continues to be revised as our understanding of the genetics and basic biology of epilepsy improves (Berg 2010; Commission 1981; Commission 1989)

The simplest dichotomy in epilepsy is between focal onset (or partial) and generalised onset seizures. Focal onset seizures originate in one part of the brain and include simple focal, complex focal and secondary generalised seizures (Berg 2010). Generalised onset seizures originate in both cerebral hemispheres simultaneously and include generalised tonic-clonic seizures, absence seizures and myoclonic seizures. In this review, we focus on this dichotomy rather than specific epilepsy syndromes.

Description of the intervention

For the treatment of focal and generalised onset seizures, we included in our evidence base the following 12 AEDs, which were licensed and used in clinical practice for use as monotherapy in at least one country at the time of this review update (eMC 2021; FDA 2021):

1. carbamazepine;
2. phenobarbitone;
3. phenytoin;
4. sodium valproate;
5. oxcarbazepine;
6. lamotrigine;
7. gabapentin;
8. topiramate;
9. levetiracetam;
10. zonisamide;
11. eslicarbazepine acetate;
12. lacosamide.

Carbamazepine, sodium valproate, phenytoin and phenobarbitone are among the earliest drugs licensed for treating epileptic seizures. Carbamazepine and sodium valproate have been commonly used as monotherapy for focal onset and generalised onset seizures for over 30 years (Shakir 1980), while phenytoin and phenobarbitone have been used in monotherapy for over 50 years (Gruber 1962).

These traditionally used drugs have all been recommended as first-line treatments due to their effects across a range of seizure types, however, they are also associated with a number of adverse effects. Phenytoin and phenobarbitone are no longer considered as first-line agents in the USA and much of Europe due to worries over adverse events (Wallace 1997; Wilder 1995). Both drugs have been shown to be teratogenic (associated with malformations of an embryo or fetus) and are associated with low folic acid levels and megaloblastic anaemia (a blood disorder marked by the appearance of very large red blood cells (Carl 1992; Gladstone 1992; Meador 2008; Morrow 2006; Nulman 1997)). Phenytoin is particularly associated with fetal hydantoin syndrome, the name given to a group of birth defects associated with exposure to phenytoin (Scheinfeld 2003), and phenobarbitone has been associated with behavioural disturbances, particularly in children (De Silva 1996; Trimble 1988). These agents are, however, still used as first-line drugs in low- to middle-income countries (Ogunrin 2005; Pal 1998).

Carbamazepine and sodium valproate are also associated with congenital abnormalities (Canger 1999; Gladstone 1992; Morrow 2006; Nulman 1997; Tomson 2011). Systematic reviews have shown sodium valproate to have the highest incidence of congenital malformations of traditional first-line AEDs (Meador 2008; Weston 2016), particularly spina bifida, as well as cardiac, craniofacial, skeletal and limb defects known as 'valproate syndrome' (Ornoy 2009). A recent study has shown an increased prevalence of neurodevelopmental disorders following prenatal sodium valproate exposure (Bromley 2013). A recently published Cochrane Review found that levetiracetam and lamotrigine exposure carried the lowest risk of overall congenital malformation, however, information regarding specific malformations was lacking (Weston 2016).

In the last 20 years, a second-generation of AEDs including oxcarbazepine, lamotrigine, gabapentin, topiramate and, most recently, a third-generation of AEDs, levetiracetam, zonisamide, eslicarbazepine acetate and lacosamide have been licensed as monotherapy following demonstrations of efficacy, or non-inferiority within the European Union, compared to the traditional AEDs (Baulac 2012; Baulac 2017; Bill 1997; Brodie 1995a; Brodie 1999; Brodie 2007; Chadwick 1998; Christe 1997; Dam 1989; Guerreiro 1997; SANAD A 2007, SANAD B 2007; Privitera 2003; Reunanen 1996; Rowan 2005; Steiner 1999; Trinka 2013; Trinka 2018). Comparative studies have also shown the newer AEDs to be generally well tolerated as monotherapy in both adults and children and related to fewer adverse events, fewer serious adverse events, fewer teratogenic effects and fewer drug interactions with concomitant AEDs and other concomitant medications than the

traditional first-line AEDs (French 2004; French 2007; Kwok 2017; Mula 2016).

Current guidelines from the National Institute for Health and Care Excellence (NICE) for adults and children recommend carbamazepine or lamotrigine as first-line treatment for focal onset seizures and sodium valproate for generalised onset seizures, on the condition that women and girls of childbearing age are made aware of the potential teratogenic effects of the drugs (NICE 2012).

How the intervention might work

AEDs suppress seizures by reducing neuronal excitability, hence reducing the probability that a seizure will occur. Different AEDs have different mechanisms of action; therefore, certain AEDs are more effective at treating different seizure types. For example, there are reports of efficacy for sodium valproate in generalised epilepsy syndromes such as juvenile myoclonic epilepsy and absence epilepsy (Bourgeois 1987; Delgado-Escueta 1984; Grünewald 1993; Jeavons 1977; Penry 1989), while carbamazepine, on the other hand, is reported to exacerbate some generalised seizure types such as myoclonic and absence seizures (Liporace 1994; Shields 1983; Snead 1985).

The majority of traditional AEDs are thought to have multiple mechanisms of action such as blocking ion channels, binding with neurotransmitter receptors or inhibiting the metabolism or reuptake of neurotransmitters. However, the precise mechanism of action is not known for all AEDs, particularly sodium valproate. It is thought that one of the mechanisms of action of phenytoin, sodium valproate, carbamazepine, oxcarbazepine and lamotrigine is via blocking of sodium channels (Abdelsayed 2013; Almeida 2007; Beyreuther 2007; Brodie 1996; Faigle 1990; Granger 1995; Grant 1992; Lees 1993; McLean 1986; Pinder 1977; Ragsdale 1991; Soares da Silva 2015; Willow 1985), while phenobarbitone binds with gamma-aminobutyric acid (GABA) A receptors (Rho 1996).

Zonisamide is thought to have multiple mechanisms of action (Endoh 1994; Kawai 1994; Okada 1998; Sackellares 2004; Schauf 1987; Suzuki 1992; Zhu 1999), while the mechanism of actions of gabapentin and topiramate are not fully understood (Brodie 1996; Coulter 1993; Hill 1993; McClean 1995; McLean 1999; White 1997). Levetiracetam has a novel mode of action which is different from that of other AEDs (Cho 2011); it is thought to exhibit its antiepileptic effect by binding to synaptic vesicle protein 2A (encoded within the SV2A gene), influencing excitatory neurotransmitter release (Gillard 2006; Lynch 2004).

Why it is important to do this review

Given that up to 70% of individuals with a new epilepsy diagnosis enter a long-term remission of seizures shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), the correct choice of first-line antiepileptic therapy for individuals with newly diagnosed seizures is of great importance. There are currently over 50 AEDs available worldwide for the treatment of all epilepsy syndromes (eMC 2021; FDA 2021) and, therefore, it is important that the choice of first AEDs is based on the highest-quality evidence regarding potential benefits and harms of various treatments.

We have published a series of Cochrane systematic reviews investigating pairwise monotherapy comparisons using individual participant data (Marson 2000; Nevitt 2018a; Nevitt 2018b; Nevitt 2018c; Nevitt 2018d; Nevitt 2019a; Nevitt 2019b; Nevitt 2019c). Each Cochrane Review and meta-analysis provides high-quality evidence for each pair of drugs but does not inform a choice among the range of drugs available. Furthermore, direct evidence from randomised controlled trials (RCTs) is not available for some drug comparisons such as between oxcarbazepine and phenobarbitone; therefore, it is not possible to make pairwise comparisons of treatment effects between all 12 drugs included in this review. Also, pairwise comparisons between certain drugs are unlikely to be made in the future, such as comparisons with phenobarbitone, which is no longer considered to be a first-line treatment, so it is unlikely that an RCT will be designed in the future to compare oxcarbazepine with phenobarbitone (Tudur Smith 2007). However, it is possible to estimate an indirect treatment effect size between oxcarbazepine and phenobarbitone using existing evidence comparing oxcarbazepine with phenytoin and phenytoin with phenobarbitone (Nevitt 2018b; Nevitt 2019b). By similar methodology, an indirect pairwise comparison is possible for all 12 drugs in our treatment network. Indirect comparisons are also valuable in the case that a limited amount of data are available to inform a direct comparison or in the case that evidence informing a direct comparison is of poor methodological quality. The power and precision of a treatment effect estimate can be increased by 'borrowing strength' from the indirect evidence in the network of treatments (Bucher 1997). Eight of the AEDs included in this review have been included in an IPD network meta-analysis of epilepsy monotherapy drugs (Tudur Smith 2007) and ten of the AEDs were included in a previous version of this review (Nevitt 2017a). We wish to update the information in this network meta-analysis with new evidence from trials published since 2016 and including evidence for two additional drugs (eslicarbazepine acetate and lacosamide), which were licensed for use as monotherapy since the protocol of this review was published in 2014 (Nolan 2014).

As noted in the series of Cochrane Reviews investigating pairwise monotherapy comparisons, the important efficacy outcomes in epilepsy monotherapy trials often require analysis of time-to-event data (for example, time to first seizure after randomisation or time to withdrawal of allocated treatment). Although methods have been developed to synthesise time-to-event data using summary information (Parmar 1998; Williamson 2002), the appropriate statistics are not commonly reported in published epilepsy trials (Nevitt 2017b; Nolan 2013a).

Furthermore, although seizure data have been collected in most epilepsy monotherapy trials, we have seen little uniformity in the definition and reporting of outcomes. For example, trials may report time to 12-month remission but not time to first seizure or vice versa, or some trials may define time to first seizure from the date of randomisation but others use date of achieving a maintenance dose. Trial investigators have also adopted differing approaches to the analysis, particularly with respect to the censoring of time-to-event data. For these reasons, we performed the pairwise meta-analyses using IPD, which helps to overcome these problems and is considered to be the 'gold standard' approach to synthesis of censored data (Parmar 1998). We therefore also performed the network meta-analysis of epilepsy monotherapy drugs as an IPD analysis.

OBJECTIVES

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, and 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).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs using either:

1. an adequate method of allocation concealment (e.g. sealed, opaque envelopes);
2. a quasi method of randomisation (e.g. allocation by date of birth).

Trials may be double-blind, single-blind or unblinded. We included only trials of a monotherapy design; in other words, all participants were randomised to treatment with a single drug. We excluded trials with an add-on (polytherapy), or withdrawal to monotherapy designs.

We included trials of parallel-group designs. We excluded trials of a cross-over design, as this design is not appropriate for assessing treatment decisions at the time of epilepsy diagnosis and the cross-over design is also inappropriate for measuring our primary time-to-event outcome 'time to treatment failure', as treatment failure in the first treatment period would mean than the participant could not cross into the second treatment period, potentially leading to a large amount of incomplete outcome data and therefore a reduction in statistical power. Furthermore, the use of cross-over designs is no longer recommended in epilepsy due to concerns over trial duration, large proportions of dropouts, unblinding of masked treatments as participants cross into the second period, and potential carryover effects; a particular concern in trials of a monotherapy design that aim to assess the effect of a single treatment (Engel 2008; Wyllie 2006).

Types of participants

Children or adults with focal onset seizures (simple focal, complex focal, or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures (with or without other generalised seizure types). We did not include participants with other generalised seizure types alone (for example absence seizures alone without generalised tonic-clonic seizures) as guidelines for the first-line treatment of other generalised seizure types are different from the guidelines for generalised tonic-clonic seizures (NICE 2012), and due to documented evidence that certain drugs of interest in our review may exacerbate some generalised seizure types (How the interventions might work). We also considered individuals with a new diagnosis of epilepsy, or who had had a relapse following antiepileptic monotherapy withdrawal, due to differences in first-line treatment guidelines for individuals with refractory epilepsy (NICE 2012).

We excluded trials that considered AEDs as treatment for conditions other than epilepsy.

Types of interventions

We included the 12 AEDs currently licensed and commonly used as monotherapy in our network of treatments: carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate, and lacosamide.

Included trials had to make at least one pairwise comparison between at least two of the 12 AEDs included in our network. For trials with three treatment arms or more, we included treatment arms only of the 12 AEDs included in our network; treatment arms of drugs not included in our network were excluded from analysis. We did not make pairwise comparisons (direct or indirect) between any AEDs not specified above. We made pairwise comparisons (based on direct or indirect evidence, or both) between all 12 AEDs (regardless of dose) as nodes in the network (Data synthesis).

We included trials with multiple arms of the same drug as long as at least one arm of another drug from our network was included (e.g. multiple doses of gabapentin compared to carbamazepine in Chadwick 1998). We pooled multiple dose arms of the same drug in our analysis; dose comparisons are outside the scope of this review.

Assessment of transitivity

A key assumption made in network meta-analysis is that the treatment effect is 'exchangeable' across all included trials; in other words, the indirect comparison made between two treatments is a feasible comparison to make (known as the transitivity assumption) and that the indirect evidence is consistent with the direct evidence where a comparison exists (known as the consistency assumption, described in the Data synthesis section).

Transitivity requires that all treatments are "jointly randomisable"; in other words, all 12 AEDs could feasibly be randomised in the same trial and those that are not treatment arms in any given trial are "missing at random" (Lu 2006). This assumption cannot be formally tested statistically; transitivity must be judged by careful consideration of trial settings and characteristics, treatment mechanisms and participant demographics to investigate if any differences would be expected to modify relative treatment effects. Given that all of the 12 drugs within this network are licensed as monotherapy treatments for individuals with newly diagnosed focal onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types) and have all been used within trials of similar designs, we have no concerns over the transitivity assumption in this network.

Types of outcome measures

We investigated the following outcomes in this review (Primary outcomes; Secondary outcomes). Reporting of these outcomes in the original trial report was not an eligibility requirement for inclusion in this review.

Primary outcomes

Time to treatment failure (retention time). This was a combined outcome reflecting both efficacy and tolerability, as the following may have led to failure of treatment: continued seizures, side effects, non-compliance or the initiation of additional add-on treatment. This is an outcome to which the participant makes a contribution and is the primary outcome measure recommended

by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Glauser 2006; ILAE 1998).

Time to treatment failure is considered according to the following three definitions.

1. Time to treatment failure for any treatment-related reason (continued seizures, side effects, non-compliance or the initiation of additional add-on treatment).
2. Time to treatment failure due to adverse events (i.e. side effects).
3. Time to treatment failure due to lack of efficacy (i.e. continued seizures).

Secondary outcomes

1. Time to achieve 12-month seizure-free period (remission) after randomisation.
2. Time to achieve six-month seizure-free period (remission) after randomisation.
3. Time to first seizure post-randomisation.
4. Occurrence of adverse events (to be reported narratively) (Data synthesis).

Search methods for identification of studies

Electronic searches

Searches were run for the original review on 29 July 2013. Subsequent searches were run on 8 September 2014, 26 July 2016, 26 April 2018, and 12 September 2019. For the latest update, we searched the following databases on 12 April 2021 with no language restrictions.

1. The Cochrane Register of Studies (CRS Web) using the search strategy outlined in Appendix 1.
2. MEDLINE (Ovid, 1946 to April 09, 2021) using the search strategy outlined in Appendix 2

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 Specialised Registers of Cochrane Review Groups including Epilepsy. In MEDLINE (Ovid), the coverage end date always lags a few days behind the search date. We previously searched SCOPUS (1823 to 9 September 2014), using the search strategy outlined in Appendix 3, as an alternative to Embase, but this is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

Searching other resources

We also reviewed reference lists of retrieved trials to search for additional reports of relevant trials, reviewed relevant conference proceedings and contacted experts in the field for details of any ongoing or unpublished trials.

Data collection and analysis

Selection of studies

One author (SJN) screened all titles and abstracts of all records identified by the electronic searches as described in Search methods for identification of reviews, according to the inclusion criteria specified above (Types of studies; Types of participants; Types of interventions). Subsequently, two authors (SJN and AGM) independently assessed full-text publications according to the same inclusion criteria specified above. We resolved disagreements by discussion or by consulting a third author (CT), where necessary. We recorded the reasons for exclusion of trials at both stages of screening. We contacted trial authors for clarification if the eligibility of a trial was unclear from the published information.

Data extraction and management

Requesting individual participant data

For all trials meeting our inclusion criteria, two authors (SJN and AGM) sent a data-request form to the first or corresponding author, or both, of the trial or to the trial sponsor, where appropriate (referred to as data providers in this review).

Our data-request form asked data providers if the following information was available (tick yes or no).

1. Trial methods:
   a. method of generation of random list;
   b. method of concealment of randomisation;
   c. stratification factors;
   d. blinding methods.
2. Participant covariates:
   a. sex;
   b. age;
   c. seizure types;
   d. epilepsy status (newly diagnosed/relapsed seizures following drug withdrawal);
   e. time between first seizure and randomisation;
   f. number of seizures prior to randomisation (with dates);
   g. presence of neurological signs;
   h. electroencephalography (EEG) results;
   i. computed tomography (CT) or magnetic resonance imaging (MRI) results;
   j. aetiology of seizures (if known).
3. Follow-up data:
   a. treatment allocation;
   b. date of randomisation;
   c. dates of follow-up;
   d. dates of seizures post-randomisation or seizure frequency data between follow-up visits;
   e. dates of treatment failure and reason(s) for treatment failure or withdrawal;
   f. starting dose of treatment;
   g. dates of dose changes;
   h. adverse events reported.

We also requested any available, related documents such as case report forms, trial protocols, clinical summaries etc. from data providers.

In the event of no response to our IPD request, we sent a follow-up email to the original data provider contacted. If we still received no response for a particular trial, we attempted to contact another trial author or sponsor, where appropriate. If a data provider was unable to make IPD available to us, we recorded the quoted reason why IPD

could not be made available, and we requested any aggregate data related to our outcome not reported in the publication.

If data could not be obtained (no response to any requests or IPD was not available), two independent authors (SJN and SC, or MS for the previous version of the review) assessed whether any relevant and appropriate aggregate level data was reported in the trial publication or could be indirectly estimated via the methods described in Parmar 1998 and Williamson 2002. We resolved any disagreements on extracted aggregate data by discussion or by consulting a third author (CT) if necessary.

Management of individual participant data

We stored all obtained data on a secure, dedicated network drive accessible only to the statisticians performing analysis (SJN and CT, or MS for the previous version of the review). We checked all provided data for consistency and prepared them for analysis according to a prespecified procedure prepared by one author (SJN) (available on request) and piloted by two authors (SJN and MS). For each trial where IPD were supplied, we reproduced results from trial findings, where possible, and we performed the following consistency checks:

- trial details cross-checked against any published report of the trial; original trial authors to be contacted if missing data, errors or inconsistencies were found;
- review of the chronological randomisation sequence by checking the balance of prognostic factors, taking account of factors stratified for in the randomisation procedure.

We discussed any inconsistencies in the provided data with the corresponding data providers. If large or major inconsistencies were present, which could not be resolved by data providers, we did not include the data in any analyses. If minor inconsistencies were present, we analysed the data and conducted sensitivity analyses to test the robustness of results (Sensitivity analysis).

Following consistency checking and data cleaning, we prepared datasets for analysis and calculated outcomes for this review according to the methodology summarised below. We followed a 'standard operating procedure' (Nevitt 2017b) for the data cleaning and preparation of data for analysis for all datasets to ensure a standardised and consistent approach to analysis throughout this review.

Preparation of individual participant data for analysis

We accepted follow-up and outcome data in any format provided. If seizure data were provided or recorded in terms of the number of seizures recorded between clinic visits rather than specific dates of seizures, to enable the calculation of time-to-event outcomes, we applied linear interpolation to estimate dates of seizures between follow-up visits. For example, if the trial recorded four seizures between two visits that occurred on 1 March 2010 and 1 May 2010 (interval of 61 days), then the date of the first seizure would be approximately 13 March 2010. This allowed the computation of an estimate of the time to six-month remission, 12-month remission, and first seizure.

We calculated time to six-month and 12-month remission from the date of randomisation to the date (or estimated date) the individual had first been free of seizures for six or 12 months respectively. If the person had one or more seizures in the titration period, a six-month or 12-month seizure-free period could also occur between the estimated date of the last seizure in the titration period and the estimated date of the first seizure in the maintenance period.

We calculated time to first seizure from the date of randomisation to the date that their first seizure was estimated to have occurred. If seizure data were missing for a particular visit, these outcomes were censored at the previous visit. These outcomes were also censored if the individual died or if follow-up ceased prior to the occurrence of the event of interest.

For the analysis of time to treatment failure as a time-to-event outcome, we defined an 'event' as either the treatment failure due to poor seizure control or adverse events, or both. We also classed non-compliance with the treatment regimen or the addition of another AED as 'events'. We censored the outcome if treatment was withdrawn because the individual achieved a period of remission, if a participant withdrew from allocated treatment for reasons not related to the treatment (such as loss to follow-up), or if the individual was still on allocated treatment at the end of follow-up. Two authors (SJN and AG) independently reviewed reasons for treatment failure for classification as events or censored observations, and we resolved any disagreements by mutual discussion or by involving a third author (CT).

Two trials were designed in strata, based on whether recommended treatment would be carbamazepine or sodium valproate (Privitera 2003; Trinka 2013). Within the two strata, participants were randomised to topiramate (Privitera 2003) or levetiracetam (Trinka 2013) compared to the recommended treatment of carbamazepine or sodium valproate, depending on the strata. To ensure that randomised comparisons were made, we analysed data for these two trials according to the separate strata in this review (i.e. treated as two trials Privitera 2003 carbamazepine branch and Privitera 2003 sodium valproate branch).

Assessment of risk of bias in included studies

Two authors (SJN and SC; also JW for the previous version of the review) independently assessed risk of bias in all included trials using the Cochrane tool for assessing risk of bias (Higgins 2011). The following methodological criteria were assessed according to this tool:

1. Selection bias (sequence generation and allocation concealment).
2. Performance bias (blinding of participants and personnel).
3. Selection bias (blinding of outcome assessment).
4. Attrition bias (incomplete outcome data).
5. Reporting bias (selective outcome reporting).
6. Other sources of bias.

We resolved any disagreements by discussion. In theory, a review using IPD should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated. Any selective reporting bias detected could be assessed with the Outcome Reporting Bias in Trials (ORBIT) classification system (Kirkham 2010). As specified in Data extraction and management, we asked the data providers to provide trial methods such as randomisation and blinding methods, and we discussed any missing data or inconsistencies, or both with them.

Measures of treatment effect

We summarised all time-to-event outcomes using the hazard ratio (HR) as the measure of treatment effect. We calculated outcomes from IPD provided, where possible, or extracted summary statistics from published trials. We did not attempt to analyse or synthesise adverse event data; a large range of different adverse events are thought to be associated with the 12 different drugs and such data were collected and presented in different ways across trials. For these reasons, we believe a synthesis of adverse event data would present only selective, and potentially misleading information, while a narrative description of adverse event data from IPD or extracted from published trials would be the most informative way of presenting these data.

Unit of analysis issues

We did not encounter any unit of analysis issues. For inclusion in the review, the unit of allocation had to be the individual. Trials of a repeated-measures (longitudinal) nature or of a cross-over design were not eligible for inclusion.

Dealing with missing data

For all included trials, we conducted an assessment of the proportion of missing outcome, demographic and covariate data and made a judgement regarding the extent and nature of missing data (e.g. missing at random, missing not at random). We attempted to contact all trial authors in order to request relevant data; we included any information regarding missing data in such requests (Data extraction and management). If further information regarding missing data could not be provided, and we judged that an important proportion of data (particularly outcome data) were missing, we conducted sensitivity analyses to investigate the potential impact of the missing data (for example, best case scenario or worst case scenario analyses, assuming those with missing outcome data all had a favourable or unfavourable outcome, respectively).

Assessment of heterogeneity

We used a fixed-effect model for all pairwise and network meta-analyses in the first instance as we anticipated that our specific inclusion criteria would result in eligible studies of a similar design and populations, and we used IPD to standardise definitions of outcomes. Also, our previous reviews of this topic have not showed any important heterogeneity (Marson 2000; Nevitt 2018a; Nevitt 2018b; Nevitt 2018c; Nevitt 2018d; Nevitt 2019a; Nevitt 2019b; Nevitt 2019c); see Data synthesis for further details of pairwise and network meta-analysis.

For each pairwise comparison, we assessed the presence of heterogeneity statistically using the Q test (P value less than 0.10 for significance) and the I^2 statistic with the following interpretation (Higgins 2003):

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: considerable heterogeneity.

We also assessed the presence of heterogeneity by visually inspecting forest plots, particularly in terms of the magnitude and direction of effects. If substantial or considerable heterogeneity (i.e. I^2 of 50% or over) was found to be present for pairwise comparisons, which we were not able to explain by differences in characteristics of the trials and participants, we planned to also present network meta-analysis with a random-effects model.

It was not possible to directly calculate an I^2 statistic for the network meta-analysis due to the between-study covariance structure required for the network meta-analysis model (see Data synthesis). However, for this model, we were able to estimate an R statistic, which compares the impact of heterogeneity in the fixed-effect and random-effects models (Jackson 2012) and it has been previously shown that R can be used to calculate I^2 as follows: $I^2 = (R^2 - 1)/R^2$ (Higgins 2002).

Therefore, we estimated an I^2 statistic for the whole treatment network for each analysis and interpreted this as above. We also presented an estimate of Tau^2 (an estimate of the between-study variance in random-effects meta-analysis) for each analysis, and we have taken both statistics into account when interpreting the presence of any important heterogeneity in the treatment network.

Assessment of reporting biases

Two authors (SJN and SC; also JW for the previous version of the review) undertook a full risk of bias assessment for each eligible trial, including risk of reporting biases. In theory, a review using IPD can overcome issues of reporting biases, as unpublished data can be provided and unpublished outcomes calculated. As specified in Data extraction and management, we asked the data providers for trial methods, such as randomisation and blinding methods, and we discussed any missing data and inconsistencies with them.

If we suspected selective reporting bias in the review, we intended to assess the magnitude and impact of this selective reporting bias using the ORBIT classification system (Kirkham 2010), however, we did not have any major concerns about selective reporting bias in this review.

We considered that formal assessment of publication bias via comparison-adjusted funnel plots (Chaimani 2013) was not appropriate for this review as IPD was available for only a subset of the studies for each outcome and, for the majority of studies providing IPD, the outcomes of interest to this review were not measured directly within the original studies but could be calculated from IPD collected. Instead, we consider the presence of 'availability bias' (Ahmed 2012) within our discussion of Overall completeness and applicability of evidence; in other words, whether the subset of IPD available could be considered representative of the wider evidence base of all eligible studies.

Data synthesis

Figure 1 and Figure 2 visually present the network of 66 pairwise comparisons from the 12 antiepileptic treatments of interest to this review. The primary analysis approach used IPD only; where IPD were not available, but aggregate data could be extracted from studies for one of more outcomes, aggregate data were incorporated into network meta-analysis in Sensitivity analysis.

Figure 1. Network plot of pairwise comparisons regardless of whether any outcome data (IPD or aggregate data) were available; all individuals included within the review, (total 22,040 participants), participants with focal seizures and participants with generalised tonic-clonic seizures with or without other seizure types (shortened to 'generalised seizures' for brevity). Out of a total of 22,040 participants, 15,148 participants were classified as experiencing focal onset seizures (69% of total), 5268 participants were classified as experiencing generalised onset seizures (24% of total) and 1624 had an unclassified or missing seizure type (7% of total). Note that the size of the node indicates the number of studies the drug is included in and the thickness of the edges corresponds to the number of participants contributing to the comparison (i.e. larger node = more studies, thicker edge = more participants). CBZ: carbamazepine; ESL: eslicarbazepine acetate; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PHB: phenobarbitone; PHT: phenytoin; TPM: topiramate; VPS: sodium valproate; ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures.

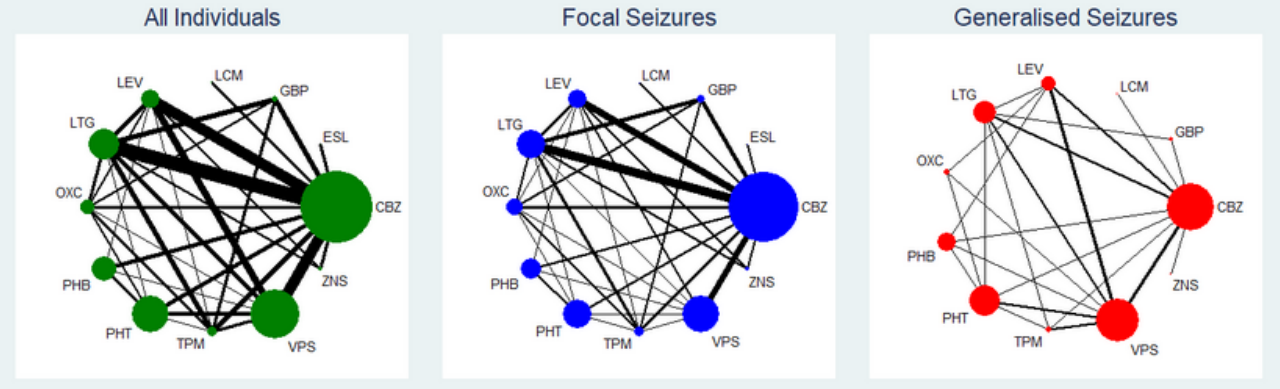
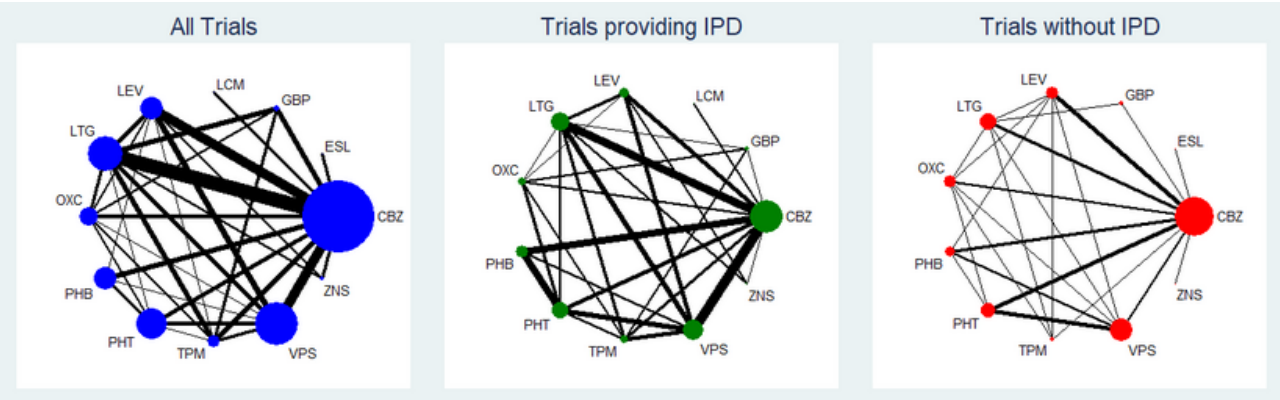


Figure 2. Network plot of pairwise comparisons in all included studies, studies providing individual participant data (IPD) and studies without IPD Note that the size of the node indicates the number of studies the drug is included in and the thickness of the edges corresponds to the number of participants contributing to the comparison (i.e. larger node = more studies, thicker edge = more participants). CBZ: carbamazepine; ESL: eslicarbazepine acetate; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PHB: phenobarbitone; PHT: phenytoin; TPM: topiramate; VPS: sodium valproate; ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures.



Pairwise and Network meta-analysis

We used the statistical software package SAS (version 9.4) (SAS 2013) to perform all data cleaning, consistency checking and data preparation (see Data extraction and management) and Stata version 14 (StataCorp 2015) to perform all syntheses of direct and indirect evidence.

We took an intention-to-treat approach (as far as possible) to analysis; in other words, we analysed participants in the group to which they had been randomised in an individual trial, irrespective of which treatment they had actually received. Therefore, for time-to-event outcomes, 'time to six-month remission', 'time to 12-month remission' and 'time to first seizure post-randomisation', participants were not censored if treatment was withdrawn. For the primary outcome, time to treatment failure, we considered

treatment failures due to lack of efficacy (i.e. recurrent seizures), poor tolerability (i.e. adverse events) or a combination of both poor efficacy and tolerability. Other withdrawals such as losses to follow-up, non treatment-related deaths, administrative trial reasons etc. were censored at the time of withdrawal.

For all time-to-event outcomes, we fitted a Cox proportional hazards regression model, stratified by trial to preserve the within-trial randomisation, to the entire individual participant dataset. We fitted this model via the 'mvmeta_make' command in Stata version 14 to produce a dataset in the correct format to perform network meta-analysis with the 'mvmeta' command (White 2009); in other words, a dataset with trial-specific estimates of treatment effect (log HR), the associated variance of the treatment effect and covariances, where applicable (i.e. correlation between treatment-effects for trials with more than two treatment arms).

The Cox proportional hazards model assumes that the ratio of hazards (risks) between the two treatment groups is constant over time. To assess the validity of this assumption, we tested the statistical significance of time-varying covariates for all covariates in the primary model. If we had reason to believe that the proportional hazards assumption had been violated in the primary model, in sensitivity analysis, we fitted a parametric, accelerated failure-time model, stratified by trial, to the entire individual participant dataset via the 'mvmeta_make' command and compared these results to those of the primary analysis (White 2009). An accelerated failure-time model assumes that treatment effect accelerates or decelerates over time, rather than remains constant as assumed by the Cox proportional hazards model.

We calculated direct pairwise treatment effect estimates (where possible) using the 'metan' command (Palmer 2016) in Stata version 14 to pool trial-specific log hazard ratios from the Cox proportional hazards model, as described above.

Network meta-analysis provided treatment effect estimates combining direct and indirect evidence. We performed network meta-analysis via the 'mvmeta' command in Stata version 14, assuming equal heterogeneity for all comparisons (i.e. a between-study covariance structure (variance-covariance matrix) proportional to unknown parameter Tau^2) (White 2009). It was necessary to make an assumption regarding the between-study covariance structure for a network without pairwise comparisons between all treatments of interest. However, due to this assumption regarding heterogeneity, we could not calculate an I^2 statistic directly from the model and had to estimate it (see Assessment of heterogeneity).

We performed pairwise and network meta-analyses with a treatment by epilepsy type interaction (see Subgroup analysis and investigation of heterogeneity for further details).

For clinical interest and relevance, we have presented HR estimates from the network model (direct and indirect evidence combined) for each AED in the network compared to the current recommended first-line treatments (carbamazepine or lamotrigine for focal onset seizures and sodium valproate for generalised onset seizures) and for all comparisons by epilepsy type in the main results of this review via forest plots.

Often rankings of treatments (i.e. the probability that each treatment in the network is the best) are presented for network meta-analysis; however, due to the treatment by epilepsy type interaction in this model, we could not directly calculate rankings by epilepsy type. Instead, we informally 'ranked' treatments by ordering according to their treatment-effect sizes compared to the reference treatment (e.g. better or worse than carbamazepine) on the forest plots presented.

Investigation of consistency in network meta-analysis

The consistency assumption can be evaluated statistically comparing the difference between the direct treatment effect estimate and the indirect estimate for each loop of evidence. Given the complexity of the network model fitted (with treatment by epilepsy type interaction) and the number of multi-arm trials included in analysis, we performed node splitting in Stata version 14 via the command 'network sidesplit' (Dias 2010; White 2015) to formally estimate differences between direct and indirect evidence for each comparison. In order to examine any clinical inconsistency (i.e. important differences in numerical results between direct, indirect and network results), we have presented HR estimates for direct evidence, indirect evidence (from the node splitting model) and direct plus indirect evidence from the network models for each pairwise comparison via forest plots, and discussed the potential origins and implications of any apparent inconsistency. Secondly, we fitted a 'design-by-treatment' inconsistency model in Stata version 14 via mvmeta (White 2009); this method evaluates both loop and design inconsistencies, particularly within multi-arm trials (Higgins 2012).

Adverse events

Due to the wide range of events reported in the trials and the different methods of recording and reporting of adverse events, we have not analysed adverse event data in meta-analysis but have provided a narrative report according to the definition of the events within the data provided to us or in the published paper.

Subgroup analysis and investigation of heterogeneity

There are strong clinical beliefs that certain AEDs are more effective in certain seizure types than others, for example, carbamazepine is more effective in focal onset seizures and sodium valproate is more effective in generalised onset seizures (Marson 2000), suggesting that there is a treatment-by-seizure-type (focal or generalised) interaction. Without taking account of this potential interaction in our analysis, we believe that the key assumption of an exchangeable treatment effect across all included trials would be violated.

To account for this, we conducted all analyses separately by epilepsy type (focal onset or generalised onset) according to the classification of main seizure type at baseline and performed all network meta-analysis with a treatment-by-epilepsy-type interaction. We classified focal seizures (simple or complex) and focal secondarily generalised seizures as focal epilepsy. We classified primarily generalised seizures as generalised epilepsy. We then judged exchangeability of treatment effect separately by analyses of seizure type.

We also performed an analysis adjusted for age at entry into the trial (an interaction between treatment and age (centred) added to the initial Cox proportional hazards model described in Data synthesis) and we compared results to primary analysis with adjustment only for seizure type. For one trial (Baulac 2017), exact age was not

provided in IPD and age intervals only were provided; for this analysis, we estimated participant age as the middle of the age interval.

We would have liked to explore other participant covariates specified in Data extraction and management as potential modifiers of treatment effect and as potential sources of heterogeneity or inconsistency, or both, such as seizure frequency before randomisation (time since first ever seizure and/or number of seizures before randomisation) and aetiology of seizures (if known according to pretreatment investigations such as EEG, CT and/or MRI scan); however, due to large proportions of missing data for most of these covariates and variability in the definitions of data provided to us for these covariates (see Included studies), an additional adjusted analysis was not appropriate. We will consider other options to explore these covariates for updates of this review, if appropriate data become available.

Sensitivity analysis

As described in Data synthesis, we applied a fixed-effect model principally to pairwise and network meta-analysis, and fitted a random-effects model to both pairwise and network meta-analysis models in sensitivity analysis, and compared the results.

Also. as described in Data synthesis, we applied a Cox proportional hazards model principally to pairwise and network meta-analysis. We fitted an accelerated failure-time model, which does not make the assumption of constant treatment effect over time, to both pairwise and network meta-analysis models in sensitivity analysis and compared the results.

As specified in Data extraction and management, we discussed any inconsistencies in the provided data with the corresponding data providers and performed sensitivity analyses to investigate the impact of any missing data (see Dealing with missing data). If large or major inconsistencies were present, which could not be resolved by the data providers, we would not include the data in any analyses. If minor inconsistencies were present, we included the data in analyses and pursued sensitivity analyses to test the robustness of results included in these data. We performed the following sensitivity analyses due to inconsistencies in IPD provided and compared the results of sensitivity analyses to those of the primary analysis:

1. In Stephen 2007, there were minor inconsistencies between rates of seizure recurrence and reasons for treatment failure between the data provided and the published paper, which the trial authors could not resolve. Therefore, we performed sensitivity analysis excluding Stephen 2007 from all analyses.
2. In Reunanen 1996, participants were considered to have completed the trial and hence treatment was withdrawn if they experienced a seizure after week six. This does not correspond with the treatment failure definition used in this review (see Primary outcomes and Data extraction and management). Therefore, we performed sensitivity analysis excluding Reunanen 1996 for the analysis of 'time to treatment failure'.
3. In Banu 2007, there were minor inconsistencies between rates of seizure recurrence between the data provided and the published paper, which the authors could not resolve. Therefore, we performed sensitivity analysis excluding Banu 2007 from analysis of 'time to first seizure' (data for first seizure recurrence only were available, so this trial did not contribute to outcomes of time to six-month remission and time to 12-month remission).
4. Nieto-Barrera 2001 did not include seizures that occurred during the first four weeks of the trial in efficacy analyses, and dates of seizures before week four were not supplied to us. Therefore, we calculated seizure outcomes as the time to first seizure and time to six-month remission after week four rather than after randomisation. We performed sensitivity analysis excluding seizure data for Nieto-Barrera 2001 from analysis of 'time to first seizure' (this trial was 24 weeks' duration so did not contribute to outcomes of time to six-month remission and time to 12-month remission).
5. In Placencia 1993, there were minor inconsistencies between reasons for treatment failure between the data provided and the published paper. We compared reasons for treatment failure in the data provided with reasons reported in the publication and performed a sensitivity analysis for the analysis of 'time to treatment failure', with treatment failures reclassified according to definitions from the published paper (this sensitivity analysis was also performed in a previously published Cochrane Review, see Nevitt 2018d for further details).

Given that misclassification of seizure type is a recognised problem in epilepsy (whereby some individuals with generalised seizures have been mistakenly classed as having focal onset seizures and vice versa) and such misclassification did impact upon the results of a review in our series of pairwise reviews for monotherapy in epilepsy comparing phenytoin and sodium valproate in which nearly 50% of participants analysed may have had their seizure type misclassified (Nevitt 2018b), we investigated the potential impact of misclassification on results in a sensitivity analysis. Given clinical evidence that individuals with generalised onset seizures are unlikely to have an 'age of onset' greater than 25 to 30 years (Malafosse 1994), we examined the distribution of age at onset for individuals with generalised seizures. We identified 1780 participants classified as experiencing generalised seizures and estimated age of onset as greater than 30 years (age of first seizure provided directly in IPD or estimated to be within one year of age of entry into trial for newly diagnosed participants), or with a missing seizure classification at baseline. We performed two sensitivity analyses to investigate misclassification:

1. reclassification of all individuals with generalised seizures and age of onset greater than 30 years as having focal onset seizures. We then repeated network meta-analysis with the interaction term of treatment by seizure type with the reclassified seizure type.
2. reclassification of all individuals with generalised seizure types and age at onset greater than 30 years and those with missing seizure type into an 'unclassified seizure type' group. We then repeated network meta-analysis with the interaction term of treatment by seizure type, where seizure type was focal epilepsy compared to generalised or unclassified epilepsy.

We were unable to perform network meta-analysis with a 'three-way' interaction (i.e. focal epilepsy compared to generalised epilepsy compared to unclassified epilepsy) due to small numbers of participants with unclassified epilepsy on some of the treatments.

Where possible, if IPD were not available for analysis, we attempted to extract aggregate data. Where aggregate hazard ratios and standard errors or confidence intervals could be extracted or estimated from trial publications by seizure type for our outcomes of interest, we incorporated these estimates into network meta-analysis and compared the results of these sensitivity analyses to those of the primary analysis.

We requested data for one trial, Biton 2001, via the data sharing portal ClinicalStudyDataRequest.com and the data were provided to us via a remote secure data access system that allowed analysis in SAS-based statistical software and export of analysis results. We were unable to combine this dataset with the other datasets to perform the analyses described below in Stata version 14, therefore, we treated the results exported from the data access system as aggregate data in sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We have presented six summary of findings tables for our primary outcome and first secondary outcome by epilepsy type and by reference treatment (see Data synthesis for further information):

1. Time to treatment failure for any reason for individuals with focal seizures (reference treatment carbamazepine) (see Summary of findings 1);
2. Time to treatment failure for individuals with focal seizures (reference treatment lamotrigine) (see Summary of findings 2);
3. Time to treatment failure for individuals with generalised seizures (reference treatment sodium valproate) (see Summary of findings 3);
4. Time to 12-month remission for individuals with focal seizures (reference treatment carbamazepine) (see Summary of findings 4);
5. Time to 12-month remission for individuals with focal seizures (reference treatment lamotrigine) (see Summary of findings 5);
6. Time to 12-month remission for individuals with generalised seizures (reference treatment sodium valproate) (see Summary of findings 6).

We have presented the tables based on the approach of Salanti 2014; we presented the relative effects from direct evidence and from network meta-analysis, number of studies and participants contributing to direct evidence, and the proportion of direct evidence contributing to the network meta-analysis estimates. We assessed the confidence in the NMA results (i.e. the certainty of the evidence) according to the CINeMA approach (Nikolakopoulou 2020), which assesses six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence (inconsistency). We downgraded evidence by one level if we considered the limitation relating to a domain to be serious and two levels if we considered it to be very serious.

RESULTS

Description of studies

Results of the search

Within the original review (Nevitt 2017a), we identified 6762 records from the databases and search strategies outlined in Search methods for identification of studies. We found three further records by handsearching and checking reference lists of included studies. We removed 3032 duplicate records and screened 3733 records (title and abstract) for inclusion in the review. We excluded 3591 records based on title and abstract and assessed 142 full-text articles for inclusion in the review. We excluded 31 studies (described in 32 full-text articles) from the review (see Excluded studies below) and included 77 trials in the review, which were reported in 95 full-text articles (see Included studies below). We identified seven studies as ongoing (EpiNet-First Trial 2; EpiNet-First Trial 3; EpiNet-First Trial 4; EpiNet-First Trial 5; EpiNet-First Trial 1; NCT01891890; NCT02201251) and seven studies (described in eight records) as awaiting classification (translation: Chen 2013; Korean Zonisamide Study 1999; Park 2001; Rysz 1994; Xu 2012) or further information (IRCT201202068943N1; NCT00154076).

For the updated review, we identified 945 records from the databases and search strategies outlined in Search methods for identification of studies. We found four further records by handsearching and checking reference lists of included studies. We removed 166 duplicate records and screened 1073 records (title and abstract) for inclusion in the review. We excluded 1014 records based on title and abstract and assessed 59 full-text articles for inclusion in the review. We excluded four studies from the review which were not randomised (Foldvary-Schaefer 2017; Tabrizi 2019), not a monotherapy study (Hu 2012) and did not randomise participants individually (Loring 2020). We also excluded one study which was previously identified as ongoing, as new information showed that this study terminated early, with no relevant results to this review available (NCT01891890) and two studies which were previously awaiting assessment after translation; one study was not randomised (Rysz 1994) and the other study included children with ineligible seizure types for this review (Park 2001).

We included nine new trials, which were described in 32 full-text articles (Akter 2018; Baulac 2017; Giri 2016; Maiti 2018; SANAD II A 2021; SANAD II B 2021; Sidhu 2018; Trinka 2018; Wu 2018) and we also included three studies, described in four full-text articles, which were previously awaiting assessment following translation (Chen 2013; Korean Zonisamide Study 1999; Xu 2012). We identified six additional studies as ongoing (CTRI/2017/11/010605; CTRI/2017/11/010605; CTRI/2019/04/018520; CTRI/2019/05/018990; CTRI/2020/09/027792; IRCT20120215009014N351; IRCT20170216032603N2) and ten additional studies as awaiting classification (Ahadi 2020; Akhondian 2020; CTRI/2011/08/001959; Du 2016; Goyal 2016; NCT00154076; Shi 2020; Suo 2021; Wang 2016; Zhou 2019).

We added five records as additional references to trials previously included in the review, and we identified a full-text publication of a trial previously included in the review as ClinicalTrials.gov summary NCT01498822 (Kim 2017).

Therefore, in total, 89 trials, which were described in 136 full-text articles were included in this updated version of the review. See Figure 3 for PRISMA study flow diagram (Moher 2009).

Figure 3. Study flow diagram

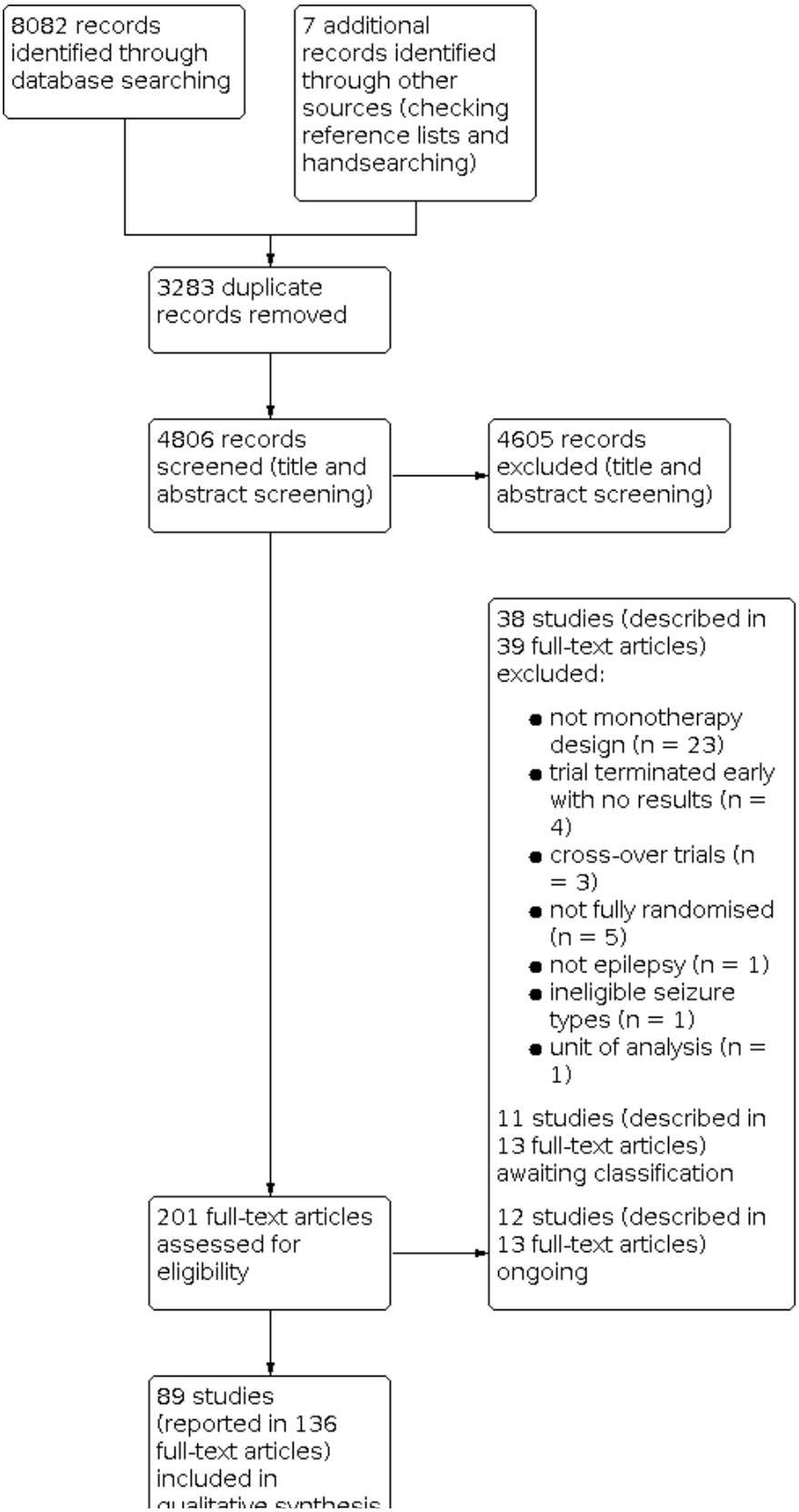
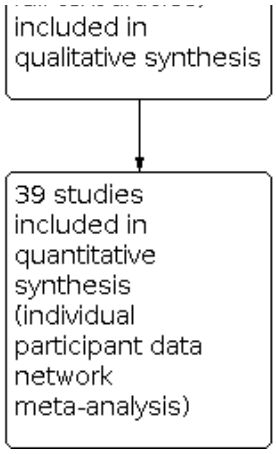


Figure 3. (Continued)



Included studies

We included 89 trials in the review (Aikia 1992; Akter 2018; Banu 2007; Baulac 2012; Baulac 2017; Bidabadi 2009; Bill 1997; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2002; Brodie 2007; Callaghan 1985; Capone 2008; Castriota 2008; Chadwick 1998; Chen 1996; Chen 2013; Cho 2011; Christe 1997; Consoli 2012; Cossu 1984; Craig 1994; Czapinski 1997; Dam 1989; De Silva 1996; Dizdarer 2000; Donati 2007; Eun 2012; Feksi 1991; Forsythe 1991; Fritz 2006; Gilad 2007; Giri 2016; Guerreiro 1997; Heller 1995; Jung 2015; Kalviainen 2002; Kim 2017; Kopp 2007; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Kwan 2009; Lee 2011; Lukic 2005; Maiti 2018; Mattson 1985; Mattson 1992; Mitchell 1987; Miura 1990; Motamedi 2013; NCT01954121; Nieto-Barrera 2001; Ogunrin 2005; Pal 1998; Placencia 1993; Privitera 2003; Pulliainen 1994; Ramsay 1983; Ramsay 1992; Ramsay 2007; Ramsay 2010; Rastogi 1991; Ravi Sudhir 1995; Resendiz 2004; Reunanen 1996; Richens 1994; Rowan 2005; Saetre 2007; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Shakir 1981; Sidhu 2018; So 1992; Steiner 1999; Steinhoff 2005; Stephen 2007; Suresh 2015; Thilothammal 1996; Trinka 2013; Trinka 2018; Turnbull 1985; Verity 1995; Werhahn 2015; Wu 2018; Xu 2012)

Seven trials were available in abstract form only (Bidabadi 2009; Czapinski 1997; Fritz 2006; Kalviainen 2002; Kopp 2007; Lukic 2005; Ramsay 2007), one trial was published only as an abstract and the author provided an unpublished manuscript on request (Akter 2018), one was available in English only as a clinical trial summary report (Korean Lamotrigine Study Group 2008) and one trial was available only as an online summary (NCT01954121). Three trials were published in Italian (Capone 2008; Castriota 2008; Cossu 1984), two in Chinese (Chen 2013; Xu 2012), one in Korean (Korean Zonisamide Study 1999), one in Persian (Motamedi 2013) and one in Spanish (Resendiz 2004) and were translated into English. One of the published reports contained results on two separate RCTs run on very similar protocols; although the two trials were reported within the same publication, we treated them as separate trials within this review (Brodie 1995a; Brodie 1995b).

Trial design characteristics

Thirty-five trials were single-centre; they were conducted in Bangladesh (Banu 2007) Iran (Bidabadi 2009; Motamedi 2013), Ireland (Callaghan 1985), Italy (Capone 2008; Castriota 2008; Cossu 1984), Taiwan (Chen 1996), Republic of Korea (Cho 2011), China (Chen 2013; Xu 2012; Wu 2018), the UK (Craig 1994; Forsythe 1991; Stephen 2007; Turnbull 1985), Turkey (Dizdarer 2000), Kenya (Feksi 1991), Israel (Gilad 2007), Germany (Kopp 2007), Serbia and Montenegro (Lukic 2005), USA (Mitchell 1987), Japan (Miura 1990), Nigeria (Ogunrin 2005), India (Akter 2018; Giri 2016; Maiti 2018; Pal 1998; Rastogi 1991; Ravi Sudhir 1995; Sidhu 2018; Suresh 2015; Thilothammal 1996), Ecuador (Placencia 1993) and Finland (Pulliainen 1994).

Fifty trials were multicentre; they were conducted in centres across the USA (Biton 2001; Mattson 1985; Mattson 1992; Ramsay 1983; Ramsay 1992; Ramsay 2007; Ramsay 2010; Rowan 2005), UK (Brodie 1995a; Brodie 1995b; Brodie 1999; De Silva 1996; Heller 1995; Richens 1994; SANAD A 2007; SANAD II A 2021; SANAD B 2007; SANAD II B 2021; Steiner 1999; Verity 1995), UK and New Zealand (Shakir 1981), Europe (Consoli 2012; Dam 1989; Donati 2007; Kalviainen 2002; Saetre 2007; Steinhoff 2005; Werhahn 2015), Europe and Australia (Brodie 2002; Reunanen 1996; Trinka 2013), Europe and South Africa (Brodie 2007), Europe and Mexico (Nieto-Barrera 2001), Europe, South America and South Africa (Christe 1997), Europe, North America and Asia Pacific (Baulac 2017); South America and South Africa (Bill 1997; Guerreiro 1997), Republic of Korea (Eun 2012; Jung 2015; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Lee 2011; Kim 2017), China (NCT01954121), Hong Kong (Kwan 2009), Mexico (Resendiz 2004), Asia, Australia and Europe (Baulac 2012), Asia, Australia, Europe and South America (Trinka 2018), Europe, Australia, Canada and South Africa (Chadwick 1998), USA, Canada, Europe and South America (Privitera 2003).

Four trials did not state whether they were single- or multicentre; these trials were conducted in Finland (Aikia 1992), Poland (Czapinski 1997), Germany (Fritz 2006) and the USA (So 1992).

Participant characteristics

Thirty trials were designed to recruit individuals with focal seizures only (Baulac 2012; Bidabadi 2009; Castriota 2008; Chadwick 1998; Chen 2013: Cho 2011; Cossu 1984; Czapinski 1997; Dizdarer 2000; Donati 2007; Eun 2012; Gilad 2007; Jung 2015; Lee 2011; Maiti 2018; Mattson 1985; Mattson 1992; Mitchell 1987; Kim 2017; NCT01954121; Nieto-Barrera 2001; Ramsay 2007; Resendiz 2004; SANAD A 2007; SANAD II A 2021; So 1992; Suresh 2015; Trinka 2018; Werhahn 2015; Xu 2012). Five trials were designed to

recruit individuals with generalised tonic-clonic seizures with or without other generalised seizure types or unclassified seizure types only (Giri 2016; Ramsay 1992; SANAD B 2007; SANAD II B 2021; Thilothammal 1996). The remaining 54 trials recruited individuals with focal or generalised tonic-clonic seizures with or without other generalised seizure types (Aikia 1992; Akter 2018; Banu 2007; Baulac 2017; Bill 1997; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2002; Brodie 2007; Callaghan 1985; Capone 2008; Chen 1996; Christe 1997; Consoli 2012; Craig 1994; Dam 1989; De Silva 1996; Feksi 1991; Forsythe 1991; Fritz 2006; Guerreiro 1997; Heller 1995; Kalviainen 2002; Kopp 2007; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Kwan 2009; Lukic 2005; Miura 1990; Motamedi 2013; Ogunrin 2005; Pal 1998; Placencia 1993; Privitera 2003; Pulliainen 1994; Ramsay 1983; Ramsay 2010; Rastogi 1991; Ravi Sudhir 1995; Reunanen 1996; Richens 1994; Rowan 2005; Saetre 2007; Shakir 1981; Sidhu 2018; Steiner 1999; Steinhoff 2005; Stephen 2007; Trinka 2013; Turnbull 1985; Verity 1995; Wu 2018). However, five trials did not describe the number of participants with each seizure type recruited (Capone 2008; Dam 1989; Forsythe 1991; Fritz 2006; Saetre 2007).

Fifty-five trials recruited only individuals with new onset seizures and no previous AED treatment at all (i.e. treatment-naive) or within the weeks or months preceding recruitment into the trial (Aikia 1992; Baulac 2012; Baulac 2017; Bill 1997; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; Castriota 2008; Chen 1996; Cho 2011; Christe 1997; Cossu 1984; Craig 1994; Czapinski 1997; Dam 1989; De Silva 1996; Donati 2007; Eun 2012; Forsythe 1991; Guerreiro 1997; Giri 2016; Heller 1995; Jung 2015; Kalviainen 2002; Kopp 2007; Korean Zonisamide Study 1999; Lukic 2005; Maiti 2018; Mitchell 1987; Miura 1990; Motamedi 2013; Kim 2017; NCT01954121; Ogunrin 2005; Pal 1998; Placencia 1993; Privitera 2003; Pulliainen 1994; Ramsay 1983; Ramsay 1992; Ravi Sudhir 1995; Resendiz 2004; Saetre 2007; SANAD II A 2021; SANAD II B 2021; Sidhu 2018; Steiner 1999; Steinhoff 2005; Stephen 2007; Suresh 2015; Thilothammal 1996; Turnbull 1985; Werhahn 2015; Xu 2012). Three trials recruited individuals with new onset post-stroke seizures (Consoli 2012; Capone 2008; Gilad 2007), seven trials recruited individuals with new onset or long-term untreated seizures (Banu 2007; Callaghan 1985; Feksi 1991; Lee 2011; Korean Lamotrigine Study Group 2008; Nieto-Barrera 2001; Trinka 2013), six trials recruited individuals with new onset, untreated or under-treated seizures (Mattson 1985; Mattson 1992; Ramsay 2007; Ramsay 2010; Rowan 2005; So 1992), five trials recruited individuals with new onset or relapsed seizures following a period of remission (Chadwick 1998; Kwan 2009; Reunanen 1996; Richens 1994; Verity 1995), three trials recruited individuals with new onset, relapsed seizures following a period of remission or individuals whose previous treatment with an AED had failed (SANAD A 2007; SANAD B 2007; Shakir 1981) and 10 trials did not state if individuals had received previous AED treatment (Akter 2018; Biton 2001; Brodie 2002; Bidabadi 2009; Chen 2013; Dizdarer 2000; Fritz 2006; Rastogi 1991; Trinka 2018; Wu 2018).

Twenty-two trials recruited adults and children (Biton 2001; Brodie 1995a; Brodie 1995b; Callaghan 1985; Chadwick 1998; Cho 2011; Feksi 1991; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Nieto-Barrera 2001; Placencia 1993; Privitera 2003; Ramsay 1992; Ramsay 2010; Rastogi 1991; Reunanen 1996; SANAD A 2007; SANAD II A 2021; SANAD B 2007; SANAD II B 2021; Shakir 1981; Steinhoff 2005; Stephen 2007; Xu 2012).

Seventeen trials recruited children: four trials recruited children under the age of 12 years (Bidabadi 2009; Eun 2012; Mitchell 1987; Thilothammal 1996), two trials recruited children under 14 years (Chen 2013; Forsythe 1991), four trials recruited children under 15 years (Akter 2018; Banu 2007; Chen 1996; Dizdarer 2000), three trials recruited children under 16 years (De Silva 1996; Jung 2015; Verity 1995), one trial recruited children under 17 years (Donati 2007) and three trials recruited children under 18 years (Guerreiro 1997; Pal 1998; Resendiz 2004).

Forty-four trials recruited adults: two trials defined adults as over the age of 13 years (Heller 1995; So 1992), four trials defined adults as over the age of 14 years (Ogunrin 2005; Ravi Sudhir 1995; Steiner 1999; Turnbull 1985); four trials defined adults as over the age of 15 years (Cossu 1984; Dam 1989; Fritz 2006; Pulliainen 1994), ten trials defined adults as over the age of 16 years (Baulac 2017; Bill 1997; Brodie 2002; Brodie 2007; Christe 1997; Lee 2011; Kim 2017; NCT01954121; Richens 1994; Trinka 2013), twelve trials defined adults as over the age of 18 years (Baulac 2012; Consoli 2012; Czapinski 1997; Giri 2016; Kwan 2009; Lukic 2005; Maiti 2018; Mattson 1985; Mattson 1992; Ramsay 1983; Suresh 2015; Trinka 2018) and five trials did not state the minimum age of an 'adult' in the trial (Aikia 1992; Capone 2008; Castriota 2008; Gilad 2007; Wu 2018).

Seven trials recruited elderly participants: two trials recruited participants over the age of 65 years (Brodie 1999; Saetre 2007) and five trials recruited individuals over the age of 60 years (Craig 1994; Motamedi 2013; Ramsay 2007; Rowan 2005; Werhahn 2015). One trial measuring reproductive hormone levels among female participants receiving AEDs recruited female participants between the ages of 12 and 40 years (Sidhu 2018). Three trials did not state the age ranges of eligible participants (Kalviainen 2002; Kopp 2007; Miura 1990).

Interventions

Table 1 shows the number of participants randomised to each of the 12 drugs, split according to the trials for which individual participant data were available and not available:

1. 6120 participants were randomised to carbamazepine in 58 trials, and we were provided with 62% of IPD (3815 participants from 25 trials);
2. 3537 participants were randomised to lamotrigine in 29 trials, and we were provided with 67% of IPD (2354 participants from 15 trials)
3. 2627 participants were randomised to sodium valproate in 30 trials, and we were provided with 77% of IPD (2025 participants from 15 trials)
4. 2617 participants were randomised to levetiracetam in 20 trials, and we were provided with 70% of IPD (1843 participants from six trials)
5. 1383 participants were randomised to phenytoin in 23 trials, and we were provided with 73% of IPD (1009 participants from 12 trials)
6. 1267 participants were randomised to topiramate in seven trials, and we were provided with 92% of IPD (1163 participants from five trials)
7. 1140 participants were randomised to oxcarbazepine in 14 trials, and we were provided with 42% of IPD (478 participants from four trials)

8. 948 participants were randomised to gabapentin in four trials, and we were provided with 63% of IPD (595 participants from two trials)
9. 822 participants were randomised to phenobarbitone in 14 trials, and we were provided with 53% of IPD (439 participants from seven trials)
10. 685 participants were randomised to zonisamide in three trials, and we were provided with 89% of IPD (612 participants from two trials)
11. 445 participants were randomised to lacosamide in one trial, and we were provided with IPD for all participants in this trial (100% of IPD)
12. 401 participants were randomised to eslicarbazepine acetate in one trial, but we did not receive IPD for this trial (0% of IPD)

One trial with 37 participants (Ramsay 2010, IPD not provided) randomised individuals to carbamazepine or levetiracetam but did not state how many individuals were randomised to each drug and, for 11 individuals, the randomised drug was missing from the IPD.

In total, we were provided with data for 14,789 out of a total of 22,040 eligible participants (67% of total data) from 39 out of the 89 eligible trials (43%).

Trials providing individual participant data

Individual participant data were available for 39 trials recruiting 14,789 participants (Banu 2007; Baulac 2012; Baulac 2017; Bill 1997; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; Chadwick 1998; Craig 1994; De Silva 1996; Dizdarer 2000; Eun 2012; Guerreiro 1997; Heller 1995; Kwan 2009; Lee 2011; Mattson 1985; Mattson 1992; Nieto-Barrera 2001; Ogunrin 2005; Pal 1998; Placencia 1993; Privitera 2003; Ramsay 1992; Ramsay 2010; Reunanen 1996; Richens 1994; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Stephen 2007; Trinka 2013; Turnbull 1985; Verity 1995; Werhahn 2015).

Participant characteristics

Table 2, Table 3 and Table 4 show the participant characteristics from the trials providing IPD.

Data were available for the following participant characteristics (percentage of 14,789 participants with data available): sex (99.9%, data missing for 17 participants), seizure type (99%, data missing for 150 participants), drug randomised (99.9%, data missing for 11 participants), age at randomisation (99.7%, data missing for 98 participants), number of seizures in six months prior to randomisation (85.8%, data missing for 2096 participants), and time since first seizure to randomisation (47%, data missing for 7820 participants).

Eighteen trials (Baulac 2012; Baulac 2017; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; De Silva 1996; Eun 2012; Heller 1995; Lee 2011; Ogunrin 2005; Pal 1998; Reunanen 1996; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999) provided the results of neurological examinations for 7823 participants (53%). Twenty-two trials (Banu 2007; Baulac 2017; Bill 1997; Brodie 1995a; Brodie 1995b; Chadwick 1998; Craig 1994; Dizdarer 2000; Eun 2012; Guerreiro 1997; Lee 2011; Mattson 1985; Placencia 1993; Reunanen 1996; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Stephen 2007; Turnbull 1985; Werhahn 2015) provided electroencephalographic (EEG) results for 6776 participants (45%). Twenty trials (Banu 2007; Baulac 2017; Bill 1997; Brodie 1995a; Brodie 1995b; Brodie 1999; Dizdarer 2000; Eun 2012; Guerreiro 1997; Lee 2011; Mattson 1985; Ogunrin 2005; Reunanen 1996; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Turnbull 1985; Werhahn 2015) provided computerised tomography/magnetic resonance imaging (CT/MRI) results for 5776 participants (39%).

Trials without individual participant data provided

The remaining 50 trials recruiting 7251 participants did not provide IPD for the review (Aikia 1992; Akter 2018; Bidabadi 2009; Brodie 2002; Callaghan 1985; Capone 2008; Castriota 2008; Chen 1996; Chen 2013; Cho 2011; Christe 1997; Consoli 2012; Cossu 1984; Czapinski 1997; Dam 1989; Donati 2007; Feksi 1991; Forsythe 1991; Fritz 2006; Gilad 2007; Giri 2016; Jung 2015; Kalviainen 2002; Kim 2017; Kopp 2007; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Lukic 2005; Maiti 2018; Mitchell 1987; Miura 1990; Motamedi 2013; NCT01954121; Pulliainen 1994; Ramsay 1983; Ramsay 2007; Rastogi 1991; Ravi Sudhir 1995; Resendiz 2004; Rowan 2005; Saetre 2007; Shakir 1981; Sidhu 2018; So 1992; Steinhoff 2005; Suresh 2015; Thilothammal 1996; Trinka 2018; Wu 2018; Xu 2012).

Reasons individual participant data could not be provided

In response to our direct requests for IPD, trial authors or government sponsors of ten trials confirmed that data were no longer available (Callaghan 1985; Capone 2008; Consoli 2012; Forsythe 1991; Korean Lamotrigine Study Group 2008; Pulliainen 1994; Ramsay 1983; Shakir 1981; So 1992; Thilothammal 1996).

Data could not be provided for three pharmaceutical trials where data were requested via ClinicalStudyDataRequest.Com, due to the cost and resource of locating and preparing data (Kalviainen 2002; Saetre 2007) and due to country-specific restrictions regarding anonymisation of data (Steinhoff 2005). For three further pharmaceutical company-sponsored trials, data were not available and could not be provided due to time elapsed since the trial was completed (Brodie 2002; Christe 1997; Donati 2007).

The authors of three trials confirmed that the data we required had not been collected (Akter 2018; Chen 1996; Lukic 2005; Mitchell 1987) and the authors of two trials stated that data could not be provided due to local authority/ethical restrictions (Cho 2011; Jung 2015).

We were unable to make contact with the authors or sponsors of 22 trials to request data (Aikia 1992; Bidabadi 2009; Castriota 2008; Chen 2013; Cossu 1984; Dam 1989; Fritz 2006; Giri 2016; Kopp 2007; Korean Zonisamide Study 1999; Maiti 2018; Miura 1990; Motamedi 2013; Ramsay 2007; Rastogi 1991; Ravi Sudhir 1995; Resendiz 2004; Sidhu 2018; Suresh 2015; Trinka 2018; Wu 2018; Xu 2012).

We received an initially positive response from the authors or government sponsors of five trials but no data were provided at the time of the review update (Czapinski 1997; Gilad 2007; Kim 2017; NCT01954121; Rowan 2005).

An author of Feksi 1991 provided access to an IPD dataset, but this was not the final dataset used for the analysis published by the original trial authors. The pharmaceutical company that sponsored the trial, Ciba-Geigy, who at that time held the product licence for carbamazepine, held the final dataset. Since the trial was

undertaken, there have been a number of mergers and restructures within the industry, and the current owners of the data are Novartis. Unfortunately, Novartis were unable to locate the data for this trial. The dataset that we had for this trial contained a number of problems and inconsistencies, and we therefore decided not to include this trial in the meta-analysis. This was the only trial with major inconsistencies that prevented the inclusion of this IPD in analysis; for details of minor inconsistencies between IPD and published results, see Sensitivity analysis and Other potential sources of bias.

Two trials (Forsythe 1991; Shakir 1981) presented times at which the allocated drug was withdrawn and the reason for withdrawal for each individual in the trial publication. However, only Shakir 1981 provided this information according to seizure type, so only results for Shakir 1981 could be incorporated into the analysis of 'time to withdrawal of allocated treatment' (see Sensitivity analysis). Shakir 1981 presented 'time on trial drug' in months for each participant, therefore in order to calculate 'time to withdrawal of allocated treatment', we assumed that if 'time spent on trial drug' was five months, the individual spent five full months (152 full days) on the trial drug before withdrawal.

One trial reported a hazard ratio for time to treatment failure (Kim 2017), and three trials presented sufficient detail to extract individual treatment failure/withdrawal (Gilad 2007; Steinhoff 2005) or seizure times (Consoli 2012; Gilad 2007) from survival curves, however this information was not separated by seizure type for Consoli 2012, so we could not include the results in analysis for this trial.

A further four trials reported summary statistics or graphical data for one of more outcomes of interest of the review; however, none of these trials presented information by seizure type, so we could not include the results in analysis (Brodie 2002; Christe 1997; Rowan 2005; Saetre 2007).

The remaining 40 trials did not report any published results which could be included within the analyses of this review (Aikia 1992; Akter 2018; Bidabadi 2009; Callaghan 1985; Capone 2008; Castriota 2008; Chen 1996; Chen 2013; Cho 2011; Cossu 1984; Czapinski 1997; Dam 1989; Donati 2007; Feksi 1991; Fritz 2006; Giri 2016; Jung 2015; Kalviainen 2002; Kopp 2007; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Lukic 2005; Maiti 2018; Mitchell 1987; Miura 1990; Motamedi 2013; NCT01954121; Pulliainen 1994; Ramsay 1983; Ramsay 2007; Rastogi 1991; Ravi Sudhir 1995; Resendiz 2004; Sidhu 2018; So 1992; Suresh 2015; Thilothammal 1996; Trinka 2018; Wu 2018; Xu 2012). Details of outcomes considered and a summary of results of each trial for which IPD were not available to us can be found in Table 5.

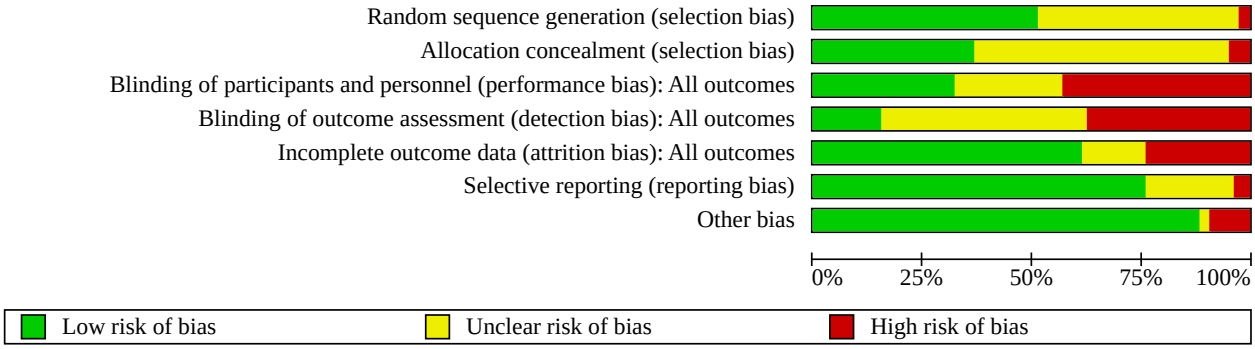
Excluded studies

We excluded 36 studies from the review; three were cross-over trials (Cereghino 1974; Gruber 1962; Loiseau 1984), four studies were terminated early with no results available (EUCTR2004-004053-26-SE; EUCTR2010-018284-42-NL; ISRCTN73223855; NCT01891890), four were not fully randomised (Baxter 1998; Hu 2012; Kaminow 2003; Rysz 1994), one did not recruit participants with epilepsy (Taragano 2003), one recruited children with ineligible seizure types (Park 2001) and the other 22 did not have a monotherapy design (Albani 2006; Alsaadi 2002; Alsaadi 2005; Ben-Menachem 2003; Beydoun 1997; Beydoun 1998; Beydoun 2000; Bittencourt 1993; Canadian Group 1999; Chung 2012; DeToledo 2000; Fakhoury 2004; Foldvary-Schaefer 2017; French 2012; Gilliam 1998; Hakami 2012; Kerr 1999; Kerr 2001; Reinikainen 1984; Reinikainen 1987; Rosenow 2012; Simonsen 1975a; Simonsen 1975b). See Characteristics of excluded studies for further information.

Risk of bias in included studies

For further details, see the Characteristics of included studies and Figure 4.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Trials for which we received IPD (information reported in published papers or provided with IPD)

One trial used alternate allocation (quasi-randomisation) which we judged to be at high risk of selection bias (Dizdarer 2000). One trial described an adequate method of randomisation, use of a random number list, but reported that allocation was concealed by sealed, opaque envelopes, although this method was not used for all participants in the trial (Placencia 1993), so we also judged this trial to be at high risk of selection bias.

Twenty-one trials described adequate methods of generation of random sequence and allocation concealment, and we judged them to be at low risk of bias. One trial used a random number list and central allocation (Ogunrin 2005). Four trials used block

randomisation, of which three concealed allocation with sealed, opaque envelopes (De Silva 1996; Heller 1995; Mattson 1992) and one used central pharmacy allocation (Chadwick 1998). Eleven trials used a computer-generated random sequence. Of these, seven concealed allocation with sealed, opaque envelopes (Bill 1997; Brodie 1995a; Brodie 1995b; Brodie 1999; Guerreiro 1997; Nieto-Barrera 2001; Reunanen 1996), two used a telephone interactive voice-response system (Baulac 2012; Baulac 2017; Brodie 2007) and one used central pharmacy allocation (Werhahn 2015). Seven trials used a computer-generated minimisation programme: four used central telephone allocation (Richens 1994; SANAD A 2007; SANAD B 2007; Verity 1995), two used a centralised web-based allocation system (SANAD II A 2021; SANAD II B 2021) and one used central pharmacy allocation (Craig 1994).

Two trials were described as randomised but gave no information about the generation of the random list (unclear risk of bias for generation of random sequence). One of these trials concealed allocation with sealed, opaque envelopes (Banu 2007) and one used a telephone interactive voice-response system (Trinka 2013) (both low risk of bias for allocation concealment). Five trials gave no information about allocation concealment (unclear risk of bias). Of these, three used a computer-generated random sequence (Biton 2001; Eun 2012; Privitera 2003) and two used random number tables (Pal 1998; Ramsay 1992) (all low risk of bias for generation of random sequence).

The remaining seven trials were described as randomised but gave no details of methods of generation of random sequence and allocation concealment, and we judged them to be at unclear risk of bias (Kwan 2009; Lee 2011; Mattson 1985; Ramsay 2010; Steiner 1999; Stephen 2007; Turnbull 1985).

Trials for which no IPD were available (information reported in published papers only)

We judged three trials to be at high risk of selection bias: one trial reported a method of quota allocation and did not report how allocation was concealed (Forsythe 1991), one trial reported a method of randomisation and allocation concealment based on two Latin squares which seemed to take into account the drug preference of participants (the “drug of first preference” was selected from the randomisation list on a sequential basis) (Callaghan 1985) and the final trial reported an adequate method of generating random numbers, but allocated groups to the two drugs based on whether the random numbers generated were odd or even; a method which does not conceal allocation (Akter 2018).

Six trials described adequate methods of generation of random sequence and allocation concealment, and we judged them to be at low risk of bias. Of these, one trial used a random number list and sealed, opaque envelopes (Feksi 1991) and six trials used a computer-generated random sequence, including three trials that used central telephone randomisation (Donati 2007; Rowan 2005; Shakir 1981), one trial that used central computer-based randomisation and allocation (Maiti 2018; Trinka 2018) and one trial that used central pharmacy allocation (Jung 2015).

Eight trials gave no information about allocation concealment (unclear risk of bias). Of these, two used block randomisation (Brodie 2002; Chen 1996), one used random number tables (Giri 2016; Korean Zonisamide Study 1999; Resendiz 2004) and three used a computer-generated random sequence (Consoli 2012; Motamedi 2013; Thilothammal 1996) (all low risk of bias for generation of random sequence). One trial was described as randomised but gave no information about the generation of the random list (unclear risk of bias for generation of random sequence), this trial concealed allocation with sealed, opaque envelopes (Chen 2013).

The remaining 31 trials were described as randomised but gave no details of methods of generation of random sequence and allocation concealment, and we judged them to be at unclear risk of bias: six were published as abstracts only (Bidabadi 2009; Czapinski 1997; Fritz 2006; Kalviainen 2002; Kopp 2007; Lukic 2005); two were published only with summary results (Korean Lamotrigine Study Group 2008; NCT01954121) and 23 were published as full-text articles (Aikia 1992; Capone 2008; Castriota 2008; Cho 2011, Christe 1997; Cossu 1984; Dam 1989; Gilad 2007; Kim 2017; Mitchell 1987; Miura 1990; Pulliainen 1994; Ramsay 1983; Ramsay 2007; Rastogi 1991; Ravi Sudhir 1995; Saetre 2007; Sidhu 2018; So 1992; Steinhoff 2005; Suresh 2015; Wu 2018; Xu 2012).

Blinding

Trials for which we received IPD (information reported in published papers or provided with IPD)

Six trials reported that participants, personnel and outcome assessors were blinded via the use of matching placebo tablets (Baulac 2012; Baulac 2017; Biton 2001; Ogunrin 2005; Ramsay 2010; Steiner 1999). Eleven trials reported that participants and personnel were double-blinded but gave no information about blinding of outcome assessors (Banu 2007; Bill 1997; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; Guerreiro 1997; Mattson 1985; Mattson 1992; Privitera 2003; Werhahn 2015). We judged all of these trials to be at low risk of performance bias but unclear risk of detection bias.

Two trials reported that outcome assessors were blinded but that participants and personnel were not blinded (Craig 1994; Pal 1998) and two trials gave no information about blinding so we judged them to be at unclear risk of performance and detection bias (Placencia 1993; Turnbull 1985).

Seventeen trials were of an open-label design and judged to be at high risk of performance and detection bias (De Silva 1996; Dizdarer 2000; Eun 2012; Heller 1995; Kwan 2009; Lee 2011; Nieto-Barrera 2001; Ramsay 1992; Reunanen 1996; Richens 1994; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Stephen 2007; Trinka 2013; Verity 1995) and one trial could not blind participants and personnel by design but did not state whether outcome assessors were blinded (Chadwick 1998).

Trials for which no IPD were available (information reported in published papers only)

Five trials reported that outcome assessors were blinded. Of these, three did not state whether participants and personnel were blinded (Chen 1996; Cho 2011; Pulliainen 1994) and, in the other two trials, participants and personnel were not blinded (Forsythe 1991; Jung 2015). Eleven trials reported that participants and personnel were double-blinded but gave no information about blinding of outcome assessors (Aikia 1992; Brodie 2002; Christe 1997; Cossu 1984; Dam 1989; Motamedi 2013; Ramsay 1983; Ramsay 2007; Rowan 2005; Saetre 2007; So 1992). We judged all of these trials to be at low risk of performance bias but unclear risk

of detection bias. One trial stated that participants, investigators, and clinical research and sponsor personnel, who administered medication, assessed outcomes, and analysed data, were masked to the allocation until all data for the primary analysis were collected so we judged this trial to be at low risk of performance and detection bias (Trinka 2018).

Sixteen trials were of an open-label design and we judged them to be at high risk of performance and detection bias (Akter 2018; Castriota 2008; Consoli 2012; Donati 2007; Gilad 2007; Giri 2016; Kim 2017; Korean Lamotrigine Study Group 2008; Lukic 2005; Maiti 2018; Mitchell 1987; NCT01954121; Resendiz 2004; Sidhu 2018; Steinhoff 2005, Suresh 2015).

Sixteen trials gave no information about blinding so we judged them to be at unclear risk of performance and detection bias. Of these, five were published as abstracts only (Bidabadi 2009; Czapinski 1997; Fritz 2006; Kalviainen 2002; Kopp 2007) and eight were published as full-text articles (Chen 2013; Callaghan 1985; Capone 2008; Feksi 1991; Miura 1990; Rastogi 1991; Ravi Sudhir 1995; Shakir 1981; Thilothammal 1996; Wu 2018; Xu 2012). Another trial, published in Korean, when translated was described as 'double-blind' but it was unclear from the translation who was blinded and how blinding was achieved so we also judged this trial to be at unclear risk of performance and detection bias (Korean Zonisamide Study 1999).

Incomplete outcome data

Trials for which we received individual participant data (information reported in published papers or provided with IPD)

In theory, a review using IPD should overcome issues of attrition bias, as unpublished data can be provided, unpublished outcomes calculated, and all randomised participants can be analysed by an intention-to-treat approach. All 39 trials (Banu 2007; Baulac 2012; Baulac 2017; Bill 1997; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; Chadwick 1998; Craig 1994; De Silva 1996; Dizdarer 2000; Eun 2012; Guerreiro 1997; Heller 1995; Kwan 2009; Lee 2011; Mattson 1985; Mattson 1992; Nieto-Barrera 2001; Ogunrin 2005; Pal 1998; Placencia 1993; Privitera 2003; Ramsay 1992; Ramsay 2010; Reunanen 1996; Richens 1994; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Stephen 2007; Trinka 2013; Turnbull 1985; Verity 1995; Werhahn 2015) provided individual participant data for all randomised individuals and reported the extent of follow-up for each individual. We queried any missing data with the original trial authors. From the information provided by the trial authors, we deemed the small amount of missing data present (see Included studies) to be missing at random and not affecting our analysis, so we judged them to be at low risk of bias.

Trials for which no IPD were available (information reported in published papers only)

Seven trials, which were published as abstracts only, did not give enough information to assess selective reporting, so we judged them to have unclear risk of bias (Bidabadi 2009; Czapinski 1997; Fritz 2006; Kalviainen 2002; Kopp 2007; Lukic 2005; Ramsay 2007). Three trials excluded the small proportion of participants who withdrew from the trial from analysis, but it is unclear whether this would have influenced analysis (Castriota 2008; Chen 1996; Suresh 2015) and three trials did not clearly report whether participants had withdrawn from the trial (Cho 2011; Rastogi 1991; Wu 2018) so we also judged these trials to be at unclear risk of bias.

Sixteen trials reported attrition rates and used an intention-to-treat approach to analysis, so we judged them to be at low risk of attrition bias (Brodie 2002; Callaghan 1985; Capone 2008; Chen 2013; Cossu 1984; Forsythe 1991; Gilad 2007; Giri 2016; Maiti 2018; Mitchell 1987; Miura 1990; Rowan 2005; Saetre 2007; Shakir 1981; Thilothammal 1996; Trinka 2018). The remaining 21 trials excluded participants from analysis and did not use an intention-to-treat approach to analysis, and we judged them to be at high risk of attrition bias (Aikia 1992; Akter 2018; Christe 1997; Consoli 2012; Dam 1989; Donati 2007; Feksi 1991; Jung 2015; Korean Lamotrigine Study Group 2008; Kim 2017; Korean Zonisamide Study 1999; Motamedi 2013; NCT01954121; Pulliainen 1994; Ramsay 1983; Ravi Sudhir 1995; Resendiz 2004; Sidhu 2018; So 1992; Steinhoff 2005; Xu 2012).

Selective reporting

Trials for which we received IPD (information reported in published papers or provided with IPD)

We requested trial protocols in all IPD requests and protocols were provided for 23 out of the 39 trials providing IPD (Baulac 2012; Baulac 2017; Bill 1997; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; De Silva 1996; Guerreiro 1997; Heller 1995; Mattson 1985; Mattson 1992; Nieto-Barrera 2001; Ogunrin 2005; Reunanen 1996; Richens 1994; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Verity 1995; Werhahn 2015).

In theory, a review using IPD should overcome issues of reporting biases, as unpublished data can be provided and unpublished outcomes calculated, so we judged all trials providing IPD to be at low risk of bias. We received sufficient IPD to calculate the four outcomes ('time to withdrawal of allocated treatment', 'time to six-month remission, 'time to 12-month remission', and 'time to first seizure') for 23 of the 39 trials (Baulac 2012; Baulac 2017; Bill 1997; Brodie 2007; De Silva 1996; Dizdarer 2000; Guerreiro 1997; Heller 1995; Kwan 2009; Mattson 1985; Mattson 1992; Placencia 1993; Privitera 2003; Richens 1994; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Stephen 2007; Trinka 2013; Turnbull 1985; Verity 1995; Werhahn 2015).

We could not calculate 'time to 12-month remission' for nine trials as the duration of the trial was less than 12 months (Biton 2001; Brodie 1995a; Brodie 1995b; Chadwick 1998; Eun 2012; Lee 2011; Ramsay 1992; Reunanen 1996; Steiner 1999) and we could not calculate 'time to 12-month remission' or 'time to six-month remission' for three trials as the duration of the trial was less than six months (Brodie 1999; Nieto-Barrera 2001; Ramsay 2010).

Withdrawal information was not available for two trials, so we could not calculate 'time to withdrawal of allocated treatment' (Craig 1994; Pal 1998). For two trials, we could only calculate 'time to first seizure': the trial duration of Ogunrin 2005 was 12 weeks, and all randomised participants completed the trial without withdrawing; and Banu 2007 did not record the dates of all seizures after randomisation and dates of withdrawal for allocated treatment for all participants.

Trials for which no IPD were available (information reported in published papers only)

Protocols were not available for any of the 50 trials without IPD available, so we made a judgement of the risk of bias based on the information included in the publications of the studies (see the Characteristics of included studies tables for more information).

In 29 trials, expected efficacy and tolerability outcomes were well reported in the methods and results, therefore, we judged these trials to be at low risk of selective reporting bias (Akter 2018; Aikia 1992; Brodie 2002; Callaghan 1985; Chen 1996; Chen 2013; Cho 2011, Christe 1997; Consoli 2012; Dam 1989; Donati 2007; Feksi 1991; Gilad 2007; Giri 2016; Jung 2015; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Maiti 2018; Mitchell 1987; Motamedi 2013; Ramsay 1983; Rastogi 1991; Resendiz 2004; Rowan 2005; Saetre 2007; Shakir 1981; So 1992; Steinhoff 2005; Thilothammal 1996).

Seven trials that were published as abstracts only (Bidabadi 2009; Czapinski 1997; Fritz 2006; Kalviainen 2002; Kopp 2007; Lukic 2005; Ramsay 2007) and two trials with a very brief description of methods (Capone 2008; Xu 2012) did not give enough information to assess selective reporting so we judged them to have unclear risk of bias. Eight trials reported only cognitive outcomes (Castriota 2008; Cossu 1984; Forsythe 1991; Miura 1990; Pulliainen 1994; Ravi Sudhir 1995) or hormonal outcomes (Sidhu 2018; Wu 2018) rather than expected efficacy or tolerability outcomes, and it was unclear if such outcomes were planned a priori, therefore we also judged these trials to have unclear risk of bias.

We judged three trials to be at high risk of reporting bias; one trial reported results for outcomes that were not defined in the methods section (Suresh 2015), one trial did not provide online results for all listed outcomes (NCT01954121) and, for one trial, the outcomes reported in the manuscript were inconsistent with outcomes listed on the trial registry entry (Kim 2017). We judged one trial to be at unclear risk of reporting bias as it was unclear why only within-group results and not between-group results were reported for quality of life outcomes (Trinka 2018).

Other potential sources of bias

We detected other sources of bias in ten trials.

Following consistency checks of IPD for Placencia 1993, Stephen 2007 and Banu 2007, we found some inconsistencies between the data provided and the results in the publications in terms of withdrawal and seizure recurrences, respectively, which the trial authors could not resolve. We performed sensitivity analysis to investigate the impact of the inconsistent data on our outcomes (see Sensitivity analysis). Furthermore, we received IPD for another trial (Feksi 1991), but too many inconsistencies were present for this data to be usable (see Included studies for further details).

We included one trial with very small participant numbers (six participants randomised to each drug) and very short-term follow-up (three weeks) (Cossu 1984), and one trial that terminated early with only 20% of target sample size recruited (Consoli 2012). It is unlikely that either of these trials were adequately powered and of sufficient duration to detect differences. Another trial had several other potential sources of bias (Mitchell 1987); the trial was likely underpowered to detect differences between the treatments, one of the tools for outcome assessment was not fully validated, and non-randomised children from a related pilot study were included in analysis for some of the outcomes. In three trials, it was unclear if all participants were receiving AED monotherapy treatment. We judged two of these trials to be at unclear risk of bias (Gilad 2007; Sidhu 2018) and one of these trials to be at high risk of bias as the design of the trial, particularly relating to the monotherapy treatment was very unclear (Xu 2012).

No other sources of bias were identified in the remaining 79 trials.

Effects of interventions

See: **Summary of findings 1** Summary of findings - Time to treatment failure for individuals with focal seizures (reference carbamazepine); **Summary of findings 2** Summary of findings - Time to treatment failure for individuals with focal seizures (reference lamotrigine); **Summary of findings 3** Summary of findings - Time to treatment failure for individuals with generalised seizures (reference sodium valproate); **Summary of findings 4** Summary of findings - Time to 12-month remission for individuals with focal seizures (reference carbamazepine); **Summary of findings 5** Summary of findings - Time to 12-month remission for individuals with focal seizures (reference lamotrigine); **Summary of findings 6** Summary of findings - Time to 12-month remission for individuals with generalised seizures (reference sodium valproate)

For brevity throughout the results section, we refer to participants with generalised tonic-clonic seizures with or without other generalised seizure types as 'participants with generalised seizures.'

Figure 1 visually presents the network of 66 pairwise comparisons from the 12 antiepileptic treatments, for participants with focal onset seizures (69% of participants), for participants with generalised onset seizures (24% of participants) and for participants with unclassified or missing seizure types (7% of total).

Figure 2 also demonstrates the network of the trials with and without IPD provided for analysis. IPD was not available for the one trial of eslicarbazepine acetate (Trinka 2018), so eslicarbazepine acetate could not be included in the network meta-analyses. Furthermore, two trials of zonisamide (ZNS) with available IPD recruited participants with focal onset seizures only (Baulac 2017; SANAD II A 2021). Therefore, 55 pairwise comparisons of 11 AEDs could be made for 10,286 participants with focal onset seizures and 45 pairwise comparisons of 10 AEDs could be made for 4215 participants with generalised onset seizures.

Table 6 shows the total number of participants contributing to each analysis and results are presented in Additional tables. Results highlighted in bold in the tables indicate statistically significant results and an HR less than 1 indicates an advantage to the second drug in the comparison. All results presented were calculated with a fixed-effect analysis. All tables and figures of results indicate the proportion of the treatment effect estimate that is contributed by direct evidence (ranging from 0% where no direct comparison existed to 100% for the carbamazepine versus lacosamide comparison, Figure 2). We note that, due to the limited amount of evidence for individuals with generalised seizures for some comparisons in the network, some confidence intervals of treatment effect sizes are very wide.

When examining inconsistency, we examined the numerical results, particularly overlap of confidence intervals of the direct evidence,

indirect evidence (estimated from node splitting) and network meta-analysis results. We anticipate that numerical results for the network meta-analysis, which include the most data, will be the most precise. We note that potentially important clinical inconsistency is present where confidence intervals of results from direct evidence and direct plus indirect evidence did not overlap, and we considered possible reasons and origins of this inconsistency. Our main concern was statistically significant differences between direct evidence and network meta-analysis results; however, we also note where confidence intervals of results from indirect evidence did not overlap with the confidence intervals of the other estimates.

We conducted a number of sensitivity analyses for each outcome (see Sensitivity analysis for further information). For brevity, we summarised only the conclusions of the sensitivity analyses below rather than presenting full numerical results, but these can be made available on request from the corresponding review author.

Time to treatment failure

The number of participants that contributed to analysis of our primary outcome was 14,290 out of 14,789 participants (97%).

Table 7 shows the reported reasons for treatment failure/withdrawal from treatment across all studies and how we treated each of these reasons in analysis. We note that, in some trials, treatment failure may have occurred for a combination of reasons; for the purpose of analysis, we have made a judgement regarding the primary reason for treatment failure. It should be noted that Table 7 did not take account of randomisation within trials and should be interpreted as exploratory.

Out of the 14,290 participants who contributed data, 5007 (35%) of individuals failed treatment, ranging from 29% of participants on phenytoin to 59% of participants on gabapentin.

The most commonly reported reason for treatment failure was due to adverse events (39% of all treatment failure events), ranging from 19% of treatment failure events on phenobarbitone to 50% of treatment failure events on topiramate, although 42% of treatment failure events on phenobarbitone were reported to be due to both adverse events and an inadequate response. Inadequate response (i.e. lack of seizure control) was reported as the reason for 26% all treatment failures; ranging from 11% of treatment failure events on phenytoin to 58% of treatment failure events on gabapentin.

We censored 9279 participants out of 14,290 (65%) in the analysis. The majority of censored participants were still taking their allocated treatment at last follow-up; ranging by drug from 73% (phenobarbitone and phenytoin) to 95% (lacosamide) of censored participants. Very few participants were lost to follow-up in the trials (ranging from 0% (gabapentin and zonisamide) to 16% (phenobarbitone)).

Direct evidence

Table 8, Table 9 and Table 10 (individuals with focal seizures) and Table 11, Table 12 and Table 13 (individuals with generalised seizures) show the number of trials and participants contributing direct evidence for each of the pairwise comparisons in the network for time to treatment failure for any reason, due to adverse events and due to lack of efficacy, respectively. Twenty-seven (29 for treatment failure due to lack of efficacy) out of 55 comparisons had no direct evidence for participants with focal onset seizures. Twenty-one (24 for treatment failure due to lack of efficacy) out of 45 comparisons had no direct evidence for participants with generalised onset seizures and a further eleven comparisons for participants with generalised onset seizures had fewer than 100 participants contributing direct evidence resulting in wide 95% CIs around the treatment-effect estimate for some of the comparisons. The comparisons with the most participants contributing to analysis were carbamazepine versus lamotrigine and carbamazepine versus levetiracetam for individuals with focal seizures and sodium valproate versus levetiracetam and sodium valproate versus topiramate for individuals with generalised seizures.

In pairwise meta-analysis (direct evidence), for participants with generalised onset seizures, no substantial heterogeneity was present (I^2 greater than 50%) for any comparison of treatment failure for any reason (Table 11) and for only one comparison of treatment failure due to adverse events (Table 12). For participants with focal onset seizures, substantial heterogeneity was present for three comparisons of treatment failure for any reason (Table 8) and for five comparisons of treatment failure due to adverse events (Table 9). Little heterogeneity was observed in direct evidence for time to treatment failure due to lack of efficacy, although limited numbers of events (i.e. participants stopping treatment due to continued seizures) were available for pairwise analysis (Table 10; Table 13).

Where observed, heterogeneity seemed to originate from differences in trial designs contributing to the pooled result for specific comparisons; i.e. pooling of trials recruiting children only, adults only or elderly participants only and pooling of double-blind and open-label trials (see Nevitt 2018c and Nevitt 2018d for further discussion of the importance of blinding for the outcome of time to treatment failure).

Network meta-analysis results (direct plus indirect evidence)

Figure 5 shows how each treatment performed compared to first-line treatment carbamazepine for individuals with focal seizures (ordered by treatment-effect estimate); for treatment failure for any reason, lamotrigine and levetiracetam were significantly better than carbamazepine, and carbamazepine was significantly better than gabapentin and phenobarbitone. For treatment failure due to adverse events, lamotrigine, levetiracetam and gabapentin were significantly better than carbamazepine, carbamazepine was significantly better than phenobarbitone and, for treatment failure due to lack of efficacy, carbamazepine was significantly better than gabapentin and phenobarbitone.

Figure 5. Network meta-analysis results (direct and indirect evidence combined) for individuals with focal seizures, all drugs compared to carbamazepine (CBZ) Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures

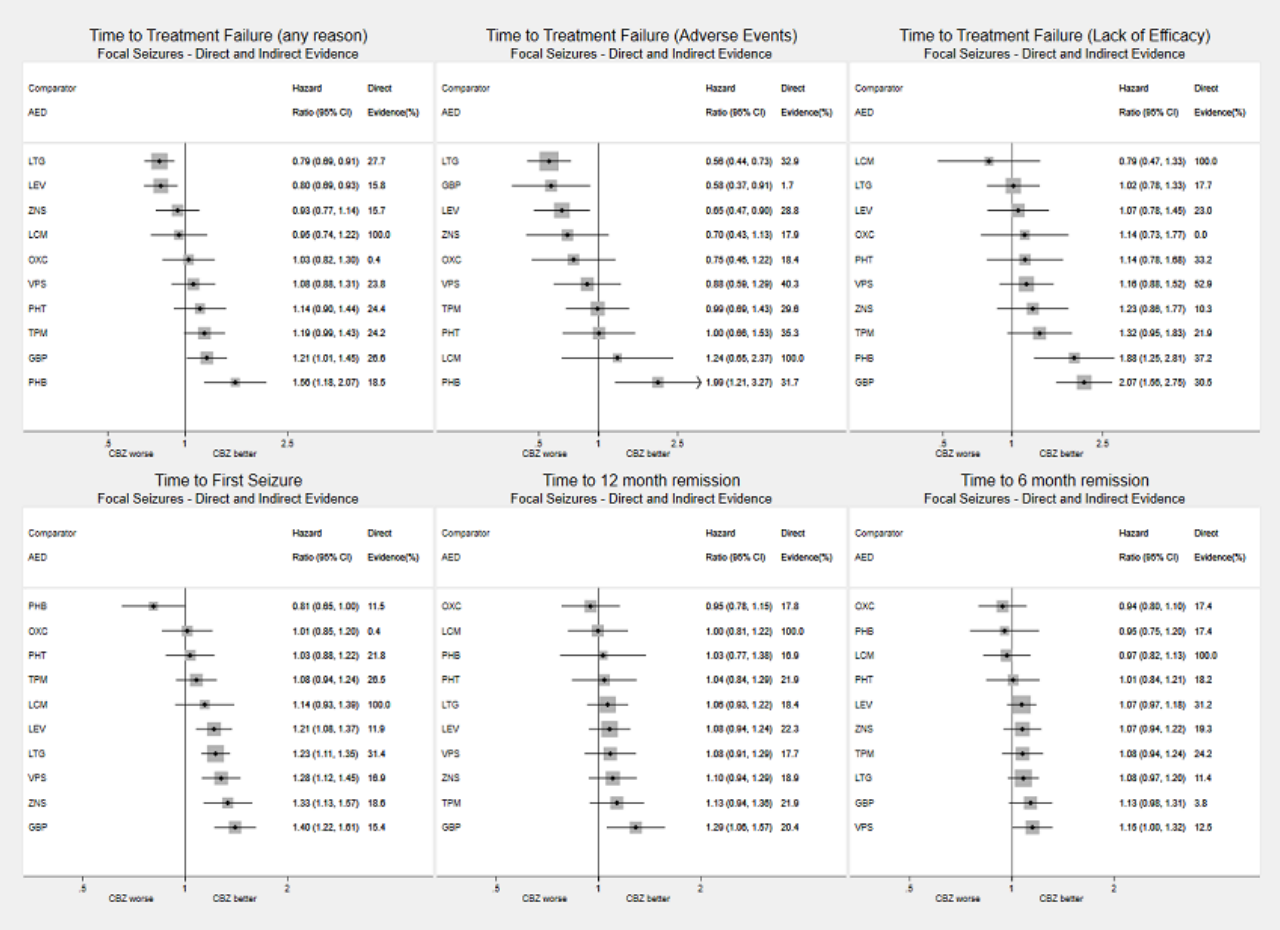


Figure 6 shows how each treatment performed compared to first-line treatment lamotrigine for individuals with focal seizures (ordered by treatment-effect estimate); for treatment failure for any reason, lamotrigine was significantly better than all treatments except for levetiracetam. For treatment failure due to adverse events, lamotrigine was significantly better than sodium valproate, topiramate, carbamazepine, phenytoin, lacosamide and phenobarbitone and, for treatment failure due to lack of efficacy, lamotrigine was significantly better than gabapentin and phenobarbitone.

Figure 6. Network meta-analysis results (direct and indirect evidence combined) for individuals with focal seizures, all drugs compared to lamotrigine (LTG) Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures

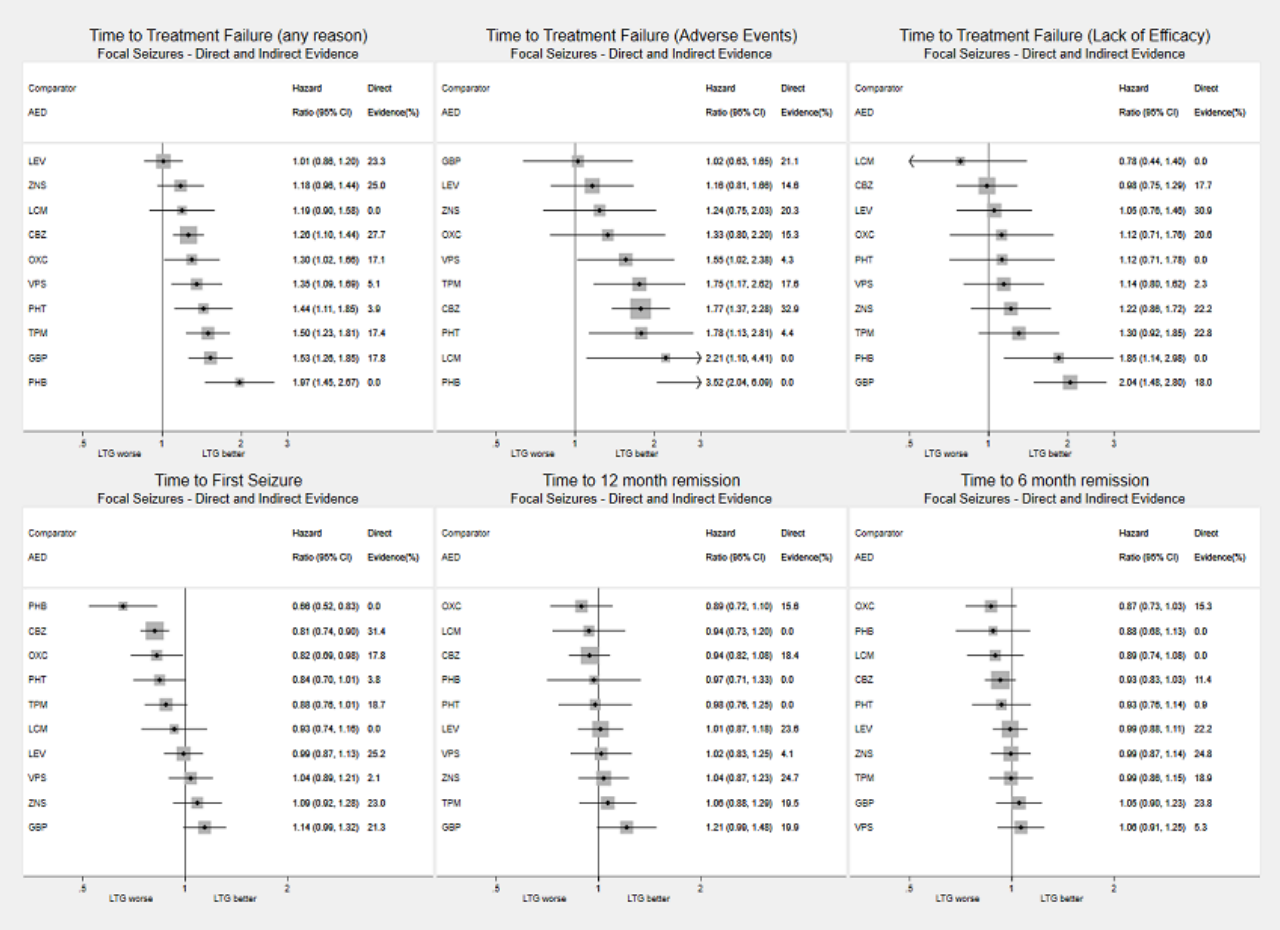


Figure 7 shows how each treatment performed compared to first-line treatment sodium valproate for individuals with generalised seizures (ordered by treatment-effect estimate); for treatment failure for any reason, sodium valproate was significantly better than carbamazepine, topiramate, lacosamide and phenobarbitone. For treatment failure due to adverse events, sodium valproate was significantly better than lacosamide and, for treatment failure due to lack of efficacy, sodium valproate was significantly better than lamotrigine, gabapentin and topiramate.

Figure 7. Network meta-analysis results (direct and indirect evidence combined) for individuals with generalised seizures, all drugs compared to sodium valproate (VPS) Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. Generalised tonic-clonic seizures with or without other seizure types is shortened to 'Generalised seizures' for brevity. **AED: antiepileptic drug**
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide **To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures**

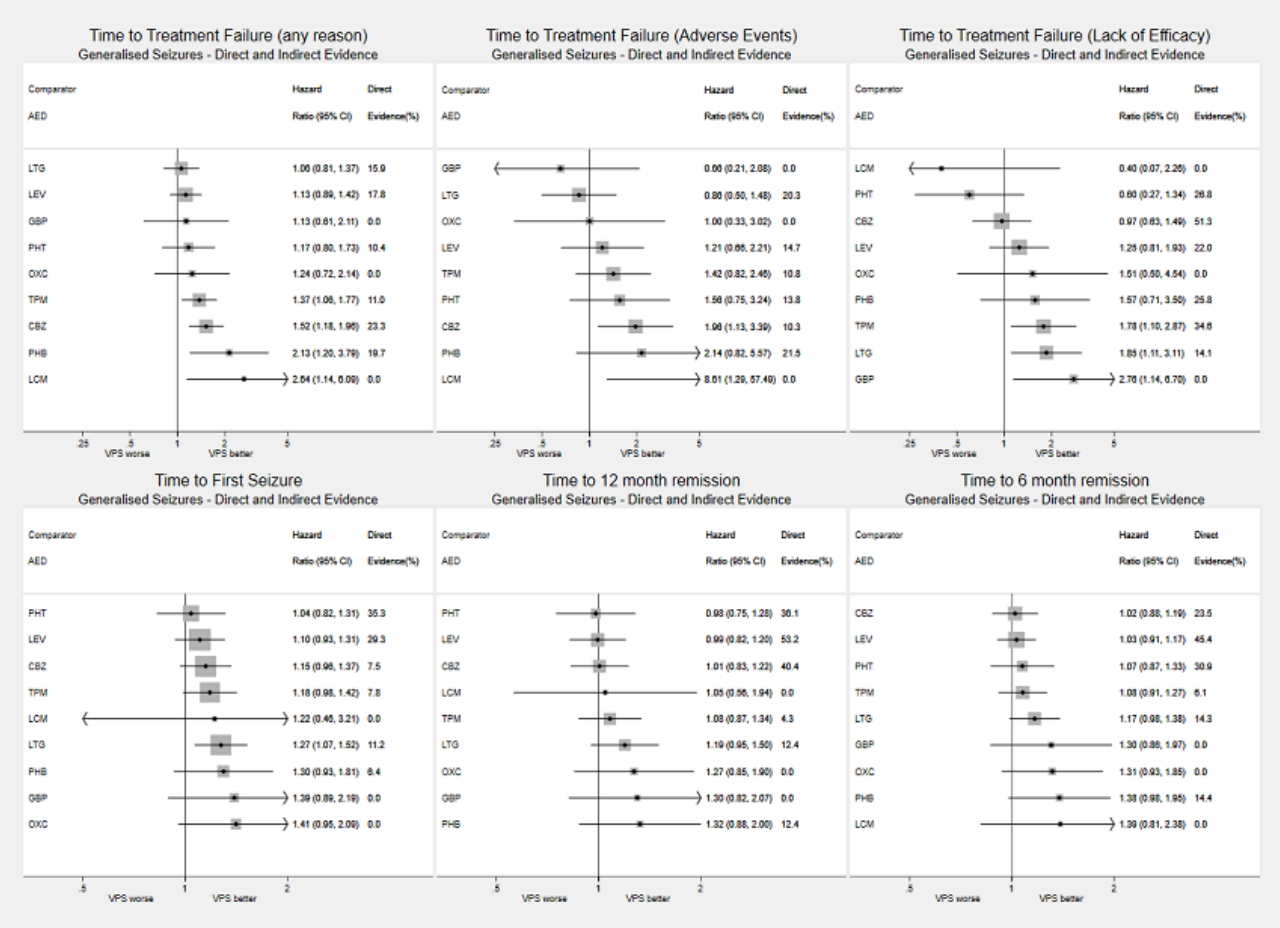


Figure 8, Table 8, Table 9 and Table 10 (individuals with focal seizures) and Figure 9, Table 11, Table 12 and Table 13 (individuals with generalised seizures) show treatment effect estimates for all pairwise comparisons in the network combining direct with indirect evidence. In addition to the results described above, for individuals with focal seizures, levetiracetam seemed to perform better than most other drugs and, for individuals with generalised seizures, lamotrigine seemed to perform better than most other drugs. For both individuals with focal seizures and individuals with generalised seizures, phenobarbitone seemed to perform worse than most other drugs.

Figure 8. Network meta-analysis results (direct and indirect evidence combined) for individuals with focal seizures, all pairwise comparisons for time to treatment failure outcomes Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. **AED: antiepileptic drug**
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide **To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures**

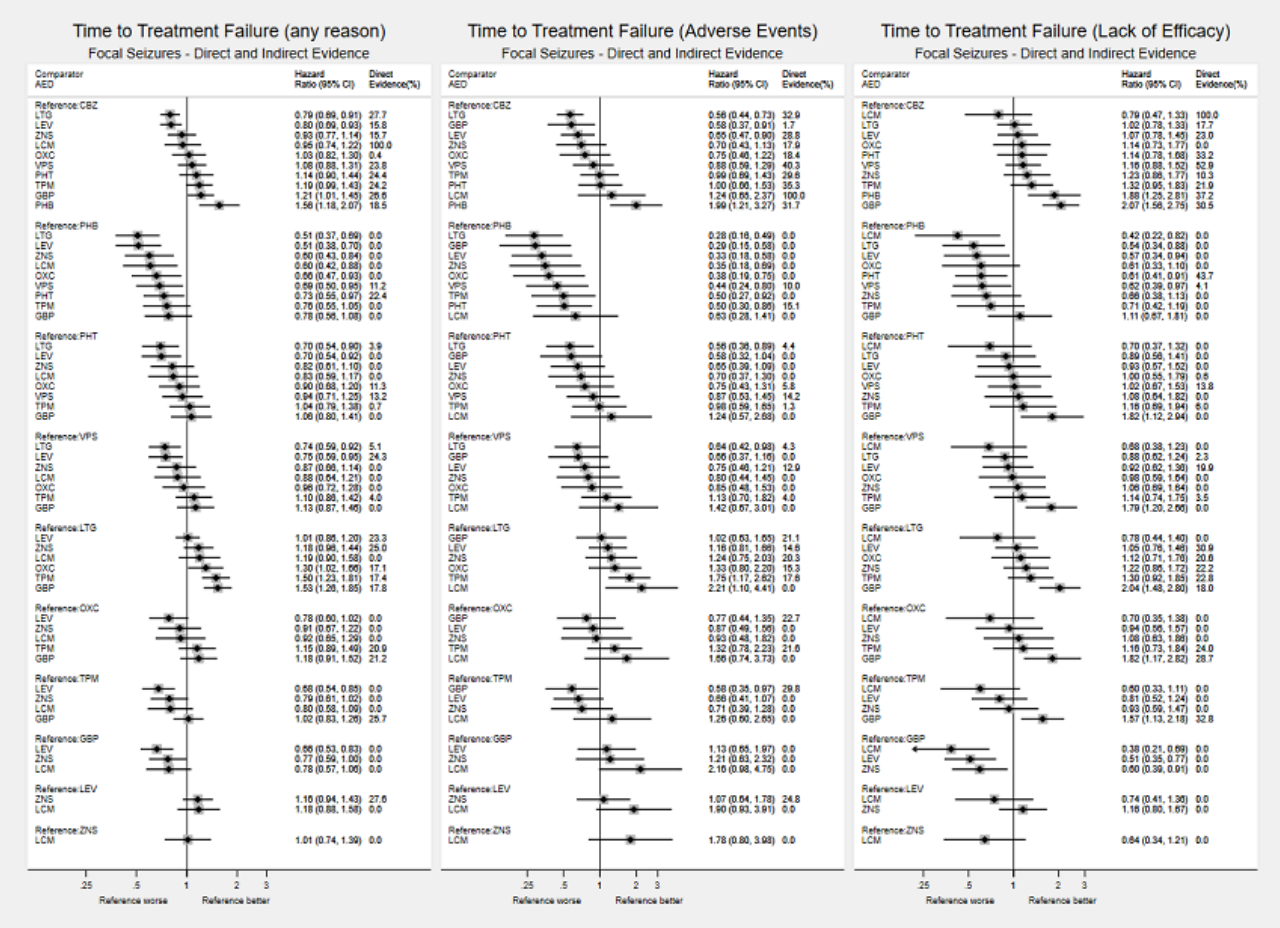


Figure 9. Network meta-analysis results (direct and indirect evidence combined) for individuals with generalised seizures, all pairwise comparisons for time to treatment failure outcomes Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. Generalised tonic-clonic seizures with or without other seizure types is shortened to 'Generalised seizures' for brevity. AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
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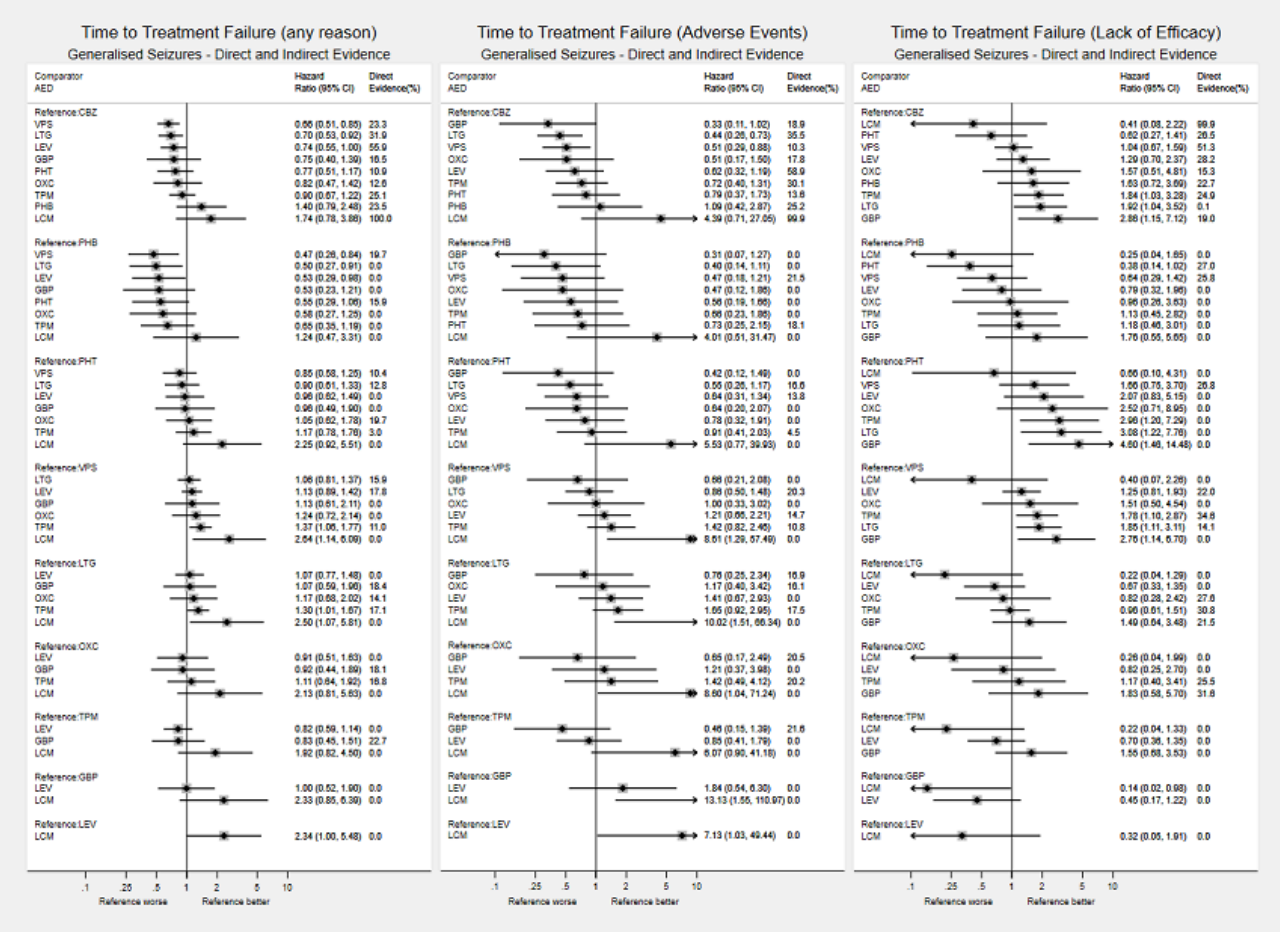

When repeating NMA with random-effects, the τ^2 statistics were 0.002, 0.07 and 0.01 and the estimated I^2 statistics were 11.7%, 50.1% and 19.5% for time to treatment failure for any reason, due to adverse events and due to lack of efficacy, respectively. Treatment-effect estimates were very similar for NMA conducted with fixed and random-effects, mostly the same to one decimal place, and conclusions remained unchanged (data not shown, available on request).

Investigation of inconsistency (node splitting)

A 'design-by-treatment' inconsistency model, accounting for the multi-arm trials, indicated that the global test for inconsistency

was not significant for any treatment failure outcome (P = 0.481 for treatment failure for any reason, P = 0.522 for treatment failure due to adverse events and P = 0.142 for treatment failure due to lack of efficacy).

Table 8, Table 9 and Table 10 (individuals with focal seizures) and Table 11, Table 12 and Table 13 (individuals with generalised seizures) show treatment effect estimates from direct evidence and from direct plus indirect evidence; Figure 10 and Figure 11 show treatment effect estimates for direct, indirect, and direct plus indirect evidence for individuals with focal seizures compared to carbamazepine and lamotrigine, respectively; and Figure 12 for individuals with generalised seizures compared to sodium valproate.

Figure 10. Consistency: direct, indirect and network estimates for individuals with focal seizures compared to carbamazepine (CBZ) for time to treatment failure outcomes. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
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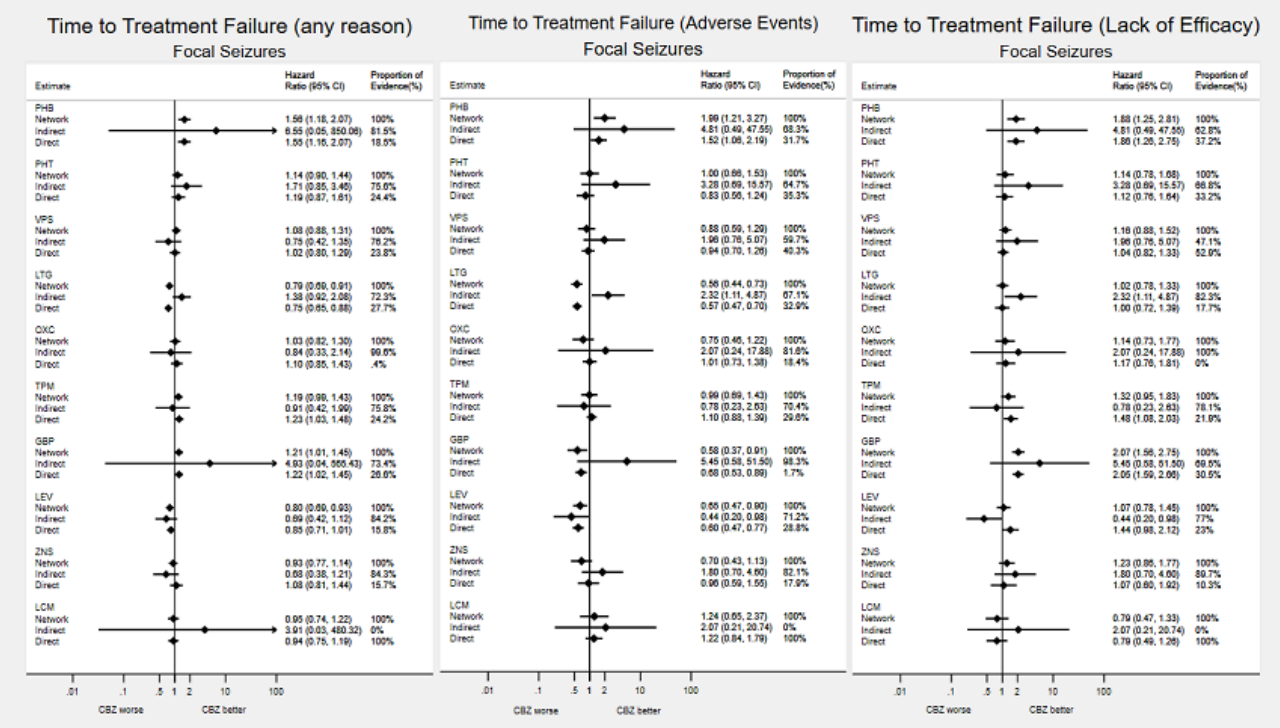

Figure 11. Consistency: direct, indirect and network estimates for individuals with focal seizures compared to lamotrigine (LTG) for time to treatment failure outcomes. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
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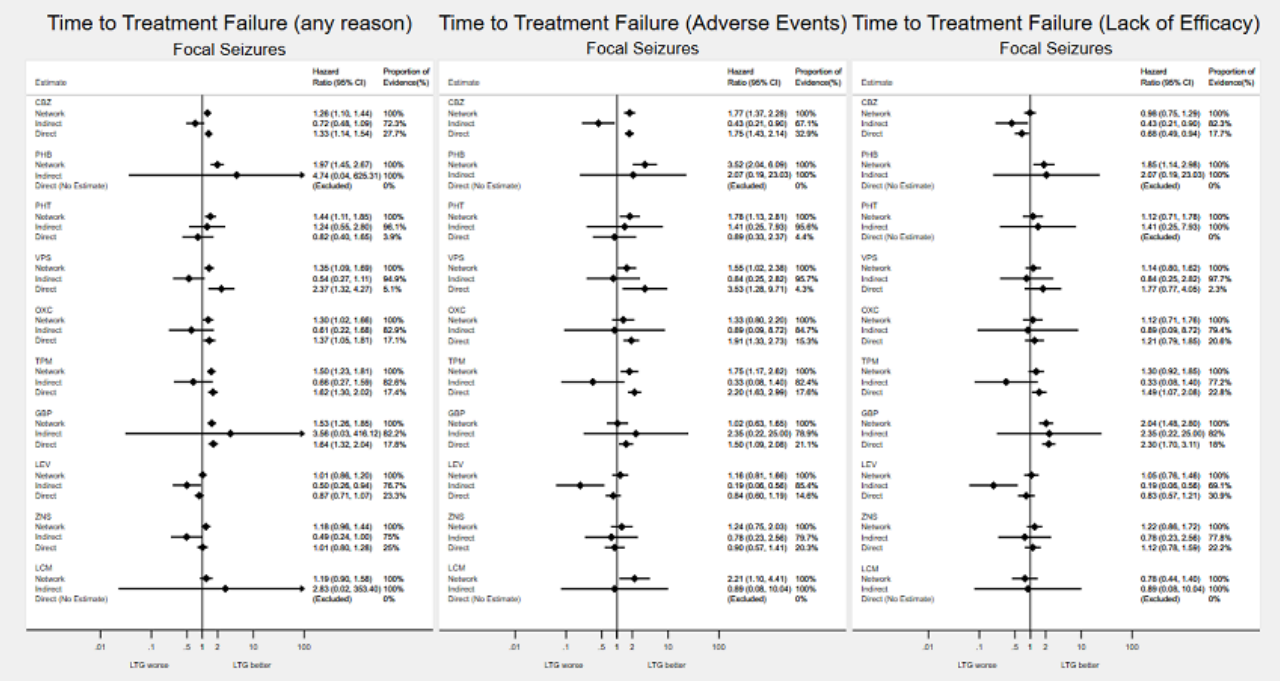


Figure 12. Consistency: Direct, indirect and network estimates for individuals with generalised seizures compared to sodium valproate (VPS) for time to treatment failure outcomes. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). Generalised tonic-clonic seizures with or without other seizure types is shortened to 'Generalised seizures' for brevity. AED: antiepileptic drug

CBZ: carbamazepine

CI: confidence interval

GBP: gabapentin

LCM: lacosamide

LEV: levetiracetam

LTG: lamotrigine

OXC: oxcarbazepine

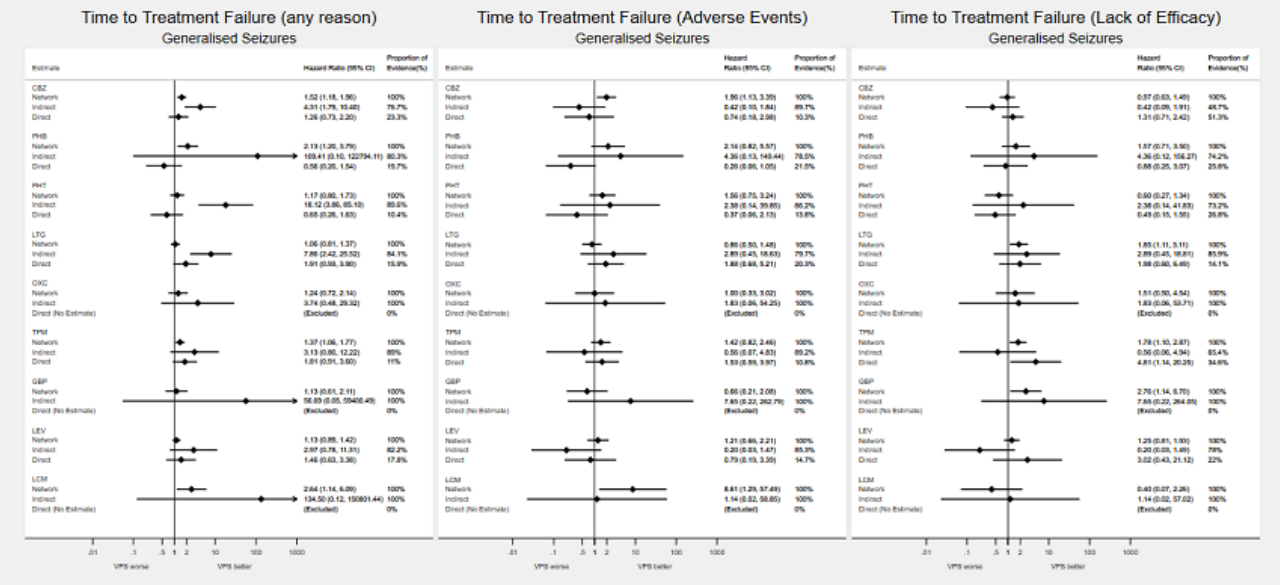
PHB: phenobarbitone

PHT: phenytoin

TPM: topiramate

VPS: sodium valproate

ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures



For most pairwise comparisons, treatment-effect estimates from direct evidence (where available), indirect evidence (estimated from node splitting) and from the network meta-analysis results were similar, mostly in the same direction, and confidence intervals of estimates overlapped. Indirect estimates were very uncertain for some comparisons, with some HR point estimates in the opposite direction to direct evidence and network meta-analysis results, particularly comparisons with the drugs with the least data that contributed to the network, such as gabapentin, lacosamide, oxcarbazepine and phenobarbitone.

For the following comparisons, conclusions that could be drawn from direct evidence (where available) and from network meta-analysis were different:

1. Direct evidence showed a significant advantage to one of the drugs and the network meta-analysis results showed no significant difference between the drugs.
   a. For time to treatment failure for any reason: carbamazepine versus phenytoin and carbamazepine versus topiramate for individuals with focal seizures.
   b. For time to treatment failure due to adverse events: sodium valproate versus levetiracetam, lamotrigine versus oxcarbazepine and lamotrigine versus gabapentin for individuals with focal seizures.
   c. For time to treatment failure due to lack of efficacy: carbamazepine versus topiramate and lamotrigine versus topiramate for individuals with focal seizures.

2. Direct evidence showed no significant difference between the drugs and network meta-analysis showed a significant advantage for one of the drugs.
   a. For time to treatment failure for any reason: carbamazepine versus levetiracetam, phenytoin versus lamotrigine and sodium valproate versus lamotrigine for individuals with focal seizures; carbamazepine versus sodium valproate, carbamazepine versus lamotrigine, carbamazepine versus levetiracetam, sodium valproate versus topiramate and lamotrigine versus topiramate for individuals with generalised seizures.
   b. For time to treatment failure due to adverse events: phenytoin versus lamotrigine for individuals with focal seizures; carbamazepine versus sodium valproate and carbamazepine versus lamotrigine for individuals with generalised seizures.
   c. For time to treatment failure due to lack of efficacy: phenobarbitone versus sodium valproate for individuals with focal seizures; carbamazepine versus lamotrigine, carbamazepine versus gabapentin, carbamazepine versus topiramate and sodium valproate versus lamotrigine for individuals with generalised seizures.

Despite some differences in conclusions that could be drawn from direct evidence and network meta-analysis results; confidence intervals overlapped for all estimates. Furthermore, the 'design-by treatment' inconsistency model did not show any significant evidence of inconsistency within the network. Therefore, we are not concerned about any impact of this observed inconsistency of numerical results on the conclusions of the review.

Subgroup and sensitivity analysis

For the following additional analyses, numerical results were very similar (i.e. the same, to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

1. Sensitivity analysis excluding one trial (Stephen 2007) due to inconsistencies in provided data for all analyses of treatment failure.
2. Sensitivity analysis excluding one trial (Reunanen 1996) due to the definition of treatment failure in the trial (see Sensitivity analysis) for all analyses of treatment failure.
3. Sensitivity analysis for one trial (Placencia 1993) with different definitions of treatment failure (see Sensitivity analysis) for time to treatment failure for any reason and time to treatment failure due to adverse events. No participants in Placencia 1993 failed treatment due to lack of efficacy, so sensitivity analysis was not required for time to treatment failure due to lack of efficacy.
4. Additional analysis adjusting for age for all analyses of treatment failure.
5. Repeated analysis using an accelerated failure time model to assess the validity of the proportional hazards assumption made the Cox model for all analyses of treatment failure for individuals with focal seizures.
6. Reclassification of seizure type 1 (see Sensitivity analysis) for all treatment failure outcomes for individuals with focal seizures.
7. Reclassification of seizure type 2 (see Sensitivity analysis) for time to treatment failure for any reason and time to treatment failure due to adverse events.

For the following additional analyses, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions.

1. Repeated analysis using an accelerated failure time model to assess the validity of the proportional hazards assumption made the Cox model for all analyses of treatment failure for individuals with generalised seizures.
2. Sensitivity analysis with reclassification of seizure type to focal epilepsy and generalised or unclassified epilepsy for time to treatment failure due to lack of efficacy.
3. Reclassification of seizure type 2 (see Sensitivity analysis) for time to treatment failure due to lack of efficacy.

In the first sensitivity analysis for reclassification of seizure type (see Sensitivity analysis), all individuals originally classified as experiencing generalised seizures in the one trial of lacosamide (Baulac 2017) were reclassified to have focal seizures, so lacosamide did not feature in the network for individuals with generalised seizures. For all other pairwise comparisons, for all treatment failure outcomes for individuals with generalised seizures, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions.

We were able to incorporate aggregate or extracted individual-level data for 824 participants for five additional trials for time to treatment failure for any reason; Kim 2017 and Gilad 2007 recruited individuals with focal onset seizures only and, for Biton 2001, Steinhoff 2005 and Shakir 1981, data were available separately for individuals with focal onset seizures and for individuals with generalised onset seizures. No additional data were available for time to treatment failure due to adverse events or due to lack of efficacy.

Numerical results of these sensitivity analyses were similar; for individuals with focal onset seizures, there were some changes in direction of effect size and some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions. For individuals with generalised onset seizures, following sensitivity analysis, there was no significant difference between sodium valproate and the other treatments.

Time to achieve 12-month seizure-free period (remission) after randomisation

The number of participants that contributed to analysis of our secondary outcome, 'time to achieve 12-month seizure-free period' was 11,911 out of 14,789 participants (81%).

Direct evidence

Table 14 (individuals with focal seizures) and Table 15 (individuals with generalised seizures) show the number of trials and participants contributing direct evidence for each of the pairwise comparisons in the network. Twenty-nine out of 55 comparisons had no direct evidence for individuals with focal seizures. Twenty-three out of 45 comparisons had no direct evidence for individuals with generalised seizures and ten comparisons for

individuals with generalised seizures had fewer than 20 individuals contributing direct evidence, resulting in wide confidence intervals around the treatment-effect estimate for these comparisons. The comparisons with the most participants contributing to analysis were carbamazepine versus levetiracetam and carbamazepine versus topiramate for individuals with focal seizures and sodium valproate versus levetiracetam and sodium valproate versus topiramate for individuals with generalised seizures.

Table 14 and Table 15 also show estimates of heterogeneity in the direct treatment effects. For one comparison of individuals with focal seizures and for three comparisons of individuals with generalised seizures, substantial heterogeneity was present (I^2 greater than 50%). The heterogeneity in these comparisons seemed to originate from differences in trial designs contributing to the pooled result; that is, pooling of trials recruiting children only, adults only or elderly participants only and pooling trials with or without treatment strata (see Data extraction and management for further details).

Network meta-analysis results (direct plus indirect evidence)

Figure 5 shows how each treatment performed compared to first-line treatment carbamazepine for individuals with focal seizures (ordered by treatment-effect estimate); carbamazepine was significantly better than gabapentin.

Figure 6 shows how each treatment performed compared to first-line treatment lamotrigine for individuals with focal seizures (ordered by treatment-effect estimate); there was no significant difference between lamotrigine and the other treatments.

Figure 7 shows how each treatment performed compared to first-line treatment sodium valproate for individuals with generalised seizures (ordered by treatment-effect estimate); there was no significant difference between sodium valproate and the other treatments.

Table 14 and Figure 8 (individuals with focal seizures) and Table 15 and Figure 9 (individuals with generalised seizures) show treatment effect estimates for all pairwise comparisons in the network combining direct with indirect evidence. In addition to the results described above, there were few notable differences between any of the treatments for either individuals with focal seizures or individuals with generalised seizures.

When repeating NMA with random-effects, the τ^2 statistic was 0.002 and the estimated I^2 statistic was 13.7%. Treatment-effect estimates were very similar for NMA conducted with fixed and random-effects, mostly the same to one decimal place, and conclusions remained unchanged (data not shown, available on request).

Investigation of inconsistency (node splitting)

A ‘design-by-treatment’ inconsistency model, accounting for the multi-arm trials, indicated that the global test for inconsistency was not significant (P = 0.989).

Table 14 (individuals with focal seizures) and Table 15 (individuals with generalised seizures) show treatment effect estimates from direct evidence, and from direct plus indirect evidence; Figure 10 and Figure 11 show treatment effect estimates for direct, indirect, and direct plus indirect evidence for individuals with focal seizures compared to carbamazepine and lamotrigine, respectively; and Figure 12 for individuals with generalised seizures compared to sodium valproate.

For most pairwise comparisons, treatment-effect estimates from direct evidence (where available), indirect evidence (estimated from node splitting), and from the network meta-analysis results were similar, mostly in the same direction and confidence intervals of estimates overlapped. Indirect estimates were very uncertain for some comparisons, with some HR point estimates in the opposite direction to direct evidence and network meta-analysis results, particularly comparisons with the drugs with the least data that contributed to the network, such as gabapentin, lacosamide, oxcarbazepine and phenobarbitone.

For the following comparisons, conclusions that could be drawn from direct evidence (where available) and from network meta-analysis were different.

1. Direct evidence showed a significant advantage to one of the drugs and the network meta-analysis results showed no significant difference between the drugs: carbamazepine versus topiramate, lamotrigine versus gabapentin and oxcarbazepine versus topiramate for individuals with focal seizures; carbamazepine versus phenobarbitone for individuals with generalised seizures.

Despite some differences in conclusions that could be drawn from direct evidence and network meta-analysis results, confidence intervals overlapped for all estimates. Furthermore, the 'design-by treatment' inconsistency model did not show any significant evidence of inconsistency within the network. Therefore, we are not concerned about any impact of this observed inconsistency of numerical results on the conclusions of the review.

Subgroup and sensitivity analysis

For the following additional analyses, numerical results were very similar (the same, to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

1. Sensitivity analysis excluding one trial (Stephen 2007) due to inconsistencies in provided data.
2. Additional analysis also adjusting for age.
3. Reclassification of seizure type 1 (see Sensitivity analysis) for individuals with focal seizures.

For the following additional analyses, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions:

1. Repeated analysis using an accelerated failure time model to assess the validity of the proportional hazards assumption.
2. Reclassification of seizure type 2 (see Sensitivity analysis).

In the first sensitivity analysis for reclassification of seizure type (see Sensitivity analysis), all individuals originally classified as experiencing generalised seizures in the one trial of lacosamide (Baulac 2017) were reclassified to have focal seizures, so lacosamide did not feature in the network for individuals with generalised seizures. For all other pairwise comparisons, for

individuals with generalised seizures, numerical results were very similar (the same to one decimal place) and conclusions remained unchanged.

No trials reported aggregate or summary data for this outcome, therefore, we did not perform any sensitivity analysis incorporating aggregate data.

Time to achieve six-month seizure-free period (remission) after randomisation

The number of participants that contributed to analysis of our secondary outcome, 'time to achieve six-month seizure-free period' was 13,448 out of 14,789 participants (91%).

Direct evidence

Table 16 (individuals with focal seizures) and Table 17 (individuals with generalised seizures) show the number of trials and participants contributing direct evidence for each of the pairwise comparisons in the network. Twenty-eight out of 55 comparisons had no direct evidence for individuals with focal seizures. Twenty-two out of 45 comparisons had no direct evidence for individuals with generalised seizures and a further ten comparisons for individuals with generalised seizures had fewer than 100 individuals contributing direct evidence, resulting in wide confidence intervals around the treatment-effect estimate for these comparisons. The comparisons with the most participants contributing to analysis were carbamazepine versus levetiracetam and carbamazepine versus lamotrigine for individuals with focal seizures and sodium valproate versus levetiracetam and sodium valproate versus topiramate for individuals with generalised seizures.

Table 16 and Table 17 also show estimates of heterogeneity in the direct treatment effects. For one comparison of individuals with focal seizures and for two comparisons of individuals with generalised seizures, substantial heterogeneity was present (I^2 greater than 50%). The heterogeneity in these comparisons seemed to originate from differences in trial designs contributing to the pooled result; that is, pooling of trials recruiting children only, adults only or elderly participants only and pooling trials with or without treatment strata (see Data extraction and management for further details).

Network meta-analysis results (direct plus indirect evidence)

Figure 5 shows how each treatment performed compared to first-line treatment carbamazepine for individuals with focal seizures (ordered by treatment-effect estimate); carbamazepine was significantly better than sodium valproate.

Figure 6 shows how each treatment performed compared to first-line treatment lamotrigine for individuals with focal seizures (ordered by treatment-effect estimate); there was no significant difference between lamotrigine and the other treatments.

Figure 7 shows how each treatment performed compared to first-line treatment sodium valproate for individuals with generalised seizures (ordered by treatment-effect estimate); there was no significant difference between sodium valproate and the other treatments.

Table 16 and Figure 13 (individuals with focal seizures) and Table 17 and Figure 14 (individuals with generalised seizures) show treatment effect estimates for all pairwise comparisons in the network combining direct with indirect evidence. In addition to the results described above, there were few notable differences between any of the treatments for either individuals with focal seizures or individuals with generalised seizures.

Figure 13. Network meta-analysis results (direct and indirect evidence combined) for individuals with focal seizures, all pairwise comparisons for time to 12-month remission, time to six-month remission and time to first seizure Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures

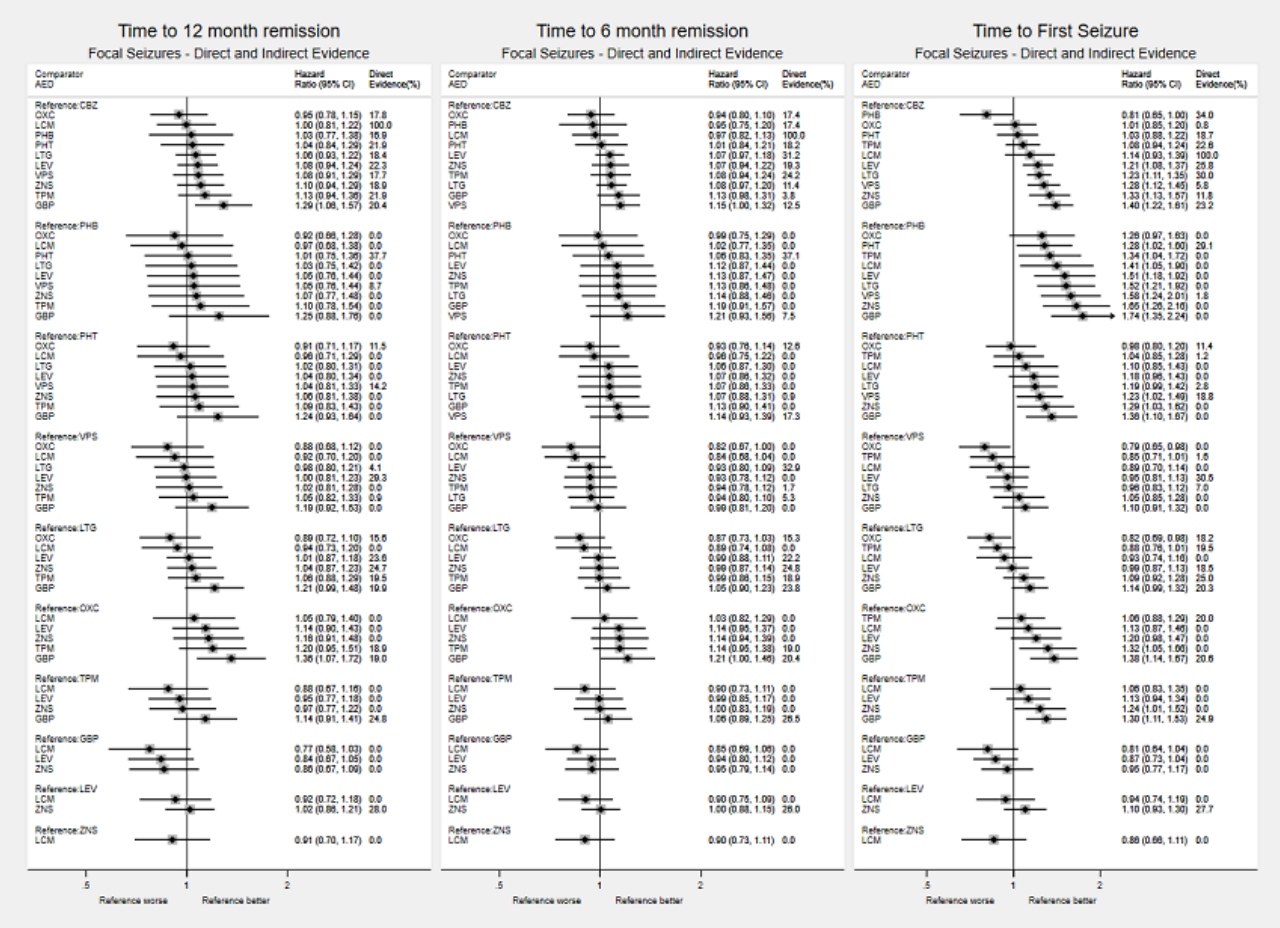
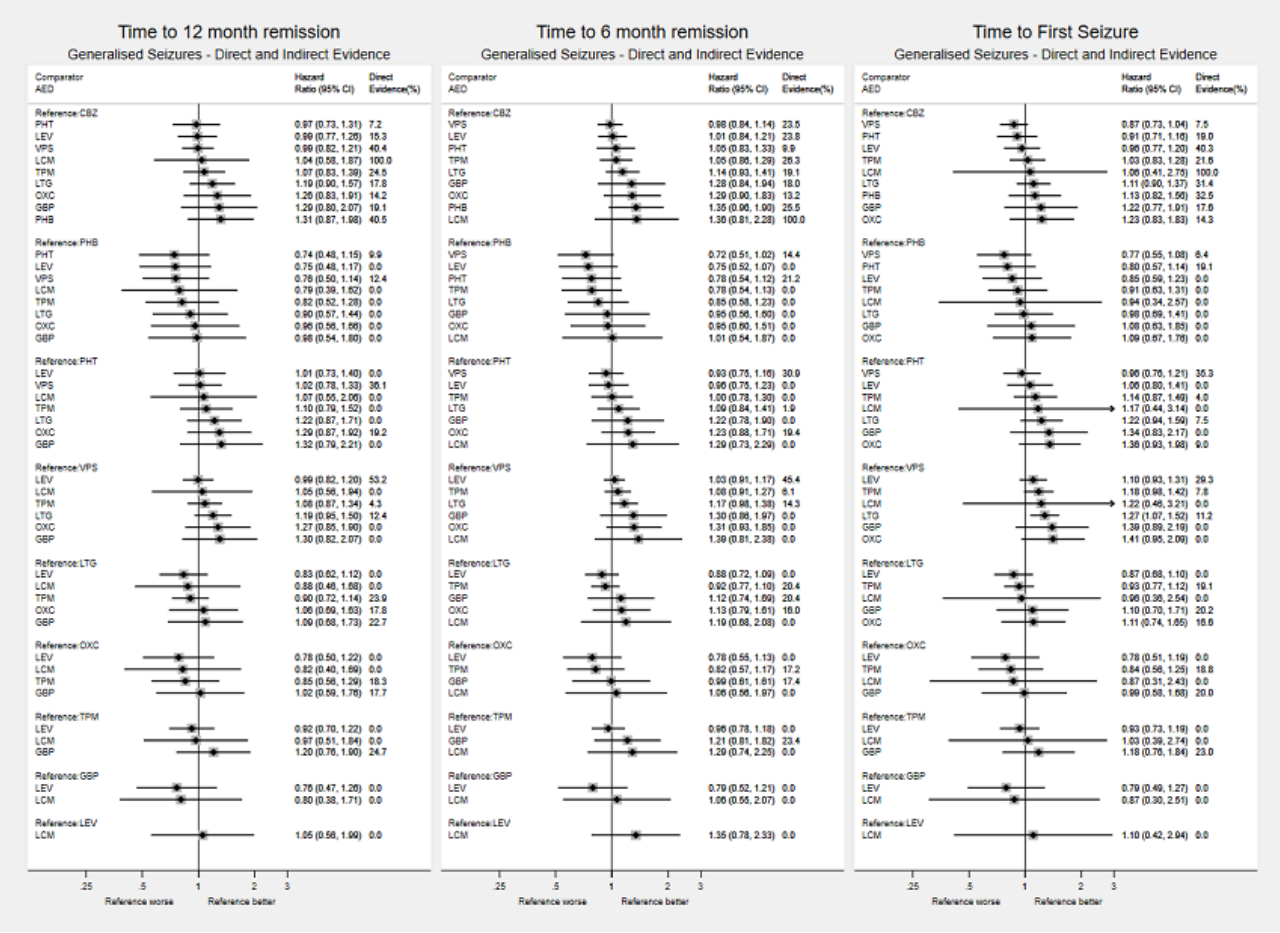


Figure 14. Network meta-analysis results (direct and indirect evidence combined) for individuals with generalised seizures, all pairwise comparisons for time to 12-month remission, time to six-month remission and time to first seizure Note: direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence. Generalised tonic-clonic seizures with or without other seizure types is shortened to 'Generalised seizures' for brevity. **AED: antiepileptic drug**
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide **To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures**



When repeating NMA with random-effects, the τ^2 statistic was 4.4 x 10^{-15} and the estimated I^2 statistic was 0%. Treatment-effect estimates were very similar for NMA conducted with fixed and random-effects, mostly the same to one decimal place, and conclusions remained unchanged (data not shown, available on request).

Investigation of inconsistency (node splitting)

A 'design-by-treatment' inconsistency model, accounting for the multi-arm trials, indicated that the global test for inconsistency was not significant (P = 0.908).

Table 16 (individuals with focal seizures) and Table 17 (individuals with generalised seizures) show treatment effect estimates from direct evidence, and from direct plus indirect evidence, Figure 15 and Figure 16 show treatment effect estimates for direct, indirect, and direct plus indirect evidence for individuals with focal seizures compared to carbamazepine and lamotrigine, respectively, and Figure 17 for individuals with generalised seizures compared to sodium valproate.

Figure 15. Consistency: direct, indirect and network estimates for individuals with focal seizures compared to carbamazepine (CBZ) for time to 12-month remission, time to six-month remission and time to first seizure. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures

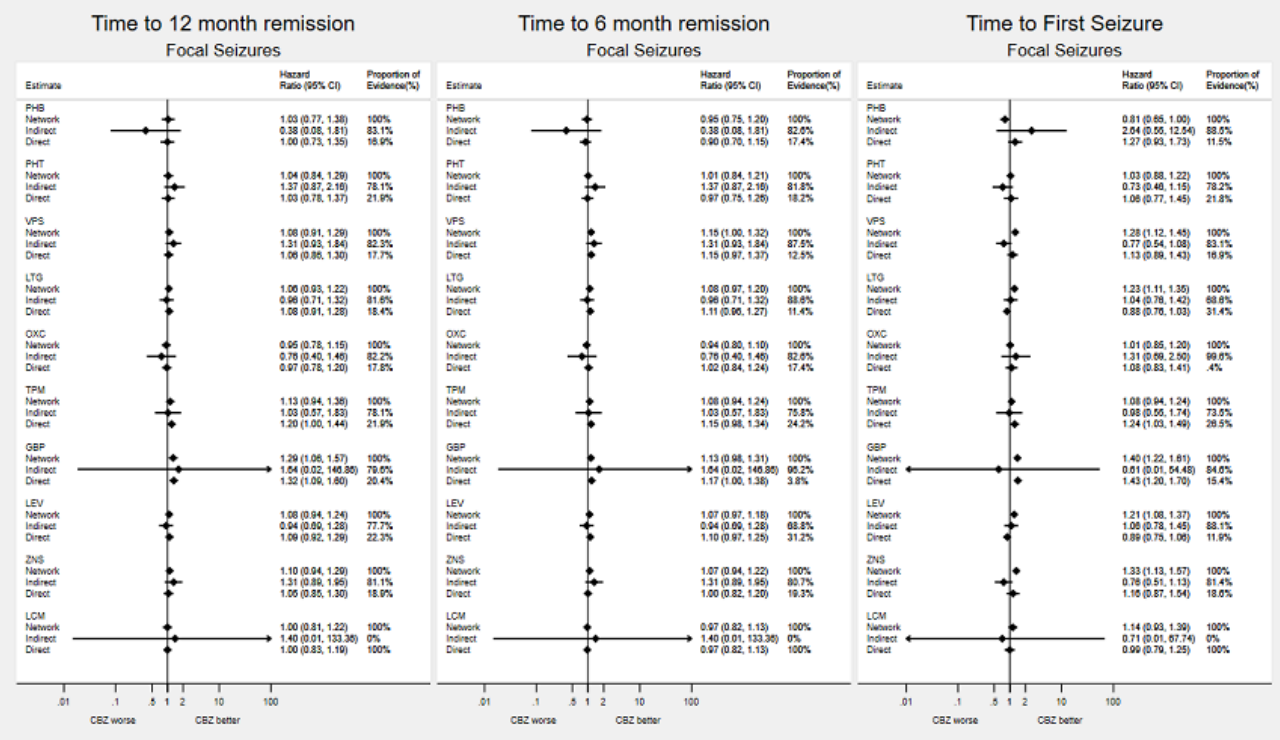


Figure 16. Consistency: direct, indirect and network estimates for individuals with focal seizures compared to lamotrigine (LTG) for time to 12-month remission, time to six-month remission and time to first seizure. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures

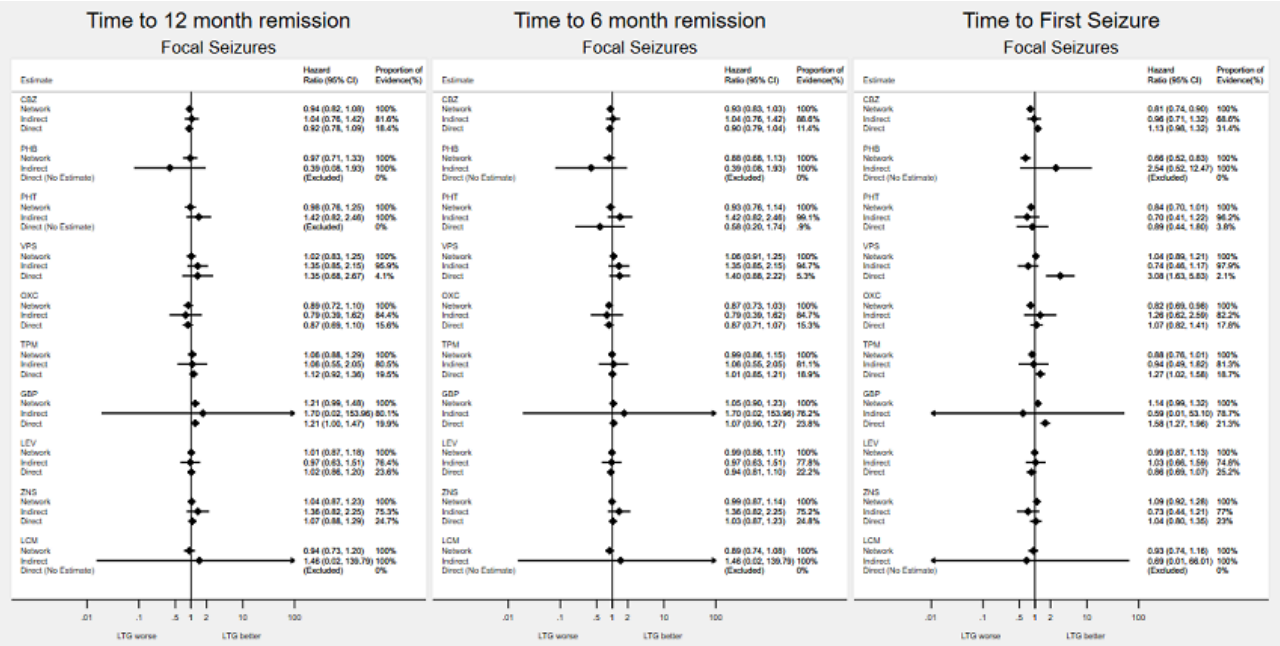
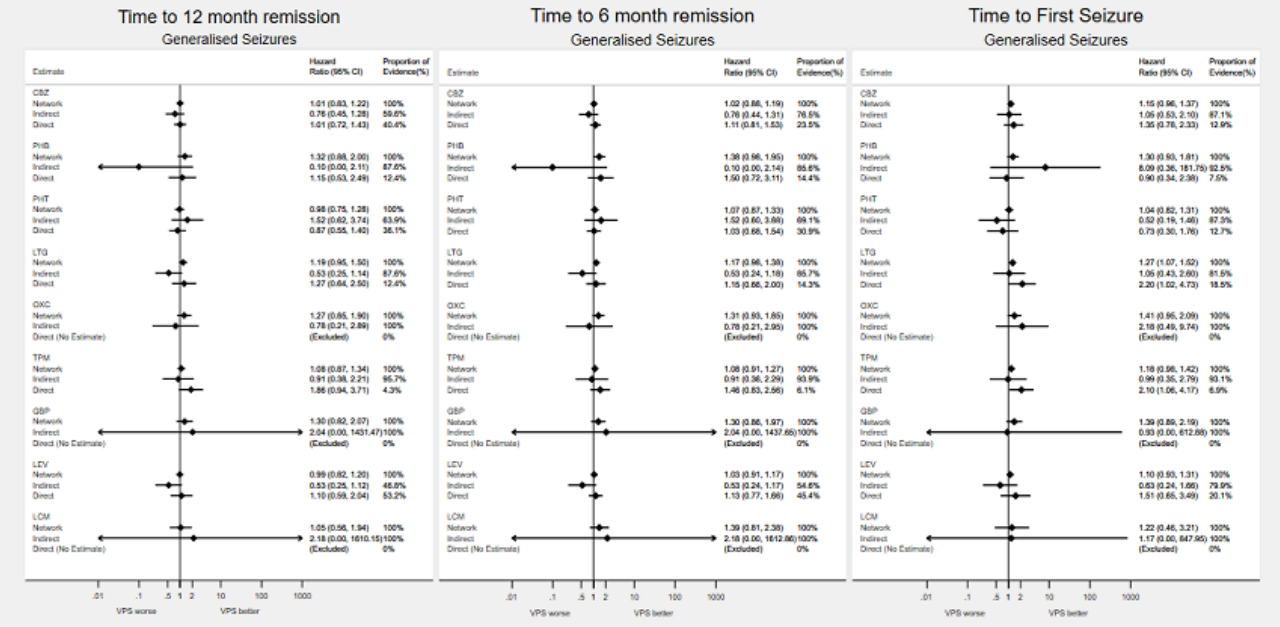


Figure 17. Consistency: direct, indirect and network estimates for individuals with generalised seizures compared to sodium valproate (VPS) for time to 12-month remission, time to six-month remission and time to first seizure. Numerical results from investigations of inconsistency for all pairwise comparisons are available from the corresponding author on request. Note: direct evidence comes from studies that compared the drugs (head-to-head comparisons), indirect evidence comes from studies that did not compare the drugs (indirect comparisons) and network evidence comes from the whole network (head-to-head and indirect comparisons for all drugs). Generalised tonic-clonic seizures with or without other seizure types is shortened to 'Generalised seizures' for brevity. AED: antiepileptic drug
CBZ: carbamazepine
CI: confidence interval
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide **To see a magnified version of this figure, please see https://epilepsy.cochrane.org/network-meta-analysis-figures**



For most pairwise comparisons, treatment-effect estimates from direct evidence (where available), indirect evidence (estimated from node splitting), and from the network meta-analysis results were similar, mostly in the same direction and confidence intervals of estimates overlapped. Indirect estimates were very uncertain for some comparisons, with some HR point estimates in the opposite direction to direct evidence and network meta-analysis results, particularly comparisons with the drugs with the least data that contributed to the network, such as gabapentin, lacosamide, oxcarbazepine and phenobarbitone.

For the following comparisons, conclusions that could be drawn from direct evidence (where available) and from network meta-analysis were different.

1. Direct evidence showed a significant advantage to one of the drugs and the network meta-analysis results showed no significant difference between the drugs: carbamazepine versus gabapentin for individuals with focal seizures; carbamazepine versus phenobarbitone for individuals with generalised seizures.
2. Direct evidence showed no significant difference between the drugs and network meta-analysis shows a significant advantage for one of the drugs: carbamazepine versus sodium valproate for individuals with focal seizures.

Despite some differences in conclusions that could be drawn from direct evidence and network meta-analysis results; confidence intervals overlapped for all estimates. Furthermore, the 'design-

by treatment' inconsistency model did not show any significant evidence of inconsistency within the network. Therefore, we are not concerned about any impact of this observed inconsistency of numerical results on the conclusions of the review.

Subgroup and sensitivity analysis

For the following additional analyses, numerical results were very similar (the same to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

1. Sensitivity analysis excluding one trial (Stephen 2007) due to inconsistencies in provided data.
2. Additional analysis also adjusting for age.

For the following additional analyses, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions.

1. Repeated analysis using an accelerated failure time model to assess the validity of the proportional hazards assumption.
2. Reclassification of seizure type 2 (see Sensitivity analysis).
3. Reclassification of seizure type 1 (see Sensitivity analysis) for individuals with focal seizures.

In the first sensitivity analysis for reclassification of seizure type (see Sensitivity analysis), all individuals originally classified as experiencing generalised seizures in the one trial of lacosamide (Baulac 2017) were reclassified to have focal seizures, so lacosamide did not feature in the network for individuals with generalised seizures. For all other pairwise comparisons, for individuals with generalised seizures, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment but no change in statistical significance for any estimate and no change to conclusions.

We were able to incorporate aggregate data for 82 participants with focal seizures and 46 participants with generalised seizures for one additional trial (Biton 2001). Numerical results of this sensitivity analysis were very similar (the same to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

Time to first seizure post-randomisation

The number of participants that contributed to analysis of our secondary outcome, 'time to first seizure post-randomisation' was 14,591 out of 14,789 participants (99%).

Direct evidence

Table 18 (individuals with focal seizures) and Table 19 (individuals with generalised seizures) show the number of trials and participants contributing direct evidence for each of the pairwise comparisons in the network. Twenty-seven out of 55 comparisons had no direct evidence for individuals with focal seizures. Twenty-one out of 45 comparisons had no direct evidence for individuals with generalised seizures and a further ten comparisons for individuals with generalised seizures had fewer than 100 individuals contributing direct evidence resulting in wide confidence intervals around the treatment-effect estimate for these comparisons. The comparisons with the most participants contributing to analysis were carbamazepine versus levetiracetam and carbamazepine versus lamotrigine for individuals with focal seizures and sodium valproate versus levetiracetam and sodium valproate versus topiramate for individuals with generalised seizures.

Table 18 and Table 19 also show estimates of heterogeneity in the direct treatment effects. For four comparisons of individuals with focal seizures and for three comparisons of individuals with generalised seizures, substantial heterogeneity was present (I^2 greater than 50%). The heterogeneity in these comparisons seemed to originate from differences in trial designs contributing to the pooled result; that is, pooling of trials recruiting children only, adults only or elderly participants only and pooling trials with or without treatment strata (see Data extraction and management for further details).

Network meta-analysis results (direct plus indirect evidence)

Figure 5 shows how each treatment performed compared to first-line treatment carbamazepine for individuals with focal seizures (ordered by treatment-effect estimate); phenobarbitone was significantly better than carbamazepine and carbamazepine was significantly better than levetiracetam, sodium valproate, lamotrigine, zonisamide and gabapentin.

Figure 6 shows how each treatment performed compared to first-line treatment lamotrigine for individuals with focal seizures (ordered by treatment-effect estimate); phenobarbitone, carbamazepine and oxcarbazepine were significantly better than lamotrigine.

Figure 7 shows how each treatment performed compared to first-line treatment sodium valproate for individuals with generalised seizures (ordered by treatment-effect estimate); sodium valproate was significantly better than lamotrigine.

Table 18 and Figure 13 (individuals with focal seizures) and Table 19 and Figure 14 (individuals with generalised seizures) show treatment effect estimates for all pairwise comparisons in the network combining direct with indirect evidence. In addition to the results described above, for individuals with focal seizures, phenobarbitone and phenytoin seemed to perform better than most other drugs and for individuals with generalised seizures, phenytoin seemed to perform better than most other drugs. There were few notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, levetiracetam, zonisamide and lacosamide) for either individuals with focal seizures or individuals with generalised seizures.

When repeating NMA with random-effects, the τ^2 statistic was 8.5×10^{-16} and the estimated I^2 statistic was 0%. Treatment-effect estimates were very similar for NMA conducted with fixed and random-effects, mostly the same to one decimal place, and conclusions remained unchanged (data not shown, available on request).

Investigation of inconsistency (node splitting)

A 'design-by-treatment' inconsistency model, accounting for the multi-arm trials, indicated that the global test for inconsistency was not significant (P = 0.991).

Table 18 (individuals with focal seizures) and Table 19 (individuals with generalised seizures) show treatment effect estimates from direct evidence, and from direct plus indirect evidence, Figure 15 and Figure 16 show treatment effect estimates for direct, indirect, and direct plus indirect evidence for individuals with focal seizures compared to carbamazepine and lamotrigine, respectively, and Figure 17 for individuals with generalised seizures compared to sodium valproate.

For most pairwise comparisons, treatment-effect estimates from direct evidence (where available), indirect evidence (estimated from node splitting), and from the network meta-analysis results are similar, mostly in the same direction and confidence intervals of estimates overlapped. Indirect estimates were very uncertain for some comparisons, with some HR point estimates in the opposite direction to direct evidence and network meta-analysis results, particularly comparisons with the drugs with the least data that contributed to the network, such as gabapentin, lacosamide, oxcarbazepine and phenobarbitone.

For the following comparisons, conclusions that could be drawn from direct evidence (where available) and from network meta-analysis were different.

1. Direct evidence showed a significant advantage to one of the drugs and the network meta-analysis results showed no significant difference between the drugs: carbamazepine versus topiramate, sodium valproate versus lamotrigine, lamotrigine versus topiramate, lamotrigine versus gabapentin for individuals with focal seizures; sodium valproate versus topiramate for individuals with generalised seizures.
2. Direct evidence showed no significant difference between the drugs and network meta-analysis showed a significant advantage for one of the drugs: carbamazepine versus phenobarbitone, carbamazepine versus sodium valproate, carbamazepine versus lamotrigine, phenobarbitone versus phenytoin, phenobarbitone versus sodium valproate, phenytoin versus sodium valproate for individuals with focal seizures.

For the following comparisons for individuals with focal seizures, confidence intervals for the results from direct evidence and from network meta-analysis did not overlap, which indicated potential inconsistency was present (see Table 18, Figure 15 and Figure 16): carbamazepine and lamotrigine, carbamazepine and levetiracetam, lamotrigine and sodium valproate.

For the comparison of carbamazepine and lamotrigine, from direct evidence from nine trials (2184 participants), there was no statistically significant difference between treatments (HR 0.88, 95% CI 0.76 to 1.03), however, from the network meta-analysis, a statistically significant advantage to carbamazepine over lamotrigine was shown (HR 1.23, 95% CI 1.11 to 1.35). For this comparison, 31.4% of the network estimate was contributed from direct evidence and no heterogeneity was present in direct evidence (I^2 = 0%).

For the comparison of carbamazepine and levetiracetam, from direct evidence from three trials (1552 participants), there was no statistically significant difference between treatments (HR 0.89, 95% CI 0.75 to 1.06), however, from the network meta-analysis, a statistically significant advantage to carbamazepine over levetiracetam was shown (HR 1.21, 95% CI 1.08 to 1.37). For this comparison, 11.9% of the network estimate was contributed from direct evidence and substantial heterogeneity was present in direct evidence (I^2 = 68%).

For the comparison of lamotrigine and sodium valproate, from direct evidence from three trials (257 participants), a statistically significant advantage to lamotrigine over sodium valproate was shown (HR 0.44, 95% CI 0.26 to 0.74), however, from the network meta-analysis, there was no statistically significant difference between treatments (HR 0.96, 95% CI 0.83 to 1.12). For this comparison, 2.1% of the network estimate was contributed from direct evidence and substantial heterogeneity was present in direct evidence (I^2 = 55%).

For the comparisons, carbamazepine and levetiracetam and lamotrigine and sodium valproate, given the relatively small contribution of direct evidence to the network estimate and substantial heterogeneity (see 'Direct Evidence' above for discussion of potential sources of heterogeneity), and given that the 'design-by treatment' inconsistency model did not show any significant evidence of inconsistency within the network, we are not concerned about any impact of this observed inconsistency of numerical results on the conclusions of the review for these comparisons.

However, for the comparison of first-line treatments carbamazepine and lamotrigine, given the larger number of trials and participants contributing direct evidence, absence of heterogeneity in direct evidence, greater contribution of direct evidence to the network estimate and no known potential sources of the inconsistency between direct evidence and network estimates, we encourage caution when comparing carbamazepine and lamotrigine in terms of time to first seizure.

Subgroup and sensitivity analysis

For the following additional analyses, numerical results were very similar (the same to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

1. Sensitivity analyses excluding Stephen 2007 and Banu 2007 due to inconsistencies in provided data and excluding Nieto-Barrera 2001 due to missing seizure dates from the first four weeks of the trial (separate sensitivity analyses excluding one trial at a time).
2. Additional analysis also adjusting for age.
3. Reclassification of seizure type 1 (see Sensitivity analysis) for individuals with focal onset seizures.

For the following additional analyses, numerical results were similar; there were some changes in direction of effect size or some changes in the order or 'rank' of treatments compared to the reference treatment, but no change in statistical significance for any estimate and no change to conclusions:

1. Repeated analysis using an accelerated failure time model to assess the validity of the proportional hazards assumption.

2. Reclassification of seizure type 2 (see Sensitivity analysis).

In the first sensitivity analysis for reclassification of seizure type (see Sensitivity analysis), all individuals originally classified as experiencing generalised seizures in the one trial of lacosamide (Baulac 2017) were reclassified to have focal seizures, so lacosamide did not feature in the network for individuals with generalised seizures. For all other pairwise comparisons, for individuals with generalised seizures, numerical results were very similar (the same to one decimal place) and conclusions remained unchanged.

We were able to incorporate aggregate data for 82 participants with focal seizures and 46 participants with generalised seizures from one additional trial (Biton 2001) and for 64 participants with focal seizures from another additional trial (Gilad 2007). Numerical results of this sensitivity analysis were very similar (the same to two decimal places for individuals with focal seizures and one or two decimal places for individuals with generalised seizures) and conclusions remained unchanged.

Occurrence of adverse events

We were provided with individual participant data for adverse events experienced during the trial for 26 trials (Banu 2007; Baulac 2012; Baulac 2017; Biton 2001; Brodie 1995a; Brodie 1995b; Brodie 1999; Brodie 2007; Chadwick 1998; Dizdarer 2000; Eun 2012; Kwan 2009; Lee 2011; Nieto-Barrera 2001; Ogunrin 2005; Privitera 2003; Ramsay 2010; Reunanen 1996; SANAD A 2007; SANAD B 2007; SANAD II A 2021; SANAD II B 2021; Steiner 1999; Stephen 2007; Trinka 2013; Werhahn 2015). The remaining 13 trials providing IPD, did not provide detailed IPD for adverse events, so we extracted information regarding adverse events from the trial publications of 10 of these studies (Bill 1997; Craig 1994; De Silva 1996; Guerreiro 1997; Heller 1995; Mattson 1985; Mattson 1992; Pal 1998; Placencia 1993; Ramsay 1992; Richens 1994; Turnbull 1985; Verity 1995). No adverse events data was reported in three of these publications (De Silva 1996; Heller 1995; Turnbull 1985).

We were also able to extract a summary of adverse event data from 32 trials not providing IPD (Akter 2018; Brodie 2002; Callaghan 1985; Capone 2008; Chen 2013; Christe 1997; Consoli 2012; Dam 1989; Donati 2007; Feksi 1991; Gilad 2007; Giri 2016; Jung 2015; Kalviainen 2002; Korean Lamotrigine Study Group 2008; Korean Zonisamide Study 1999; Maiti 2018; Motamedi 2013; Kim 2017; NCT01954121; Pulliainen 1994; Ramsay 1983; Rastogi 1991; Resendiz 2004; Rowan 2005; Saetre 2007; Shakir 1981; So 1992; Steinhoff 2005; Suresh 2015; Thilothammal 1996; Trinka 2018).

No adverse event data was reported in 18 publications (Aikia 1992; Bidabadi 2009; Castriota 2008; Chen 1996; Cho 2011; Cossu 1984; Czapinski 1997; Forsythe 1991; Fritz 2006; Kopp 2007; Lukic 2005; Mitchell 1987; Miura 1990; Ramsay 2007; Ravi Sudhir 1995; Sidhu 2018; Wu 2018; Xu 2012).

Due to the wide range of events reported in the trials and the different methods of recording and reporting of adverse events, we have not analysed adverse event data in meta-analysis and have provided a narrative report. We took the following approach to the negative synthesis of adverse events. One review author (SJN) grouped verbatim or reported terms extracted from publications or provided in IPD under high level general definitions and discussed any uncertainties in definition with the senior clinical author (AGM).

We took the definitions used in this review from a previous review in our series of IPD monotherapy reviews (Nevitt 2018a), with further definitions added as appropriate when reviewing the reported terms.

For each type of event, the number of events was extracted, where reported. Where only the number of participants experiencing the event was reported, it was assumed that each participant experienced the event once. Therefore, the frequency of some events may be underestimated. Also, where provided within IPD or trial publications, 'treatment-emergent' adverse events only were extracted, but if this information was not provided, any information regarding adverse events was extracted. Therefore, not all adverse events necessarily occurred while a participant was taking their randomised treatment, and it was also unclear whether adverse events were related to the allocated treatment.

Table 20 describes the adverse event data available and the number of participants experiencing adverse events respectively by drug.

Adverse event data were available from studies recruiting 20,275 participants (92% of all participants included in this review), ranging between 76% to 78% of data available from studies of phenytoin and phenobarbitone to 100% of data available from studies of gabapentin, zonisamide, lacosamide, and eslicarbazepine acetate. Adverse events were reported in 62% of participants in the studies where adverse event data were available, ranging from 43% to 76% of participants across the drugs.

Table 21 describes the frequency of some of the most commonly reported side effects of AEDs by drug.

The most commonly occurring adverse events across all drugs were drowsiness or fatigue, headache or migraine, dizziness or faintness, gastrointestinal disturbances, and rash or skin disorders.

Drowsiness or fatigue was the most commonly reported adverse event of carbamazepine, phenytoin, sodium valproate, oxcarbazepine, gabapentin and eslicarbazepine acetate. Headache or migraine was the most commonly reported adverse event of lamotrigine, levetiracetam, zonisamide and lacosamide. Paraesthesia (tingling or 'pins and needles') was the most commonly reported adverse event of topiramate and cognitive disorders (memory or concentration difficulties, confusion etc.), mood or behaviour changes (including aggression) were the most commonly reported adverse event of phenobarbitone.

We emphasise that, as not all studies reported adverse event data and some trial publications reported only limited information on the “most common” adverse events, the totals and frequencies are likely to be an underestimation of the true number of events and number of individuals experiencing events. Furthermore, in general, more detailed information was provided in the more recent trial publications and IPD requests of more recent trials often involving newer AEDs such as lamotrigine, levetiracetam and topiramate; which may indicate that these newer drugs are associated with more adverse events than older drugs such as phenobarbitone and phenytoin, for which less detailed information was available.

Limitations of this narrative synthesis must be taken into account when interpreting Table 20 and Table 21 as well as the definitions of adverse events in the review, which were often defined by the

review authors rather than according to dictionary terminology (such as MedDRA®). We encourage only general comparison of the relative frequencies of different adverse events experienced by participants on different drugs, and we do not encourage direct interpretation of numerical frequencies of adverse events.

DISCUSSION

Summary of main results

Individual participant data were provided for at least one outcome of this review for 14,789 participants with focal onset seizures or generalised onset seizures randomised to carbamazepine, phenytoin, sodium valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide or lacosamide in 39 trials. We calculated 'direct estimates' via meta-analysis of the head-to-head comparisons of the drugs within the trials and performed network meta-analysis to combine this direct evidence with indirect evidence across the network of 11 treatments. Network meta-analysis provided a total of 55 pairwise comparisons for individuals with focal seizures and 45 pairwise comparisons for individuals with generalised seizures (no participants with generalised onset seizures were randomised to zonisamide).

Direct estimates could be calculated for around half of comparisons across the outcomes of the review, however, for many of the comparisons, data were contributed by only a single trial or by a small number of participants, or both. Where pooling of head-to-head data was possible, direct evidence was generally consistent with NMA results, and there was no evidence of important heterogeneity or inconsistency in the NMAs.

Network meta-analysis showed that for our primary outcome, 'time to treatment failure,' for individuals with focal seizures: lamotrigine performed significantly better than most other treatments in terms of treatment failure for any reason and due to adverse events, including other first-line treatment, carbamazepine. 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, no other treatment performed better than first-line treatment, sodium valproate, but there was no significant difference between sodium valproate and lamotrigine or levetiracetam in terms of treatment failure.

For 'time to 12-month remission of seizures' and 'time to six-month remission of seizures,' few notable differences were shown for either seizure type, only that, for individuals with focal seizures, carbamazepine was significantly better than gabapentin (12-month remission) and significantly better than sodium valproate (six-month remission). No significant 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 that, for 'time to first seizure,' in general, the earliest licensed treatments (phenytoin and phenobarbitone) performed better than the other treatments for individuals with focal seizures; phenobarbitone performed significantly 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.

Results from network meta-analysis were more precise than results from head-to-head comparisons, often much more precise for comparisons where there was limited direct evidence, reflecting the added precision of network meta-analysis over pairwise meta-analysis. Across outcomes for the majority of pairwise comparisons, numerical results of direct evidence and network meta-analysis were similar, mostly in the same direction, confidence intervals of estimates overlapped and there was little indication of inconsistency between direct and network meta-analysis results. For the few pairwise comparisons where confidence intervals of direct estimates and network meta-analysis estimates did not overlap, generally, direct evidence was limited and contributed only a small proportion of evidence to the network meta-analysis estimates. However, for the comparison of first-line treatments, carbamazepine and lamotrigine, given the larger number of trials and participants contributing direct evidence, absence of heterogeneity in direct evidence, greater contribution of direct evidence to the network estimate and no known potential sources of the inconsistency between direct evidence and network estimates, we encourage caution when comparing carbamazepine and lamotrigine in terms of time to first seizure.

The most commonly reported adverse events across all drugs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders, with some drug-specific variations (e.g. paraesthesia (tingling or 'pins and needles') was the most commonly reported adverse event of topiramate, and cognitive disorders (memory or concentration difficulties, confusion etc.) and mood or behaviour changes (including aggression) were the most commonly reported adverse events of phenobarbitone). Due to the wide range of adverse events reported in the trials and the different methods of recording and reporting of adverse events, it was not possible to perform an analysis of adverse events. We encourage caution when interpreting frequencies of adverse events, and we do not encourage direct comparisons of adverse events frequencies across AEDs.

Overall completeness and applicability of evidence

We have gratefully received IPD for 14,789 out of a total of 22,040 eligible participants (67% of total data) from 39 out of the 89 eligible trials (43%) randomising participants to one of 11 AEDs. We received between 42% and 100% of participant data across the 10 drugs.

Data from 50 trials recruiting 7251 participants (33% of total data out of 57% of total trials) could not be provided for a variety of reasons reported by trial authors or sponsors, including data lost or no longer available, prohibitive cost and resources required to prepare data, or local authority- or country-specific restrictions. Furthermore, at the time of writing, for over 20 trials, we have been unable to make contact with an author or sponsor to request data. If data can be made available for any of these additional trials at a later date, they will be included in an update of this review.

Figure 2 shows network plots of pairwise comparisons in all included trials, trials providing IPD and trials without IPD. Visually, the plot of the trials providing IPD is quite similar to the plot of all included trials; therefore, it is likely that the 67% of participant data we received is a representative sample of all eligible participants and that the 33% of missing participant data can generally be treated as 'missing at random.' Notably, no IPD were available at

the time of analysis from the one trial of eslicarbazepine acetate (Trinka 2018) and, therefore, this IPD-NMA did not provide evidence to inform the effectiveness of eslicarbazepine acetate compared to other AEDs used in monotherapy.

Furthermore, out of all drugs included in the network, we received the lowest proportion of IPD for oxcarbazepine (42% of total participants receiving oxcarbazepine). This lack of data may have contributed to imprecision of some effect sizes relating to oxcarbazepine (see Figure 8; Figure 9; Figure 13 and Figure 14), therefore, we encourage caution when interpreting results relating to oxcarbazepine from this review. We note that the 58% of IPD missing for oxcarbazepine mostly comes from trials for which we could not establish contact with an author or sponsor to request IPD. If additional data can be included in an update for oxcarbazepine, we expect the precision of these estimates to improve.

Figure 1 shows network plots of pairwise comparisons of all eligible participants, from participants with focal seizures and from participants with generalised seizures. The majority of participants recruited into the trials within this review were classified as experiencing focal onset seizures (69% of participants in all trials and 71% of participants with IPD provided); this majority is demonstrated in the visual similarity of the network plot for individuals with focal seizures compared to the plot of all participants and reflected in the relative precision of the results of this review for focal seizures compared to generalised seizures. While a majority of focal seizures compared to generalised seizures is reflective of clinical practice (around 60% of individuals with epilepsy experience focal seizures, NINDS 2021), the proportion of individuals with focal seizures recruited to the trials in this review is even greater.

The remaining participants within the review were classified as experiencing generalised seizures (24.5% of participants in all trials and 26.5% of participants with IPD provided) or unclassified/missing seizure type (8.8% of participants in all trials and 6% of participants with IPD provided). Misclassification of seizure type is a recognised problem in epilepsy (whereby some individuals with generalised seizures have been mistakenly classed as having focal onset seizures and vice versa). The potential impact of this misclassification on results has been shown in our series of Cochrane IPD reviews of monotherapy for epilepsy (Nevitt 2018b), whereby up to 50% of individuals classified as experiencing generalised seizures may have had their seizure type misclassified, as an age of seizure onset of over 30 years is unlikely for generalised seizures (Malafosse 1994). Investigation of misclassification within this review (reclassification of 1780 participants with generalised seizures and age of onset of over 30 years, 34% of individuals originally classified at experiencing generalised seizures) did not show any important changes to treatment effect sizes and no changes to conclusions.

This does not, however, indicate that misclassification of seizure type has not occurred in these trials; rather that the primary analysis results are robust to any misclassification. The majority of trials included in this review were published between 1981 and 2015 and a proportion of trials classified generalised and focal onset seizures according to the International League Against Epilepsy (ILAE) classification of 1981 (Commission 1981), rather than the revised ILAE classification in 1989 (Commission 1989) or recently revised terminology (Berg 2010), which may have led to misclassification. Furthermore, several trials were conducted in low-income countries in Africa, Asia and Central or South America, without access to the same facilities such as EEGs or MRI scanners as trials conducted in the USA and Europe. Within these trials, it is likely that seizure type would have been classified clinically, which may have further contributed to misclassification in these trials. In reality, it is likely that fewer than 20% of participants recruited into all of these trials (17% of participants included in IPD analysis were classified as having generalised seizures following reclassification in sensitivity analysis) experienced generalised seizures which is a lower proportion than would be expected in clinical practice (NINDS 2021). For this reason, treatment effect sizes for generalised seizures, particularly those that are imprecise, should be treated as less applicable than the treatment effect sizes for focal seizures.

In order to provide more precise evidence, applicable to individuals with generalised seizures, it is important both to ensure accurate seizure classification (as far as possible) and to increase the proportion of individuals with generalised seizures recruited into trials of AEDs to better reflect the 'real world' ratio of focal to generalised seizures. Increased recruitment of participants may not be straightforward, particularly as those with new onset generalised seizures are expected to be children and adolescents, and recruitment of children into clinical trials comes with difficulties (Joseph 2015); however, if targeted recruitment strategies could be implemented and the evidence base for individuals with generalised seizures increased, this may better inform treatment decisions for this population, particularly for those of childbearing potential, for whom first-line treatment sodium valproate may not be appropriate (NICE 2012).

Quality of the evidence

This review provides mostly high-certainty evidence for the relative effectiveness of 12 commonly used antiepileptic drugs for the treatment of focal seizures and generalised tonic-clonic seizures. Where limited data were available for a comparison and confidence intervals around treatment effect size results were wide, mostly for individuals with generalised seizures, or for treatment failure due to specific reasons, we judged the certainty of the evidence to be moderate or low and additional data from future trials may impact on these treatment effect estimates (see Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

Direct estimates and network meta-analysis estimates were generally consistent despite some methodological concerns in several trials contributing to analyses, which may have introduced bias into analyses, or inconsistencies present within individual participant data, (see Risk of bias in included studies); numerous sensitivity analyses were performed to test the robustness of the results in the presence of these biases (see Sensitivity analysis for full details); and results of sensitivity analyses were numerically similar and did not lead to any changes to conclusions, therefore, it is unlikely that any methodological inadequacies of individual trials has influenced the overall pooled network meta-analysis results

Potential biases in the review process

The search strategies for this review were extensive, and we are confident that we have identified all relevant evidence for this review including ongoing trials.

We have taken an IPD approach to analysis, which has many advantages, such as allowing the standardisation of definitions of outcomes across trials, and reducing attrition and reporting biases, as we can perform additional analyses and calculate additional outcomes from unpublished data. For the outcomes we used in this review that are of a time-to-event nature, an IPD approach is considered to be the 'gold standard' approach to analysis (Parmar 1998). Furthermore, the use of IPD in this analysis has allowed us to consider the relationship between treatment effect and seizure type via an interaction term in the network meta-analysis model and present results separately according to seizure type in the context of the recommended first-line treatment of the seizure type, an approach which would not have been possible without the use of IPD.

The majority of IPD requested were provided to us directly but, for one trial (Biton 2001), we requested data via data sharing portal ClinicalStudyDataRequest.com and data were provided to us via a remote secure data access system, which allowed analysis in SAS-based statistical software and export of analysis results. We were unable to combine this dataset with the other datasets to perform the analyses described in Data synthesis, therefore, we treated the results exported from the data access system as aggregate data in sensitivity analysis (see Sensitivity analysis). As described above, numerical results were similar and conclusions unchanged following the addition of aggregate data to the IPD analyses, therefore the restricted access format of this single trial does not seem to have impacted on the results of the review. However, we are concerned for updates of this review in particular and for future meta-analyses of IPD in general, that the provision of data in different formats and the increased use of remote access systems may restrict the analyses that it is possible to perform across all eligible datasets and subsequently impact on meta-analytic results and the scope of clinical questions that are able to be addressed.

Despite the advantages of an IPD approach, for reasons out of our control, we were not able to obtain IPD for 7251 participants from 50 eligible trials and, for the majority of these trials, no aggregate data were available for our outcomes of interest in trial publications. It is inevitable that the exclusion of 33% of eligible participants may be a source of bias in our analyses, however, as discussed in more detail above in Overall completeness and applicability of evidence, we believe that the 67% of participants we were able to include in IPD analyses were a representative sample of the total participants included in all eligible trials and that the benefits of an IPD approach outweigh the limitations.

Agreements and disagreements with other studies or reviews

Previous NMAs of AED monotherapy, published in 2007 (Tudur Smith 2007) and the previous version of this review in 2017 (Nevitt 2017a) showed lamotrigine and carbamazepine to have the best profile for a combination of seizure control and treatment failure in focal onset seizures, with newer drug levetiracetam shown to be a potentially suitable alternative (Nevitt 2017a). Previous NMAs also showed valproate to have the best profile for generalised onset seizures, with lamotrigine and levetiracetam potential suitable alternatives to either of these first-line treatments, particularly for those of childbearing potential, for whom sodium valproate may not be an appropriate treatment option due to teratogenicity (Nevitt 2017a). However, the relative effectiveness of other AEDs was uncertain and evidence was limited for some of the newer AEDs.

Results of this updated review include up-to-date evidence from recently conducted trials (SANAD II A 2021; SANAD II B 2021) and this is the first NMA to include evidence for newly licensed AED, lacosamide. The results of this review generally agree with the results of previous NMAs, in addition to providing more evidence for newer AEDs, particularly levetiracetam and zonisamide. This review continues to highlight that data and, therefore, evidence for participants with generalised onset seizures is still limited.

AUTHORS' CONCLUSIONS

Implications for practice

Current guidelines from the National Institute for Health and Care Excellence (NICE) in the UK for adults and children recommend carbamazepine or lamotrigine as first-line treatment for focal onset seizures, and sodium valproate for generalised onset seizures (NICE 2012); however, given the range of treatment options available to individuals with new onset seizures, including many recently licensed 'second generation' and 'third generation' antiepileptic drugs (AEDs), the choice of first-line treatment for an individual must be made based on the highest-quality evidence of the relative effectiveness and tolerability of AEDs compared to one another.

Results of this review demonstrate that generally the earliest licensed AEDs, such as phenytoin and phenobarbitone, provide increased seizure control, in terms of delaying recurrence of first seizure and earlier remission, compared to newer AEDs. However, this comes at the expense of earlier treatment failure, and it is newer AEDs such as lamotrigine and levetiracetam that perform the best in terms of treatment retention. Considering the optimum balance of efficacy (seizure control) and tolerability (treatment retention), for individuals with focal seizures, carbamazepine, lamotrigine and levetiracetam seem to be the best treatment options, whereas for individuals with generalised tonic-clonic seizures (with or without other seizure types), sodium valproate, lamotrigine and levetiracetam seem to be the best treatment options. Zonisamide and lacosamide, the most recently licensed AEDs for monotherapy treatment, may be an effective treatment option for individuals with focal onset seizures; however, further evidence from randomised controlled trials is needed. Only a small number of participants with generalised seizures have been randomised to lacosamide in clinical trials so effectiveness evidence is very limited, and no published clinical trial has evaluated zonisamide for individuals with generalised seizures.

Overall, the high-certainty evidence provided by this review is in line with NICE guidelines that carbamazepine and lamotrigine are suitable first-line treatments for individuals with focal onset seizures and also demonstrates that levetiracetam may be a suitable alternative. High-certainty evidence from this review is also in line with the use of sodium valproate as the first-line treatment for individuals with generalised tonic-clonic seizures (with or without other seizure types) and also demonstrates that lamotrigine and levetiracetam would be suitable alternative first-line treatments, particularly for those of childbearing potential, for whom sodium valproate may not be an appropriate treatment option. Evidence for the relative effectiveness of other AEDs for individuals with generalised seizures is limited and of moderate certainty; further evidence from randomised controlled trials

recruiting individuals with generalised tonic-clonic seizures (with or without other seizure types) is needed.

Implications for research

This review highlights the need for the design of future AED monotherapy trials that are well powered to detect a difference between particular AEDs while recruiting a sample of individuals representative of the wider population in terms of age and seizure type. An approach to best reflect and inform clinical practice, as well as being statistically powerful, would be to recruit heterogeneous populations for whom epilepsy syndromes have been adequately defined, with testing for interaction between treatment and epilepsy syndrome. In view of potential problems of misclassification, syndromes will have to be well-defined, with adequate checking mechanisms to ensure that classifications are accurate and a system to recognise uncertainty surrounding epilepsy syndromes in individuals within trials.

The choice of outcomes at the design stage of a trial and the presentation of the results of outcomes, particularly of a time-to-event nature, require very careful consideration. While the majority of trials of a monotherapy design do record and report outcomes measuring efficacy and tolerability (adverse events), there is little uniformity between the definition of the outcomes and the reporting of the summary statistics related to the outcomes (Nolan 2013a; Nevitt 2017b), making an aggregate data approach to meta-analysis in reviews of monotherapy trials impossible. Where trial authors cannot or will not make individual participant data (IPD) available for analysis, review authors are left with no choice but to exclude a proportion of relevant evidence from their review, which will inevitably have some impact upon the interpretation of results of the review and applicability of the evidence and conclusions. The International League Against Epilepsy recommends that trials of a monotherapy design should adopt a primary effectiveness outcome of 'time to withdrawal of allocated treatment (retention time)' and should be of a duration of at least 48 weeks to allow for assessment of longer-term outcomes, such as remission (ILAE 1998). If trials followed these recommendations, an aggregate data approach to meta-analysis may be feasible, reducing the resources and time required from an IPD approach.

The provision of accessible, standardised and high-quality data (whether provided at the aggregate or IPD level) is essential to allow updates of this review and future reviews of AED therapy as further information becomes available, particularly for recently licensed and future treatment options.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aikia 1992

Study characteristics	
Methods	Randomised, double-blinded, parallel-group trial conducted in Finland 2 treatment arms: OXC and PHT
Participants	Adult participants with newly diagnosed epilepsy and "normal intellectual capacity" with a minimum of 2 seizures in the last 2 years or 1 seizure and an epileptiform EEG Number randomised: OXC = 19, PHT = 18 Number completed and included in analysis: OXC = 14, PHT = 15 (see Notes) 11 male participants (38%) out of 29 included participants 21 participants with focal epilepsy (72%) out of 29 included participants Mean age of included participants (SD): OXC = 33.6 (14) years, PHT = 32.7 (12.5) years
Interventions	Monotherapy with OXC or PHT 4- to 8-week titration period followed by a maintenance phase of 12 months. Doses achieved not stated Range of follow-up not stated
Outcomes	Neuropsychological assessment and cognitive functioning in 3 major areas at baseline, 6 months' and 12 months' follow-up: Verbal learning and memory Sustained attention Simple psychomotor speed
Notes	Participants experiencing inadequate seizure control, adverse events or those who were non-compliant were withdrawn from the trial and excluded from analysis (5 from OXC group and 3 from PHT group). Results presented only for 29 participants (OXC = 14 and PHT = 15) completing the trial Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were "randomly assigned" to treatment; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Low risk	"The study followed a double-blind design".

Aikia 1992 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The study followed a double-blind design"; no further information provided about whether outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT approach not taken: results reported only for 29 participants (OXC = 14 and PHT = 15) who completed 12-month follow-up. 8 participants experiencing inadequate seizure control, adverse events or those who were non-compliant (OXC = 5 and PHT = 3) were excluded from analysis and results.
Selective reporting (reporting bias)	Low risk	No protocol available and outcomes chosen for this review not reported. Neuropsychological and cognitive outcomes well reported and treatment withdrawal rates reported
Other bias	Low risk	None identified

Akter 2018

Study characteristics	
Methods	Randomised, open-label controlled trial conducted in Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from May 2015 to July 2016 2 treatment arms: LEV and PHB
Participants	Children aged between 1 month and 15 years of age diagnosed with idiopathic focal, generalised, focal with secondary generalisation epilepsy Number randomised: LEV = 75; PHB = 75; number who completed the study: LEV = 50; PHB = 68 62 boys of those who completed the study (53%) 38 focal epilepsy of those who completed the study (32%) Mean age (SD) of those who completed the study: LEV = 35.62 (31.23) months; PHB = 25.47 (26.38) months
Interventions	Monotherapy with LEV or PHB Doses not stated Study duration 1 year
Outcomes	Seizure remission up to 12 months (0 to 25%, 25 to 50%, 50 to 75%, 75 to 100% measured at 3-month intervals) Psychological assessments up to 12 months, measured at 3-month intervals EEG abnormalities Side effects
Notes	Published abstract only available. Unpublished manuscript and unpublished data provided by trial author on request. Results were only available for those who completed the study (7 from the PHB group and 25 from the LEV group excluded from all analyses) and a further 22 excluded from analyses after 6 months as other antiepileptic drugs had been added.

Akter 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly divided into groups using a random number generator in Microsoft Excel (information provided in unpublished manuscript)
Allocation concealment (selection bias)	High risk	Even numbers were assigned to LEV and odd numbers were assigned to PB (information provided in unpublished manuscript). This method does not conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was performed (information provided in unpublished manuscript).
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding was performed (information provided in unpublished manuscript).
Incomplete outcome data (attrition bias) All outcomes	High risk	Results were only available for those who completed the study (7 from the PB group and 25 from the LEV group excluded from all analyses) and a further 22 excluded from analyses after 6 months as other antiepileptic drugs had been added. Up to 36% of randomised participants were not included in analysis; this is not an ITT approach.
Selective reporting (reporting bias)	Low risk	Seizure outcomes, side effects, EEG findings and psychological assessments well reported. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Banu 2007

Study characteristics	
Methods	Single-centre, double-blind RCT of participants recruited from clinical referral to a multidisciplinary child development centre at a children's hospital in Dhaka, Bangladesh 2 treatment arms: CBZ and PHB
Participants	108 children aged 2-15 years with 2 or more generalised tonic-clonic, focal, or secondarily generalised seizures in the previous year Number randomised: CBZ = 54, PHB = 54 61 boys (56%) 59 participants with focal epilepsy (55%) 26 participants had previous AED treatment (24%) Mean age (range): 6 years (1-15 years)
Interventions	Monotherapy with CBZ (immediate release) or PHB Starting daily dose: CBZ = 1.5 mg/kg/d, PHB = 5 mg/kg/d, maximum daily dose: CBZ = 4 mg/kg/d, PHB = 16 mg/kg/d

Banu 2007 *(Continued)*

	Trial duration: 12 months, range of follow-up: 0-22 months
Outcomes	Seizure control: seizure freedom during the last quarter of the 12-month follow-up Time to first seizure after randomisation Time to treatment withdrawal due to adverse events Change in behaviour from baseline according to age-appropriate questionnaire Incidence of behavioural side-effects
Notes	We received IPD for all randomised participants from the trial author. We received reasons for treatment failure/withdrawal of allocated treatment as well as the date of the last follow-up visit, but treatment failure/withdrawal did not always coincide with the date of the last follow-up visit (i.e. several participants had the allocated treatment substituted for the other trial drug and continued to be followed up). Dates of treatment failure could not be provided; therefore, we could not calculate 'time to treatment failure'. We received the date of first seizure after randomisation, but dates of other seizures in the follow-up time could not be provided; therefore, we calculated 'time to first seizure' for all participants, but we could not calculate the time to 6- and 12-month remission.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomly assigned to treatment"; the method of randomisation was not stated and not provided by the trial authors.
Allocation concealment (selection bias)	Low risk	Allocation was concealed by sealed envelopes prepared on a different site to the site of recruitment of participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, a psychologist, and a therapist were blinded throughout the trial. The treating physician was unblinded for practical and ethical reasons.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A researcher performing outcome assessment was blinded throughout the trial but unblinded for analysis. It was unclear if this could have influenced the results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were reported. We analysed all randomised participants from the IPD provided (see footnote 2).
Selective reporting (reporting bias)	Low risk	We calculated 1 outcome for this review from the IPD provided (see footnote 2). We could not calculate other outcomes for this review as the appropriate data were not recorded/not available. All cognitive outcomes from the trial were well reported.
Other bias	High risk	There were inconsistencies between rates of seizure recurrence between the data provided and the published paper, which the trial authors could not resolve.

Baulac 2012

Study characteristics

Baulac 2012 *(Continued)*

Methods	Randomised, double-blind, parallel-group, non-inferiority trial, conducted in 120 centres in Asia, Australia, and Europe 2 treatment arms: CBZ and ZNS
Participants	Participants aged 18-75 years with newly diagnosed epilepsy, at least 2 focal seizures (with or without secondary generalisation) or generalised tonic-clonic seizures without clear focal origin in the previous 12 months and at least 1 seizure in the previous 3 months, and had not previously received AEDs or had been treated with 1 AED for no more than 2 weeks Number randomised: CBZ = 301, ZNS = 282 347 (60%) male participants 100% focal epilepsy Mean age (range): 36 (18-75 years)
Interventions	Monotherapy with CBZ or ZNS Titration over 4 weeks to a target dose of CBZ = 600 mg/d and ZNS = 300 mg/d Range of follow-up: 0-29 months
Outcomes	Proportion of participants who achieved seizure freedom for 26 weeks or more (maintenance period) in the per-protocol population Incidence of treatment-emergent results Time to 26-week (6-month) remission Time to 52-week (12-month) remission Proportion of participants with no seizures for at least 52 weeks Time to withdrawal because of absence of efficacy or adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor Eisai

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation scheme was generated centrally by computer program, which produced a randomisation list with a pseudo-random number generator.
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved by the use of a telephone interactive voice-response system to dispense the allocated treatment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, and sponsor personnel administering medication, assessing outcomes, and analysing data were masked to the allocation. Masking was maintained by use of matching placebo tablets.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, and sponsor personnel administering medication, assessing outcomes, and analysing data were masked to the allocation. Masking was maintained by use of matching placebo tablets.
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)

Baulac 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Baulac 2017

Study characteristics	
Methods	Phase III randomised multicentre, double-blind, non-inferiority trial at 185 sites in 29 countries in Europe, North America, and the Asia-Pacific region, using a stepwise design with three dose levels 2 treatment arms: LCM and CBZ-CR
Participants	Participants over the age of 16 years with recently diagnosed focal onset seizures or generalised tonic–clonic seizures, at least two unprovoked seizures separated by 48 hours or longer in the previous 12 months, of which at least one had occurred in the previous 3 months. Participants must not have received any AED treatment in the 6 months preceding the study. Number randomised: LCM = 445, CBZ-CR = 443; number in the full analysis set: LCM = 444, CBZ-CR = 442; number in the per protocol set: LCM = 408, CBZ-CR = 397 475 male participants randomised (53%) 808 participants with focal epilepsy randomised (91%) Mean age (SD) of the full analysis set: LCM = 41.9 (17.9) years, CBZ-CR = 41.8 (17.2) years
Interventions	Monotherapy with LCM or CBZ-CR Starting doses: LCM 100 mg/d, CBZ-CR 200 mg/d in divided doses before up-titration over a two-week period to LCM 200 mg/d or CBZ-CR 400 mg/d for participants who remained seizure-free throughout the 6 month assessment period If a seizure occurred during the assessment period, participants were titrated to LCM 400 mg/d or CBZ-CR 800 mg/d and to LCM 600 mg/d or CBZ-CR 1200 mg/d if another seizure occured and the assessment period began again. Participants who remained seizure-free could undergo one dose reduction during the assessment period if they were unable to tolerate the increased dose. Participants who experienced a seizure on the third dose level or following dose reduction were withdrawn from the study. Treatment duration: up to 121 weeks Range of follow-up: 0 to 24 months
Outcomes	Proportion of patients remaining free from seizures for 6 consecutive months (26 weeks) after stabilisation at the last assessed dose Proportion of patients remaining seizure-free for 12 consecutive months (52 weeks) after stabilisation at the last assessed dose Time to first seizure during 12 months of treatment at the last assessed dose Time from the first dose of trial medication to withdrawal because of an adverse event or lack of efficacy

Baulac 2017 *(Continued)*

	Incidence of treatment-emergent adverse events, withdrawals due to adverse events and serious adverse events
Notes	One participant randomised to each group did not receive treatment and was therefore excluded from the full analysis set. IPD provided for all outcomes of this review by trial sponsor UCB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned treatment in a 1:1 ratio according to a predetermined randomisation schedule generated by UCB Pharma, Brussels, Belgium, with an SAS software application (version 2.0). Randomisation was stratified by the number of seizures in the 3-month period before screening (two or fewer vs more than two).
Allocation concealment (selection bias)	Low risk	At the randomisation visit, the site investigator used a fully automated online interactive voice response system to obtain the next randomisation code. Kit numbers for trial medication were automatically allocated by the system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, patients, and trial personnel were unaware of treatment assignment. The trial medications and packaging were identical in size and colour.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators, patients, and trial personnel were unaware of treatment assignment. The trial medications and packaging were identical in size and colour.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Bidabadi 2009

Study characteristics

Methods	Six-month, systematic, simple randomised trial of children referred to a child neurology clinic (the author was from Guilan University of Medical Sciences, Iran, so it was likely that the trial was also conducted there) 2 treatment arms: CBZ and PHB
Participants	Children aged 2-12 years with focal seizures with secondary generalisation Number randomised: CBZ = 36, PHB = 35 36 boys (53%) 100% of participants with focal epilepsy Percentage newly diagnosed was not stated

Bidabadi 2009 *(Continued)*

	Age range: 2-12 years
Interventions	Monotherapy with CBZ or PHB Doses started or achieved not stated Trial duration: 6 months, range of follow-up not stated
Outcomes	Proportion seizure-free Response rate and rate of side effects Seizure frequency and seizure duration
Notes	The trial was reported in abstract form only with very limited information. Outcomes chosen for this review were not reported; IPD were not available, trial author could not be contacted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as a 'systematic simple randomised study'; no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition rates were reported; it was unclear if all participants were analysed.
Selective reporting (reporting bias)	Unclear risk	There was no protocol available; the trial was available in abstract format only. Outcomes for this review were not available.
Other bias	Low risk	None identified

Bill 1997

Study characteristics

Methods	Multicentre, double-blind, parallel-group trial conducted in centres in Argentina, Brazil, Mexico, South Africa 2 treatment arms: OXC and PHT
Participants	Participants aged 16-65 years with newly diagnosed epilepsy with focal or generalised tonic-clonic seizures A minimum of 2 seizures, separated by at least 48 hours, within 6 months preceding trial entry

Bill 1997 *(Continued)*

	No previous AED, except emergency treatment of seizures for a maximum of 3 weeks prior to trial entry Number randomised: total = 287, OXC = 143, PHT = 144 174 male participants (61%) 182 participants with focal epilepsy (63%) Mean age (range) = 26 (15-91) years
Interventions	Monotherapy with OXC or PHT 8-week titration period started with 300 mg OXC or 100 mg PHT, increased bi-weekly, based on clinical response After 8 weeks, participants were to be on a three-times-a-day regimen with daily doses of 450 mg-2400 mg OXC or 150 mg-800 mg PHT Continued during 48-week maintenance with adjustment according to clinical response A third long-term, open-label extension phase followed the maintenance period. Double-blind results only were reported. Range of follow-up = 0-19 months
Outcomes	The proportion of seizure-free participants who had at least one seizure during the maintenance period Time to premature discontinuation due to adverse experiences Rate of premature discontinuations for any reason Overall assessments of efficacy and tolerability and therapeutic effect Individual adverse experiences Laboratory values Seizure frequency during maintenance
Notes	IPD provided for all outcomes of this review from trial sponsor Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment groups randomised in 1:1 ratio across centres via computer-generated randomisation numbers over balanced blocks of size 6
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved with sequentially-numbered packages that were identical and contained identical tablets (information provided by trial statistician).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial conducted in 2 phases: 56-week, double-blind phase followed by long-term, open-label extension. Double-blind phase results reported only. Blind achieved with divisible OXC and PHT tablets identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported in both treatment phases; participants withdrawing from treatment were no longer followed up so seizure outcomes had to be

Bill 1997 *(Continued)*

All outcomes		censored at time of failure or withdrawal and therefore analyses for remission and seizure outcomes could not adopt an ITT approach.
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Biton 2001

Study characteristics	
Methods	Randomised, double-blind, parallel-group, multicentre trial conducted in the USA 2 treatment arms: LTG and VPS
Participants	Participants > 12 years with newly diagnosed or previously diagnosed epilepsy of any seizure type, not currently using an AED Number randomised: LTG = 66, VPS = 69, ITT population: LTG = 65, VPS = 68 (2 participants withdrew before drug escalation phase) 60 male participants (44%) 82 participants with focal epilepsy (60%) Proportion newly diagnosed not stated Mean age (range): 32 (12-76) years
Interventions	Monotherapy with LTG or VPS Dose-escalation phase of 8 weeks to target doses of LTG = 200 mg/d and VPS = 20 mg/kg/d Trial duration: 32 weeks
Outcomes	Weight change The proportion of participants seizure-free during the entire trial Incidence of the most common drug-related adverse events Time to withdrawal from the trial
Notes	IPD provided for remote analysis by trial sponsor Glaxo Smith Kline for time to treatment failure, time to first seizure and time to six-month remission. IPD had to be treated as aggregate data in network meta-analysis due to remote access to data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme was used.
Allocation concealment (selection bias)	Unclear risk	No information provided

Biton 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Results presented to investigator in a "blinded" fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 1995a

Study characteristics	
Methods	Randomised, double-blind, parallel-group trial conducted in 8 centres in the UK 2 treatment arms: LTG and CBZ
Participants	Adults and children > 13 years with newly diagnosed epilepsy. None had received previous AED treatment. Number randomised: LTG = 70, CBZ = 66 56 male participants (41%) 82 with focal epilepsy (60%); Mean age (range): 34 (14-71) years
Interventions	Monotherapy with LTG or CBZ 4-week escalation phase leading to LTG = 150 mg/d, CBZ = 600 mg/d Range of follow-up = 0-14 months
Outcomes	Time to first seizure after 6 weeks of treatment Time to withdrawal Proportion of randomised participants remaining seizure-free during the last 40 and 24 weeks of trial Percentages of participants who reported adverse events
Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment failure, time to first seizure and time to six-month remission

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Brodie 1995a *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer) Stratification by seizure type
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 1995b

Study characteristics	
Methods	Randomised, double-blind, parallel-group trial conducted in 8 centres in the UK 2 treatment arms: LTG and CBZ
Participants	Adults and children > 13 years with newly diagnosed epilepsy. None had received previous AED treatment. Number randomised: LTG = 61, CBZ = 63 56 male participants (45%) 62 participants with focal epilepsy (50%) Mean age (range): 30 (14-81) years
Interventions	Monotherapy with LTG or CBZ 4-week escalation phase leading to LTG = 150 mg/d, CBZ = 600 mg/d Range of follow-up = 0-13 months
Outcomes	Time to first seizure after 6 weeks of treatment Time to withdrawal Proportion of randomised participants remaining seizure-free during the last 40 and 24 weeks of trial Percentages of participants who reported adverse events

Brodie 1995b *(Continued)*

Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment failure, time to first seizure and time to six-month remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer) Stratification by seizure type
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 1999

Study characteristics

Methods	Randomised, multicentre, double-blind, parallel-group trial conducted in the UK 2 treatment arms: LTG and CBZ randomised in a 2:1 ratio
Participants	Adults > 65 years with newly diagnosed epilepsy with ≥ 2 seizures in the previous year with at least 1 seizure in the last 6 months. None had received previous AED treatment. Number randomised: LTG = 102, CBZ = 48 83 male participants (55%) 105 participants with focal epilepsy (70%) Mean age (range): 77 (65-94) years
Interventions	Monotherapy with LTG or CBZ 4-week escalation phase leading to LTG = 100 mg/d, CBZ = 400 mg/d Range of follow-up = 0-13.5 months
Outcomes	Time to first seizure after 6 weeks of treatment

Brodie 1999 *(Continued)*

	Time to withdrawal
	Percentage of participants reporting an adverse event
	Proportion of participants who were both seizure-free in the last 16 weeks of the trial and did not discontinue treatment
Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment failure and time to first seizure (plus seizure-freedom rates at 24 weeks)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer) Participants randomised in a 2:1 ratio (LTG:CBZ)
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved using LTG tablets formulated to be identical in appearance to CBZ tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded, not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Brodie 2002

Study characteristics

Methods	Randomised, multicentre, double-blind trial conducted in 41 centres in Europe and Australia
	2 treatment arms: GBP and LTG
Participants	Participants > 16 years with at least 2 focal seizures with or without secondary generalisation or primary generalised tonic-clonic seizures in the last 12 months. All participants were untreated in the previous 6 months or AED-naive.
	Number randomised: GBP = 158, LTG = 151. Evaluable population (exclusions due to protocol violations): GBP = 148, LTG = 143
	152 male participants (52%) out of evaluable population
	233 participants with focal epilepsy (80%) out of evaluable population
	Mean age of evaluable population (SD, range): GBP: 35.8 years (16.4, 13-78), LTG: 37.9 (16.7, 16-78)

Brodie 2002 *(Continued)*

Interventions	Monotherapy with GBP or LTG Titration of 2 weeks for GBP to a dose range of 1200 mg/d-3600 mg/d and titration of 6 weeks for LTG to a dose range of 100 mg/d-300 mg/d Titration period followed by 24-week maintenance period. Range of follow-up not stated
Outcomes	Time to exit Percentage of completers/time to withdrawal for any reason Time to first seizure Percentage who remained seizure-free during the final 12 weeks of the 30-week evaluation period Withdrawal rate due to adverse events
Notes	IPD requested from trial sponsor Pfizer but data could not be provided due to time elapsed since the trial was completed. Additional information provided in a clinical study report. Aggregate data extracted for time to exit from the trial and time to first seizure extracted from the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with permuted blocks, stratified within each centre by seizure type.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking was achieved by double-dummy dosing. A dose range was permitted within the trial to maintain the blind of two drugs with different titration rates (2 weeks for GBP and 6 weeks for LTG)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants included in an ITT analysis (even though demographics presented for 'evaluable population' only)
Selective reporting (reporting bias)	Low risk	All efficacy and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available.
Other bias	Low risk	None identified

Brodie 2007

Study characteristics

Methods	Randomised, double-blind, parallel-group trial conducted at 85 centres in 12 European countries and in South Africa 2 treatment arms: CBZ (controlled release) and LEV

Brodie 2007 *(Continued)*

Participants	Adults (> 16 years) with 2 focal or generalised tonic–clonic seizures separated by at least 48 h in the previous year with at least one seizure in the last 3 months Number randomised: CBZ = 291, LEV = 288 319 male participants (55%) 466 participants with focal epilepsy (80%) Mean age (range): 39 (15-82 years)
Interventions	Monotherapy with CBZ or LEV Titration for 2 weeks to target dose of CBZ = 400 mg/d, LEV = 1000 mg/d Range of follow-up = 0-28 months
Outcomes	Proportion of per-protocol (PP) participants achieving at least 6 months of seizure freedom at the last evaluated dose One year seizure-freedom rate 6-month and 1-year seizure-freedom rate by dose level Time to trial withdrawal Incidence of adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor UCB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised following a central 1:1 randomisation scheme with a statistical block size of 2 and stratified by seizure category.
Allocation concealment (selection bias)	Low risk	Participants were randomised using an interactive voice-response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To ensure blinding, LEV and CBZ-CR tablets were identically encapsulated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Callaghan 1985

Study characteristics	
Methods	Single-centre, randomised, parallel-group trial of participants referred for assessment at Cork Regional Hospital, Ireland 3 treatment arms: CBZ, PHT, VPS
Participants	Adults and children with a minimum of 2 untreated generalised or focal seizures in the 6 months preceding the trial Number randomised: PHT = 58, CBZ = 59, VPS = 64 95 male participants (52%) 79 participants (44%) with focal epilepsy Age range: 4-75 years
Interventions	Monotherapy with CBZ, PHT or VPS Mean daily dose achieved: PHT = 5.4 mg/kg, CBZ = 10.9 mg/kg, VPS = 15.6 mg/kg Duration of treatment (range in months): 14-24 months
Outcomes	Seizure control: • excellent (complete freedom of seizures) • good (> 50% reduction in seizure frequency) • poor (< 50% reduction in seizure frequency or no response) Side effects
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation based on two Latin squares without stratification. The first, second and third preference of drug for the participant appears to have been taken into account in the process. Unclear if assignment was completely random
Allocation concealment (selection bias)	High risk	An independent person (department secretary) selected the “drug of first preference” from randomisation list on a sequential basis. Allocation not adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attirition rates reported. ITT approach taken, all randomised participants analysed

Callaghan 1985 *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary outcomes (seizure control) and secondary outcomes (side effects) reported sufficiently
Other bias	Low risk	None identified

Capone 2008

Study characteristics	
Methods	Randomised trial of participants with epileptic seizures following stroke conducted in Italy 2 treatment arms: CBZ (controlled release) and LEV
Participants	Participants with "vascular epilepsy", new onset following stroke. Not stated if participants had been previously treated with AEDs Number randomised: CBZ = 17, LEV = 18 17 male participants (49%) Proportion of participants with focal epilepsy not stated Mean age (range): 70 (43-90) years
Interventions	Monotherapy with CBZ or LEV Dose achieved: CBZ: 400 mg/d-1200 mg/d, LEV = 1000 mg/d-3000 mg/d Trial duration and range of follow-up not stated
Outcomes	Seizure freedom Adverse events during the trial Discontinuations of the trial drug
Notes	The trial was published in Italian; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; IPD were not available (author confirmed that the data had been lost).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised ('randomizzazione' in Italian); no further information was available.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided

Capone 2008 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, no formal statistical analysis performed so withdrawals did not influence results.
Selective reporting (reporting bias)	Unclear risk	Methods brief; efficacy and tolerability reported in the results. Outcomes chosen for this review not reported. No protocol available so unclear which outcomes were planned a priori
Other bias	Low risk	None identified

Castriota 2008

Study characteristics	
Methods	Randomised, open-label trial to evaluate event-related potential recordings on the effect of CBZ and LEV cognitive function, conducted in Italy 2 treatment arms, CBZ (controlled release) and LEV
Participants	Participants with newly diagnosed focal epilepsy Number randomised: CBZ = 14, LEV = 13 14 male participants (52%) 100% of participants had focal epilepsy Mean age (years): CBZ = 38, LEV = 42, range not stated
Interventions	Monotherapy with CBZ or LEV Fifteen-day titration to CBZ = 800 mg/d and LEV = 100 mg/d Trial duration: 24 weeks (assessments at baseline and 12 weeks); range of follow-up not stated
Outcomes	Event-related potential recordings Neuropsychological assessments
Notes	The trial was published in Italian; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; IPD were not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised ('randomizzazione' in Italian); no further information was available.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Castriota 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates reported (3 dropouts from the CBZ group, 11% of total participants). These participants were excluded from analysis; this was not an ITT approach.
Selective reporting (reporting bias)	Unclear risk	Cognitive outcomes described in methods section well reported in results section. No seizure outcomes or adverse events reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	Low risk	None identified

Chadwick 1998

Study characteristics	
Methods	Randomised (partially), double-blind, multicentre trial conducted at 25 sites in Europe, Australia, South Africa and Canada 4 treatment arms: GBP (3 arms, 300 mg/d, 900 mg/d and 1800 mg/d) and CBZ. Dose of GBP was masked within the treatment arm but CBZ was given open-label due to difficulties of blinding tablets and capsules and differing titration periods for the two drugs.
Participants	Participants with newly diagnosed focal epilepsy, with at least 2 unprovoked focal or generalised tonic-clonic seizures in the 6 months prior to trial entry, who were AED-naive or had received fewer than 2 weeks of AED therapy, which had to be discontinued before trial entry. Participants with a seizure recurrence after at least 2 years of remission were also eligible. Number randomised: CBZ = 74, GBP = 218 157 male participants (54%) 100% participants with focal epilepsy Mean age (range): 35 (12-86 years)
Interventions	Monotherapy with GBP or CBZ Titration period of 7 d for GBP to target doses 300 mg/d, 900 mg/d or 1800 mg/d. Titration period of 21 d for CBZ to target dose 600 mg/d. Titration period followed by an evaluation period of 24 weeks and an optional open-label period Range of follow-up: 0-77 months
Outcomes	Time to exit Time to exit event plus withdrawals because of adverse events Completion rate (percentage of participants attending end-of-phase visit) Exit event rate (percentage of participants who experienced an exit event during the evaluation phase) Adverse event withdrawal rate (percentage of participants who withdrew because of adverse events during either titration or evaluation phases)

Chadwick 1998 *(Continued)*

	Exit plus adverse event withdrawal rate (the sum of the exit rate plus the adverse event withdrawal rate) Incidence of adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor Pfizer. In primary analysis, three arms of GBP were pooled and compared to CBZ (see Data extraction and management).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation schedule was prepared separately for each trial centre in blocks of four and eight.
Allocation concealment (selection bias)	Low risk	Trial medication was distributed centrally via a pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was partially double-blinded (the dose of GBP was blinded but GBP was not blinded compared to CBZ). Given that the main comparison made in this review was GBP compared to CBZ rather than comparisons between the doses of GBP, this trial was treated as an open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; ITT approach; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Chen 1996

Study characteristics

Methods	Randomised, parallel-group trial conducted in Taiwan 3 treatment arms: CBZ, PHB, VPS
Participants	Children with 2 or more previously untreated unprovoked epileptic seizures Number randomised: CBZ = 26, PHB = 25, VPS = 25; number analysed: CBZ = 25, PHB = 23, VPS = 25 (see notes) 38 boys (52%) 38 participants with focal epilepsy (52%) Mean age (range) for participants analysed: CBZ = 10.8 (7-15 years), PHB = 9.9 (7-15 years), VPS = 9.9 (7-15 years)
Interventions	Monotherapy with CBZ, PHB or VPS

Chen 1996 *(Continued)*

	Dose started or achieved not stated Trial duration: 12 months, range of follow-up: not stated
Outcomes	Cognitive/psychometric outcomes: IQ (WISC-R scale) and developmental delay (Bender-Gestalt test) Auditory event-related potentials (neurophysiological outcome) Incidence of allergic reactions Seizure control
Notes	2 children from the PHB group and 1 child from the CBZ group withdrew from the trial because of allergic reactions. Published results were presented for children who completed the trial only. Outcomes chosen for this review were not reported; IPD were not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated with "simple randomisation of block size 3".
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The cognitive assessor was "single blinded", implying that participants and personnel were unblinded, but no further information was provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The cognitive assessor was "single blinded".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal rates were reported; results were presented only for those who completed the trial (3/73 (4%) excluded from analysis). An ITT approach was not taken but unclear whether the exclusion of this small proportion of participants would influence results
Selective reporting (reporting bias)	Low risk	All cognitive, efficacy, and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Chen 2013

Study characteristics

Methods	Randomised trial conducted in the in the Department of Pediatric Neurology of the First Hospital of Jilin University (China) from October 2009 to December 2011 2 treatment arms: CBZ and OXC
Participants	Children aged between 2 and 14 years, newly diagnosed with focal epilepsy

Chen 2013 *(Continued)*

	Number randomised: CBZ = 60; OXC = 58 66 boys (56%) 100% of participants had focal epilepsy Mean age (SD): 5.9 (2.2) years
Interventions	Monotherapy with CBZ and OXC Titration weekly to a target dose of CBZ = 10 to 20 mg/kg/d; OXC = 20 to 40 mg/kg/d (both divided into two oral doses) Study duration: 26 weeks
Outcomes	Response rate (at least 50% reduction in seizure frequency from baseline) at 13 weeks and at 26 weeks Seizure-free rate at 13 weeks and at 26 weeks Adverse events at 26 weeks
Notes	The trial was published in Chinese; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were 'randomly divided' into an experimental group (oral OXC suspension) and a control group (oral CBZ tablets). No information provided about the method of randomisation
Allocation concealment (selection bias)	Low risk	"Sealed envelopes" (translated from Chinese) were used to conceal allocations.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of patients who withdrew from treatment provided (but no reasons given). All randomised patients included in analysis
Selective reporting (reporting bias)	Low risk	All seizure and adverse event outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Cho 2011

Study characteristics

Cho 2011 *(Continued)*

Methods	Randomised trial conducted in Republic of Korea 2 treatment arms: CBZ (controlled release) and LEV
Participants	Participants with newly diagnosed focal epilepsy who had their first seizure between 1 and 6 months prior to entry into the trial and had not taken any AEDs previously Number completing the trial: CBZ = 15, LEV = 16 (number randomised not stated) 22 male participants (71%) 100% of participants had focal epilepsy. Mean age (SD, range): CBZ = 29.8 (9.31, 15-49), LEV = 31.4 (15.3, 15-66) years
Interventions	Monotherapy with CBZ or LEV Treatment regimens were CBZ = 400 mg/d and LEV = 1000 mg/d. Trial duration 4-6 weeks, range of follow-up not stated
Outcomes	Change in overnight PSG scores (sleep latency, REM sleep latency, total sleep time, sleep efficiency, percentage of each sleep stage, arousal index, and Wake time After Sleep Onset) from baseline after 4-6 weeks of treatment Change in sleep questionnaires (sleep diaries, the Pittsburg Sleep Quality Index, the Korean version of the Epworth Sleepiness Scale, Beck's depression inventory-2 and the Hospital Anxiety Scale) and National Hospital Seizure Severity Scale (NHS3) from baseline after 4-6 weeks of treatment
Notes	IPD could not be provided for the trial due to concerns over institutional review board approval (information provided by corresponding author). Outcomes chosen for this review were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PSG scores were interpreted by a certified physician who was blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number randomised not stated; results provided only for those who completed the trial
Selective reporting (reporting bias)	Low risk	All sleep, efficacy, and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Christe 1997

Study characteristics	
Methods	Multicentre, double-blind, parallel-group trial conducted in centres in Europe, Brazil and South Africa 2 treatment arms: OXC and VPS
Participants	Participants aged 16-65 years with newly diagnosed epilepsy with focal or generalised tonic-clonic seizures A minimum of 2 seizures, separated by at least 48 hours, within 6 months preceding trial entry No previous AED, except emergency treatment of seizures for a maximum of 3 weeks prior to trial entry Number randomised: OXC = 128, VPS = 121 127 male participants (51%) 154 participants with focal epilepsy (62%) Mean age (range): OXC: 32.45 (15-65), VPS: 32.47 (15-64)
Interventions	Monotherapy with OXC or VPS Titration period of 8 weeks to target doses of 900 mg/d-2400 mg/d of OXC or VPS Titration period followed by 48-week maintenance period and the possibility of a long-term open-label extension of 1 year
Outcomes	The proportion of seizure-free participants who had at least 1 seizure during the maintenance period Time to premature discontinuation due to adverse experiences Rate of premature discontinuations for any reason Overall assessments of efficacy and tolerability and therapeutic effect Individual adverse experiences Seizure frequency during maintenance
Notes	IPD requested from trial sponsor Novartis but data could not be provided due to time elapsed since the trial was completed. Aggregate data extracted from graph of time to premature discontinuation in the publication

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised in a 1:1 ratio; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial treatment with OXC or VPS was administered as non-divisible film-coated tablets of identical appearance containing 300 mg of active substance.

Christe 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates reported; only those who reached the maintenance period were included in efficacy analyses. This was not an ITT approach.
Selective reporting (reporting bias)	Low risk	All efficacy and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available.
Other bias	Low risk	None identified

Consoli 2012

Study characteristics	
Methods	Multicentre, open-label randomised trial conducted in two centres in Italy 2 treatment arms: CBZ and LEV
Participants	Participants > 18 years with late post-stroke seizures (2 weeks to 3 years after stroke) seen in the Cerebrovascular Unit between September 2008 and March 2009. No previous AED treatments were allowed except for emergency treatments. Number randomised: CBZ = 66, LEV = 62. Number completing the trial: CBZ = 54, LEV = 52 58 male participants (55%) of those completing the trial 74 participants with focal epilepsy (74%) of those completing the trial Mean age of those completing trial (SD): CBZ = 69.7 (13.2), LEV = 74.1 (11.3)
Interventions	Monotherapy with CBZ or LEV 2-week titration period to CBZ: 600 mg/d or LEV: 1000 mg/d Titration period followed by 52-week maintenance period. Range of follow-up not stated
Outcomes	Frequency of seizures during the treatment period Rentention of treatment from the first intake Changes in cognitive measures and quality-of-life measures at the end of the treatment period: • Mini Mental Scale Examination to evaluate global cognitive functioning • Logical Memory from the Wechsler Memory Scale-Revised • Visual Memory assessed with the Benton Visual Memory test • Digital Span Test for attention and some executive functions • Stroop Test to investigate the inhibition process • Raven's Coloured Progressive Matrices Test for nonverbal reasoning • Corsi span and supraspan learning test • ADL index and the Instrumental-ADL (IADL) • Depression assessed with the Geriatric Depression Scale Changes in EEG assessments at the end of the treatment period

Consoli 2012 *(Continued)*

	Tolerability of treatment
Notes	Contact made with trial author who provided additional information for one of the trial centres but full IPD dataset unavailable. Aggregate data extracted from graph of time to seizure recurrence in the publication. Trial was terminated early due to financial reasons when 128 out of a target 630 participants had been recruited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation numbers were sequentially assigned across centres, and a computer-generated randomisation scheme was used to provide balanced blocks of participants for each treatment group within each centre.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates reported; only those who completed the trial were included in efficacy analyses. This was not an ITT approach.
Selective reporting (reporting bias)	Low risk	All efficacy, cognitive and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available.
Other bias	High risk	Likely that trial was underpowered from the early termination with 20% of target sample size recruited

Cossu 1984

Study characteristics

Methods	Randomised, double-blind trial to assess short-term therapy of CBZ and PHB on cognitive and memory function; conducted in Italy Three treatment arms: CBZ, PHB, and placebo
Participants	Participants with newly diagnosed and untreated temporal lobe epilepsy with no seizures in the previous month Number randomised: CBZ = 6, PHB = 6 1 man and 5 women in each group 100% focal (temporal lobe epilepsy); 100% newly diagnosed

Cossu 1984 *(Continued)*

	Mean age (SD): CBZ = 26.33 (9.73) years, PHB = 18.5 (2.56) years. Age range: 15-45 years
Interventions	Monotherapy with CBZ or PHB Dose started and achieved not stated Trial duration: 3 weeks; all participants completed in 3 weeks
Outcomes	Changes in memory function from baseline after 3 weeks of treatment (verbal, visual, (visual-verbal and visual-nonverbal), acoustic, tactile, and spatial)
Notes	The trial was published in Italian; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised ('randomizzazione' in Italian); no further information was available.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial was described as double-blind ('condizioni di doppia cecità' in Italian); we assumed this referred to participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed this short trial and contributed to analysis.
Selective reporting (reporting bias)	Unclear risk	Cognitive and memory outcomes described in methods section well reported in results section. No seizure outcomes or adverse events reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	High risk	Very small participant numbers and very short-term follow-up. Unclear if this trial was adequately powered and of sufficient duration to detect differences

Craig 1994

Study characteristics

Methods	Parallel-group design; RCT; conducted in the UK 2 treatment arms: PHT and VPS
Participants	Participants > 60 years with newly onset seizures (1 or more generalised tonic-clonic seizures or 2 or more focal seizures) Number randomised: PHT = 81, VPS = 85

Craig 1994 *(Continued)*

	71 male participants (43%) 80 participants with focal epilepsy (48%) Mean age (range): 78 (61-95 years)
Interventions	Monotherapy with PHT or VPS Starting doses: PHT: 200 mg/d, VPS: 400 mg/d Median daily dose achieved: PHT 247 mg (range 175-275); VPS: 688 mg (range 400-1000) Range of follow-up: 0-22 months
Outcomes	Psychological tests (cognitive function, anxiety and depression) Adverse event frequency Seizure control
Notes	Trial paper reported on a subset of 38 participants. The full individual participant dataset provided by trial authors and used for this review included all 166 participants randomised in the trial. IPD provided for 3/4 outcomes of this review (treatment failure information not available).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised stratified minimisation programme, stratified for age group, gender and seizure type
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled allocation; prescription disclosed to general practitioner and consultant
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main investigator performing cognitive testing was blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis undertaken with all randomised participants from IPD (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcome measures reported in published report or provided in IPD (see footnote 2)
Other bias	Low risk	None identified

Czapinski 1997

Study characteristics

Methods	36-month randomised, comparative trial conducted in Poland

Czapinski 1997 *(Continued)*

	4 treatment arms: CBZ, PHB, PHT, VPS
Participants	Adults with newly diagnosed epilepsy Number randomised: CBZ = 30, PHT = 30, PHB = 30, VPS = 30 100% of participants had focal epilepsy Age range: 18-40 years Percentage male and range of follow-up not mentioned (outcome recorded at 3 years)
Interventions	Monotherapy with CBZ, PHT, PHB or VPS Starting doses CBZ = 400 mg/d, PHT = 200 mg/d, PHB = 100 mg/d, VPS: 600 mg/d Dose achieved not stated
Outcomes	Proportion achieving 24-month remission at 3 years and exclusions after randomisation due to adverse effects or no efficacy
Notes	Abstract only. Outcomes chosen for this review were not reported; contact made with trial authors but IPD not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Trial randomised but no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Exclusion rates" reported for all treatment groups; no further information provided
Selective reporting (reporting bias)	Unclear risk	No protocol available; trial available in abstract format only. Outcomes for this review not available
Other bias	Low risk	None identified

Dam 1989

Study characteristics	
Methods	Randomised, multicentre, double-blind trial conducted in 20 centres across four European countries

Dam 1989 *(Continued)*

	2 treatment arms: CBZ and OXC
Participants	Participants aged 15-65 years with newly diagnosed and previously untreated epilepsy Number randomised: total of 235 but 41 excluded for protocol violations (number randomised by treatment group not stated) Number analysed: CBZ = 100, OXC = 94 96 male participants (49%) out of those analysed Proportion with focal epilepsy not stated Median age (range): 33 (14-63)
Interventions	Monotherapy with CBZ or OXC Starting daily dose CBZ: 200 mg, OXC: 300 mg. Mean daily dose (range) achieved CBZ: 684 (300 mg-1400 mg), OXC: 1040 (300 mg-1800 mg) Titration period of 4-8 weeks followed by a maintenance period of 48 weeks Mean (range) duration of follow-up (maintenance period): 336 (10-390) days
Outcomes	Changes in seizure frequency between baseline and the end of each maintenance period Changes in EEG tracings between baseline and the end of each maintenance period Global evaluation of therapeutic efficacy and tolerability by the investigator at the end of each maintenance period Side effects observed by participants and investigators each visit Laboratory tests (white blood cell counts and liver function tests, blood pressure and pulse, drug trough serum levels)
Notes	Trial authors could not be contacted to request IPD. Outcomes chosen for this review were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial was of double-blind design.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate reported, up to 30% of randomised participants who did not complete the trial were excluded from analyses; this was not an ITT approach.

Dam 1989 *(Continued)*

Selective reporting (reporting bias)	Low risk	Efficacy, and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

De Silva 1996

Study characteristics	
Methods	Randomised, parallel-group, open-label paediatric trial conducted in 2 centres in the UK 4 treatment arms: CBZ, PHB, PHT, VPS
Participants	Children with newly diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the trial) Number randomised: CBZ = 54, PHB = 10, PHT = 54, VPS = 49 86 boys (50%) 89 children with focal epilepsy (51%) Mean age (range): 10 (3-16) years
Interventions	Monotherapy with CBZ, PHT, PHB or VPS Median daily dose achieved: CBZ = 400 mg/d, PHT = 175 mg/d, PHB = not stated (see notes), VPS= 600 mg/d Range of follow-up (months): 10-164
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse effects and withdrawals due to adverse events
Notes	IPD provided for all randomised participants. All outcomes in this review calculated from IPD. 6 of the first 10 children assigned to PHB had unacceptable adverse effects, so no further children were assigned to PHB. The 10 children randomised to PHB were retained in analysis. IPD provided for all outcomes of this review by the Medical Research Council

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed via 4 batches of concealed, opaque envelopes
Blinding of participants and personnel (performance bias)	High risk	Unblinded; authors stated masking of treatment would not be “practicable or ethical” and would “undermine compliance.” Lack of masking could have led

De Silva 1996 *(Continued)*

All outcomes		to early withdrawal of the PHB arm from the trial, which was likely to have influenced the overall results.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded; authors stated masking of treatment would not be "practicable or ethical" and would "undermine compliance." Lack of masking could have led to early withdrawal of the PHB arm from the trial, which was likely to have influenced the overall results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Dizdarer 2000

Study characteristics	
Methods	Prospective quasi-randomised, open-label trial conducted at a single hospital in Turkey 2 treatment arms: CBZ and OXC
Participants	Children with focal epilepsy (not stated how many were newly diagnosed) Number randomised: CBZ = 26, OXC = 26 21 boys (40%) 100% of participants had focal epilepsy. Mean age (range): 11 (4-15 years)
Interventions	Monotherapy with CBZ or OXC CBZ prescribed at 20-25 mg/kg/d and OXC at 30-50 mg/kg/d Range of follow-up: 3.5 to 26 months
Outcomes	Seizure recurrence Most common side effects Number of participants switching treatment
Notes	IPD provided for all outcomes of this review by trial author. Trial publication available as abstract only; additional data provided by trial authors

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quasi-randomisation by alternately allocating participants to CBZ or OXC (information provided by trial authors)

Dizdarer 2000 *(Continued)*

Allocation concealment (selection bias)	High risk	Allocation was not concealed (alternate allocation).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open- label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open- label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Donati 2007

Study characteristics	
Methods	Multicentre, randomised, open-label trial conducted at 21 sites in seven European countries between December 2001 and December 2003 3 treatment arms: CBZ, OXC, VPS (randomised in a 1:2:1 ratio)
Participants	Children and adolescents (aged 6-17) with newly diagnosed focal seizures. Participants must have had at least 2 unprovoked focal seizures (simple and complex focal and focal evolving into secondarily generalised seizures) in the 3 months prior to study entry. Number randomised: CBZ = 28, OXC = 55, VPS = 29 51 male participants (46%) 100% of participants had focal epilepsy Median age (range): 10 (6-16)
Interventions	Monotherapy with CBZ, OXC or VPS Dose achieved (mean (SD)): CBZ =14.4 (3.6) mg/kg/d, VPS = 20.7 (7.5) mg/kg/d Study duration: 6 months, Range of follow-up not stated
Outcomes	Cognitive testing: Computerized Visual Searching Task, assessing mental information processing speed and attention. Rey Auditory Verbal Learning Test and Raven's Standard Progressive matrices for children: psychomotor speed, alertness, memory and learning, and nonverbal intelligence Percentage of participants remaining seizure-free throughout treatment Most common adverse events Treatment satisfaction on a 4-point scale from poor to very good

Donati 2007 *(Continued)*

Notes	IPD requested from trial sponsor Novartis but data could not be provided due to time elapsed since the trial was completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An interactive voice-response system was used to automate the randomisation of participants to treatment groups within age strata.
Allocation concealment (selection bias)	Low risk	An interactive voice-response system was used to automate the randomisation of participants to treatment groups within age strata.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study (justified as primary and secondary cognitive outcomes were objective)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study (justified as primary and secondary cognitive outcomes were objective)
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate reported. Most results reported only for the per-protocol population who completed the study
Selective reporting (reporting bias)	Low risk	All cognitive, efficacy, and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None detected

Eun 2012

Study characteristics

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in 7 hospitals in Republic of Korea 2 treatment arms: LTG and CBZ
Participants	Children aged 6-12 years with a new diagnosis of focal epilepsy and at least 2 seizures in the last 6 months Number randomised: LTG = 43, CBZ = 41 48 male participants (57%) 100% of participants had focal epilepsy. Not stated if any participants had received previous AED treatment Mean age (range): 9 (5-13) years
Interventions	Monotherapy with LTG or CBZ 8-week escalation phase leading to LTG = 3-6 mg/kg/d, CBZ = 10-20 mg/kg/d

Eun 2012 *(Continued)*

	Range of follow-up: 0.5-28 months
Outcomes	Seizure-free rate over 6 months (maintenance period) by treatment group Change in cognition (neuropsychological), behaviour and quality of life from screening to the end of the maintenance phase by treatment group Incidence of adverse events
Notes	IPD provided by trial author for time to treatment failure, time to first seizure and time to 6-month remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre received a separate and independent computer-generated random code list.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Feksi 1991

Study characteristics

Methods	Randomised, parallel-group trial conducted among residents of the Nakuru district, a semi-urban population of rural Kenya 2 treatment arms: CBZ and PHB
Participants	Participants had a history of generalised tonic-clonic seizures and at least 2 generalised tonic-clonic seizures within the preceding year (with or without other seizure types) and untreated in the 3 months prior to the trial. 79 (26%) participants had been treated in the past with AEDs. Number randomised: PHB = 150, CBZ = 152 173 male participants (57%) 115 of participants with focal epilepsy (38%)

Feksi 1991 *(Continued)*

	Mean age (range): 21 (6-65 years)
Interventions	Monotherapy with CBZ or PHB Starting doses: PHB: 6-10 years: 30 mg/d, 11-15 years: 45 mg/d, > 16 years: 60 mg/d CBZ: 6-10 years of age: 400 mg/d, 11-15 years of age: 500 mg/d, > 16 years of age: 600 mg/d Dose achieved not stated Range of follow-up: participants followed up for up to 1 year
Outcomes	Adverse effects Withdrawals from allocated treatment Seizure frequency (during second 6 months of trial)
Notes	IPD were made available but not used because of inconsistencies and problems with the data provided (see Included studies for further details).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised with random number list
Allocation concealment (selection bias)	Low risk	Allocation concealed via sealed, opaque envelopes (information provided by trial author)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates reported; results presented only for participants completing 12 months' follow-up (results not presented for 53 (17.5%) participants out of 302 who withdrew from treatment); approach was not ITT.
Selective reporting (reporting bias)	Low risk	No protocol available; outcomes chosen for this review not reported. Seizure outcomes and adverse events well reported
Other bias	High risk	Inconsistencies with IPD and published results so IPD could not be used (see Included studies for further details)

Forsythe 1991

Study characteristics

Methods	Single-centre, randomised, parallel-group trial conducted in the UK 3 treatment arms: CBZ, PHT, VPS

Forsythe 1991 *(Continued)*

Participants	Children with at least 3 newly diagnosed generalised or focal seizures within a period of 6 months Number randomised: CBZ = 23, PHT = 20, VPS = 21 No information on epilepsy type or sex Age range: 5-14 years
Interventions	Monotherapy with CBZ, PHT or VPS Mean dose: CBZ = 17.9 mg/d, PHT = 6.1 mg/d, VPS: 25.3 mg/d Trial duration: 12 months, range of follow-up not stated
Outcomes	Cognitive assessments Summary of withdrawals from randomised drug
Notes	Outcomes chosen for this review were not reported. IPD not available, but could be constructed from the publication of the outcome 'time to withdrawal of allocated drug'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quota allocation by sex, age, seizure type and current treatment was an inadequate randomisation method.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel and participants (and parents) unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors single-blinded for cognitive testing
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; results reported and analysed for all participants randomised and all who completed various stages of follow-up
Selective reporting (reporting bias)	Unclear risk	One of four outcomes for this review reported. Cognitive outcomes described in methods section well reported in results section. Adverse effects reported, no seizure outcomes reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	Low risk	None identified

Fritz 2006

Study characteristics

Fritz 2006 *(Continued)*

Methods	Prospective, open-label, randomised trial conducted in Germany 2 treatment arms: LTG and OXC
Participants	Participants with untreated epilepsy, number newly diagnosed not stated Number randomised: LTG = 21, OXC = 27 26 male participants (54%) Proportion of participants with focal epilepsy not stated Age range: 15-61
Interventions	Monotherapy with LTG or OXC Doses started or achieved not stated Range of follow-up and trial duration not stated
Outcomes	Seizure reduction Cognition, mood and health-related quality of life
Notes	Abstract only. Trial authors could not be contacted to request IPD Results referred to reduction of seizures to only "simple seizures" remaining so we assumed that this population of participants had the eligible seizure type for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatments were "randomly assigned"; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only; attrition rate not stated. Insufficient information to make a judgement
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to make a judgement
Other bias	Low risk	None identified

Gilad 2007

Study characteristics	
Methods	Randomised, single-centre, open-label, parallel-group trial conducted at Tel Aviv University and Medical Centre, Israel 2 treatment arms: LTG and CBZ
Participants	Adults admitted to the neurological department with a first seizure event after an ischaemic stroke Number randomised: LTG = 32, CBZ = 32 46 male participants (72%) 100% of participants had focal epilepsy. Unclear if any participants had received previous AED treatment Mean age (range): 67.5 (38-90) years
Interventions	Monotherapy with LTG or CBZ for 12 months Dose escalation phase (length not stated) leading to LTG 100 mg/d, CBZ 300 mg/d Range of follow-up: not stated
Outcomes	The appearance of a second seizure under treatment or by finishing the 12-month follow-up without seizures Tolerability: incidence of adverse events Withdrawals due to adverse events
Notes	Contact made with trial author who was willing to provide IPD but data never received. Aggregate data extracted from graphs in the publication. Stated in the title of the paper that LTG and CBZ were monotherapy treatments but Table 1 of the paper referred to 'Total no. AED'; unclear if all participants were receiving monotherapy treatment

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised in a 1:1 ratio; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate reported; all randomised participants included in analysis

Gilad 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	No protocol available. Seizure outcomes and adverse events well reported
Other bias	Unclear risk	Unclear if all participants were receiving monotherapy treatment

Giri 2016

Study characteristics	
Methods	Randomised comparative study conducted at Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh (India), during the period from April 2014 to March 2015 2 treatment arms: LTG and VPS
Participants	Adult participants (over the age of 18 years) with newly diagnosed idiopathic generalised tonic-clonic seizures with at least two generalised tonic-clonic seizures and no treatment with antiepileptic drugs in the previous year Number randomised: LTG = 30, VPS = 30 37 male participants (62%) 0% of participants had focal epilepsy (all generalised epilepsy) Ages: 18 to 20 (n = 13), 21 to 30 (n = 14), 31 to 40 (n = 15), 41 to 50 (n = 11), 51 to 60 (n = 5), 61 to 70 (n = 2)
Interventions	Monotherapy with LTG or VPS Titration over 4 weeks: LTG started at 0.5 mg/kg/d and titrated to a maximum dose of 12 mg/kg/d; VPS started at 10 mg/kg/d in divided doses and titrated to a maximum dose of 30 mg/kg/d Study duration: 12 months
Outcomes	Seizure control (seizure-free, at least 50% reduction in seizure frequency) at 3 months, 6 months and 12 months Number of seizures per month (at 12 months) Adverse events
Notes	Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was conducted using random number tables.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Giri 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients who withdrew from the LTG group before the 3-month assessment due to adverse events; however, these participants were included within an ITT analysis.
Selective reporting (reporting bias)	Low risk	All seizure and adverse event outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Guerreiro 1997

Study characteristics	
Methods	Multicentre, double-blind, parallel-group trial conducted in centres in Argentina and Brazil 2 treatment arms: OXC and PHT
Participants	Participants aged > 5 years with newly diagnosed epilepsy with focal seizures or generalised tonic-clonic seizures A minimum of 2 seizures, separated by at least 48 hours, within 6 months preceding trial entry No previous AED, except emergency treatment of seizures for a maximum of 3 weeks prior to trial entry Number randomised: OXC = 997, PHT = 94 100 male participants (52%); 143 of participants had focal epilepsy (74%). Mean age (range): 18.5 (5-53) years
Interventions	Monotherapy with OXC or PHT 8-week titration period started with 150 mg OXC or 50 mg PHT, increased bi-weekly, based on clinical response to a regimen with daily doses of 450 mg-2400 mg OXC or 150 mg-800 mg PHT Continued during 48-week maintenance with adjustment according to clinical response A third long-term, open-label extension phase followed the maintenance period. Double-blind results only were reported. Range of follow-up: 1-28 months
Outcomes	The proportion of seizure-free participants who had at least 1 seizure during the maintenance period Time to premature discontinuation due to adverse experiences Rate of premature discontinuations for any reason Overall assessments of efficacy and tolerability and therapeutic effect Individual adverse experiences Laboratory values

Guerreiro 1997 *(Continued)*

	Seizure frequency during maintenance
Notes	IPD provided for all outcomes of this review by trial sponsor Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment groups randomised in 1:1 ratio across centres via computer-generated randomisation numbers over balanced blocks of size 6
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved with sequentially-numbered packages which were identical and contained identical tablets (information provided by trial statistician).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial conducted in 2 phases: 56-week, double-blind phase followed by long-term, open-label extension. Double-blind phase results reported only. Blind achieved with divisible OXC and PHT tablets identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported in both treatment phases; participants withdrawing from treatment were no longer followed up so seizure outcomes had to be censored at time of withdrawal and therefore analyses for remission and seizure outcomes could not adopt an ITT approach.
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Heller 1995

Study characteristics	
Methods	Randomised, parallel-group, open-label trial conducted in 2 centres in the UK 4 treatment arms: CBZ, PHB, PHT, VPS
Participants	Adults with newly diagnosed epilepsy (2 or more untreated focal or generalised tonic-clonic seizures in the 12 months preceding the trial) Number randomised: CBZ = 61, PHB = 58, PHT = 63, VPS = 61 117 male participants (48%) 102 participants with focal epilepsy (42%) Mean age (range): 32 (13-77) years
Interventions	Monotherapy with CBZ, PHB, PHT or VPS Median daily dose achieved: CBZ = 600 mg/d, PHB = 105 mg/d, PHT = 300 mg/d, VPS = 800 mg/d

Heller 1995 *(Continued)*

	Range of follow-up: 0-166 months
Outcomes	Time to first seizure recurrence after start of therapy Time to 12-month remission from all seizures Adverse effects and withdrawals due to adverse events
Notes	IPD provided for all outcomes of this review by the Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed via 4 batches of concealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded; authors stated masking of treatment would not be “practical” and would have “introduced bias due to a very large dropout rate”. Lack of blinding may have influenced the withdrawal rate.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded; authors stated masking of treatment would not be “practical” and would have “introduced bias due to a very large dropout rate”. Lack of blinding may have influenced the withdrawal rate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Jung 2015

Study characteristics

Methods	Multicentre, randomised, open-label, non-inferiority trial conducted across 7 centres in Republic of Korea 2 treatment arms: CBZ and LEV
Participants	Children aged 4-16 years with newly diagnosed focal epilepsy, no previous anti-epileptic therapy and "above borderline" intelligence Number randomised: CBZ = 64, LEV = 57 (ITT population) 69 male participants (57%) 100% of participants with focal epilepsy Mean age (SD): CBZ = 8.05 (3.02), LEV = 9.28 (3.37) years

Jung 2015 *(Continued)*

Interventions	Monotherapy with CBZ or LEV 4-week dose titration period to a minimal target dose of CBZ = 20/mg/kg/d or LEV = 40/mg/kg/d Trial duration: 52 weeks; range of follow-up not stated
Outcomes	Neuropsychological outcomes; change from baseline to 52 weeks in neurocognitive (Korean-WISC-III or Korean-Wechsler Preschool and Primary Scale of Intelligence-III), behavioural (Korean-CBCL), and emotional (Children's Depression Inventory and Revised Children's Manifest Anxiety Scale) function assessments Mean percentage change in seizure frequency from baseline Seizure-freedom rates Incidence of adverse events
Notes	IPD could not be provided for the trial due to restrictions on data sharing from the Korean Food and Drug Administration (information provided by corresponding author). Outcomes chosen for this review were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised independently at each centre using a computerised random code assignment based on stratified permuted block randomisation that was designed separately and independently for each participating centre.
Allocation concealment (selection bias)	Low risk	At each centre, allocation concealment was carried out by the pharmacy in order to blind those assessing outcomes from the trial medication.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Those assessing outcomes were blinded to trial medication (pharmacy allocation)
Incomplete outcome data (attrition bias) All outcomes	High risk	7 randomised participants did not take any trial medication so were not included in ITT population. Results for neuropsychological outcomes recorded only for those who completed the trial - 81/121 participants (67%)
Selective reporting (reporting bias)	Low risk	All neuropsychological, efficacy, and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Kalviainen 2002

Study characteristics

Methods	Open-label, multicentre, randomised trial. Authors based in Denmark and Finland

Kalviainen 2002 *(Continued)*

	2 treatment arms: CBZ (slow release) and LTG
Participants	Participants with newly onset focal and/or generalised tonic-clonic seizures Number randomised: CBZ = 70, LTG = 73 No information provided about age and gender or previous AED use
Interventions	Monotherapy with CBZ or LTG for 52 weeks Mean dosage during maintenance period: CBZ = 549 mg/d, LTG = 146 mg/d Range of follow-up not stated
Outcomes	Seizure freedom Cognitive assessments
Notes	IPD requested from trial sponsor Glaxo Smith Kline but data could not be located. Abstract publication only available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatments were "randomly assigned"; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only; attrition rate not stated. Insufficient information to make a judgement
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to make a judgement
Other bias	Low risk	None identified

Kim 2017

Study characteristics	
Methods	Phase 4, randomised, parallel-design, open-label trial in Republic of Korea 2 treatment arms: LEV and OXC

Kim 2017 *(Continued)*

Participants	Participants aged 16-80 years with newly diagnosed focal epilepsy. At least two unprovoked focal seizures separated by 48 hours in the year preceding randomisation, and at least one unprovoked focal seizure in the six months preceding randomisation Partcipants must have had at least 2 seizures separated by a minimum of 48 hours and 1 in the 6 months prior to screening and no AEDs in the previous 6 months. Number enrolled: LEV = 175, OXC = 178 190 male participants (54%) 100% of participants had focal epilepsy. Mean age (SD): LEV = 39.5 (16.7), OXC = 42.7 (17.3)
Interventions	Monotherapy with LEV or OXC Titration for 2 weeks up to a maximum of LEV = 1000 mg/d-3000 mg/d, OXC = 900 mg/d-24,000 mg/d Trial duration: 50 weeks; range of follow-up not stated
Outcomes	Percentage of participants with a treatment failure after 50 weeks Time to treatment failure Time to the first seizure defined as the time from the first dose of medication to the occurrence of the first seizure during the 48 weeks' treatment period Percentage of subjects who achieved seizure freedom for 24 consecutive weeks during the 48 weeks' treatment period at any time Percentage of subjects who achieved seizure freedom during the 48 weeks' treatment period Treatment-emergent adverse events
Notes	Trial sponsored by UCB Korea, request for IPD made via Vivli and approved by the sponsor. No data received at the time of update If IPD is provided at a future date, this trial will be included in analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias)	High risk	Attrition rate reported; not all participants included in analysis which is not an ITT approach

Kim 2017 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Time to first seizure listed as an outcome on the ClinicalTrial.gov entry (NCT01498822) but not reported in the manuscript and time to treatment failure was reported in the manuscript but not listed as an outcome on the ClinicalTrial.gov entry.
Other bias	Low risk	None identified

Kopp 2007

Study characteristics	
Methods	Randomised trial of outpatients of a hospital in Berlin, Germany 3 treatment arms: CBZ, LEV, VPS
Participants	Newly diagnosed ("de novo") participants Number randomised: CBZ = 6, LEV = 6, VPS = 3 12 (80%) focal epilepsy No information on age or gender
Interventions	Monotherapy with CBZ, LEV or VPS Doses started or achieved not stated Assessments performed at 6 and 12 weeks
Outcomes	Cognitive performance Neuropsychological assessment
Notes	Abstract only. Trial authors could not be contacted to request IPD.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Treatments were "randomly assigned"; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Unclear risk	Abstract only; attrition rate not stated. Insufficient information to make a judgement

Kopp 2007 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to make a judgement
Other bias	Low risk	None identified

Korean Lamotrigine Study Group 2008

Study characteristics	
Methods	Phase IV, open-label, randomised, multicentre trial conducted in 21 centres in Republic of Korea 2 treatment arms: CBZ and LTG
Participants	Participants were untreated epileptics who had at least 2 unprovoked seizures (focal or generalised tonic-clonic) during the last 24 weeks before the study start, more than 24 hours apart Number randomised: CBZ = 129, LTG = 264 (ITT population) 154 male participants (39%) 288 participants (73%) with focal epilepsy Mean age (SD): CBZ = 37.6 (15.8), LTG = 34.2 (16.3) years
Interventions	Monotherapy with CBZ or LTG Permitted doses LTG: 100 mg/d–500 mg/d for LTG, CBZ: 400 mg/d–1200mg/d
Outcomes	Retention rate at study end Terminal 24-week seizure-free rate and time interval from the end of dose titration phase to the first seizure
Notes	Full text of the trial published in Korean. Abstract and clinical trial summary available in English. IPD requested from trial sponsor Glaxo Smith Kline but data could not be located

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial

Korean Lamotrigine Study Group 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate reported; not all participants included in analysis, which is not an ITT approach
Selective reporting (reporting bias)	Low risk	Results for all outcomes summarised for all listed outcomes
Other bias	Low risk	None identified

Korean Zonisamide Study 1999

Study characteristics	
Methods	Multicentre randomised trial conducted at eight medical centres in South Korea 2 treatment arms: CBZ and ZNS
Participants	Participants aged 12-65 years with newly diagnosed epilepsy or who had been diagnosed as being epileptic but no history of prior anti-epileptic medication At least 2 simple focal motor seizure, primary or secondary generalised tonic-clonic seizures in the previous 6 months Number randomised: CBZ = 88, ZNS = 83 Number included in 'intention to treat analysis' (those who completed the dose escalation phase): CBZ = 82; ZNS = 73 ITT population: 91 male participants (59%) ITT population: 52 with focal epilepsy (34%) ITT population: Mean age (SD): CBZ = 27.0 (10.9) years; ZNS = 27.7 (11.7) years
Interventions	Monotherapy with CBZ or ZNS Dose escalation over 4 weeks to a target dose of CBZ = 600 mg/d and ZNS = 300 mg/d Trial duration: up to 72 weeks
Outcomes	Seizure remission rate at 24 weeks Time interval to first seizure recurrence Incidence of adverse events
Notes	The trial was published in Korean; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD. Sixteen randomised patients (9% of total randomised patients) were excluded from this ITT population due to inclusion criteria violations or refused the drug.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised using a random number table (translated from Korean).

Korean Zonisamide Study 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as 'double blind' within the English translation of the abstract, but no information was provided regarding methods of blinding or who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as 'double blind' within the English translation of the abstract, but no information was provided regarding methods of blinding or who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	An 'intention to treat analysis' was described, but 16 randomised patients (9% of total randomised patients) were excluded from this ITT population due to inclusion criteria violations or refused the drug.
Selective reporting (reporting bias)	Low risk	All seizure and adverse event outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Kwan 2009

Study characteristics	
Methods	Randomised, open-label trial conducted in 2 hospitals in Hong Kong 2 treatment arms: LTG and VPS
Participants	Chinese patients, with newly diagnosed, untreated epilepsy or a recurrence of seizures after a period of remission with AED therapy completely withdrawn for at least a year, aged 18-55 years, and not receiving AED therapy, were recruited from the Prince of Wales Hospital and United Christian Hospital in Hong Kong. Number randomised: LTG = 37, VPS = 44 40 male participants (49%) 29 participants with focal epilepsy (36%) Mean age (range): 34 (16-56 years)
Interventions	Monotherapy with LTG or VPS Titration of 4 weeks to target dose of LTG = 100 mg/d and VPS = 800 mg/d Range of follow-up: 0-15 months
Outcomes	Difference in mean fasting serum insulin concentration at 12 months between the 2 treatment groups Difference in mean changes from baseline at various time points in metabolic and endocrine measurements and BMI between the 2 treatment groups and by gender Frequency of common adverse events experienced by at least 10% of participants by treatment group
Notes	IPD provided for all outcomes of this review by trial author

Kwan 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised and stratified for sex and hospital; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Lee 2011

Study characteristics	
Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the Korea 2 treatment arms: LTG and CBZ
Participants	Adults over the age of 16 with newly diagnosed focal epilepsy or untreated focal epilepsy for at least one year Number randomised: LTG = 57, CBZ = 53 57 male participants (52%) 95 participants with focal epilepsy (86%) Not stated how many participants had received previous AED treatment Mean age (range): 36 (16-60) years
Interventions	Monotherapy with LTG or CBZ 8-week escalation phase leading to LTG = 200 mg/d, CBZ = 600 mg/d Range of follow-up: 0-16.5 months
Outcomes	Change of neuropsychological and cognitive scores from baseline: general intellectual ability, learning and memory, attention and executive function (group-by-time interaction)

Lee 2011 *(Continued)*

	Frequency of psychological and health-related quality of life symptoms
	Proportion with seizure freedom during the maintenance period
Notes	IPD provided by trial author for time to treatment failure, time to first seizure and time to six-month remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (block size four) via a computer randomisation programme (information provided by trial author)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Lukic 2005

Study characteristics

Methods	Prospective, open-label randomised trial conducted in Serbia and Montenegro
	2 treatment arms: LTG and VPS
Participants	Participants with newly diagnosed, previously untreated epilepsy
	Number randomised: LTG = 35, VPS = 38
	51 (70%) with focal epilepsy
	Median age (range): 34 (18-76) years
	No information on gender
Interventions	Monotherapy with LTG or VPS
	All participants to be followed up for at least 6 months
Outcomes	Seizure freedom

Lukic 2005 *(Continued)*

	Retention on treatment
Notes	Abstract of interim results only available. Contact was made with trial author who was unable to provide IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Interim report; proportion of participants completing the trial period presented. Unclear if an ITT approach was taken to analysis
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to make a judgement
Other bias	Low risk	None identified

Maiti 2018

Study characteristics

Methods	Randomised, open-label, parallel group trial at a single epilepsy clinic in Bhubaneswar (India) conducted between April 2016 and March 2017 2 treatment arms: CBZ or OXC
Participants	Participants between the ages of 18 and 45 with focal seizures who were treatment-naïve or had not received treatment in the last 3 weeks. Participants must have had a seizure with 48 hours of recruitment to the study. Number randomised: CBZ = 30; OXC = 30 44 male participants (73%) 100% of participants with focal epilepsy Mean age (SD): CBZ = 29.3 (8.77) years; OXC = 26.4 (8.91) years
Interventions	Monotherapy with CBZ or OXC Titration over 4 weeks: CBZ started at 200 mg/d in divided doses and increased to 600mg/d; OXC started at 10 mg/kg/d in divided doses and increased to 20 mg/kg/d

Maiti 2018 *(Continued)*

	Trial duration: 4 weeks
Outcomes	Serum S100B levels Quality of Life (by the QOLIE-31) Chalfont-National Hospital seizure severity scale (NHS3) Adverse events
Notes	Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomised (allocation ratio 1:1) by simple randomisation to either carbamazepine of oxcarbazepine group using computer-generated random codes".
Allocation concealment (selection bias)	Low risk	"The random allocation codes of the participants were generated by an investigator who was not involved in the patient recruitment. The codes were assigned to a sequence of numbers which was given to another investigator who was responsible for patient recruitment. This process ensured allocation concealment".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine participants lost to follow-up but all randomised participants included in ITT analysis, with missing data imputed using multiple imputation.
Selective reporting (reporting bias)	Low risk	No protocol available and outcomes chosen for this review not reported. Biomarker, seizure severity and quality of life outcomes well reported and adverse events reported
Other bias	Low risk	None identified

Mattson 1985

Study characteristics

Methods	Multicentre, randomised, parallel-group, double-blinded trial over 10 centres in the USA with separate randomisation schemes used for each seizure type 4 treatment arms: CBZ, PHB, PHT and primidone
Participants	Adults with previously untreated or under-treated simple or complex focal or secondary generalised tonic-clonic seizures

Mattson 1985 *(Continued)*

	Number randomised: PHB: 155, PHT = 165, CBZ = 155 413 male participants (87%) 99.8% of participants with focal epilepsy Mean age (range): 41 (18-82) years
Interventions	Monotherapy with PHT or CBZ Median daily dose achieved: CBZ = 800 mg/d, PHB = 160 mg/d, PHT = 400 mg/d Range of follow-up: 0-78 months
Outcomes	Participant retention/time to drug failure (length of time participant continued to take randomised drug) Composite scores of seizure frequency (seizure rates and total seizure control) and toxicity Incidence of side effects
Notes	IPD provided for all outcomes of this review by the Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised with stratification for seizure type. Method of randomisation not stated and not provided by authors
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participants and personnel) achieved using an additional blank tablet
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Mattson 1992

Study characteristics

Methods	Double-blind, multicentre trial across 13 Veteran's Affairs medical centres (USA) 2 treatment arms: CBZ and VPS

Mattson 1992 *(Continued)*

Participants	Adults (18-70 years) with previously untreated or under-treated complex focal seizures, secondarily generalised tonic-clonic seizures Number randomised: CBZ = 236, VPS = 244 445 male participants (93%) 100% of participants had focal epilepsy. Mean age (range): 47 (18-83) years
Interventions	Monotherapy with CBZ or VPS Mean daily dose achieved by month 12 CBZ = 722 +/- 230 mg/d, VPS = 2099 +/- 824 mg/d Range of follow-up: 0-73 months
Outcomes	Total number of seizures (of each type) during 12 months Number of seizures per month Percentage of participants with seizures completely controlled Time to first seizure Seizure rating score (severity of seizures) at 12 and 24 months Composite score (combined score for the control of seizures and incidence of adverse events) Incidence of systemic and neurologic adverse events (and severity) Time to treatment failure
Notes	IPD provided for all outcomes of this review by the Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment using random permuted blocks with a different randomisation scheme for two seizure groups (complex focal and secondarily generalised tonic-clonic).
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed via sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participants and personnel) achieved with additional matching placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessment was blinded; no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)

Mattson 1992 *(Continued)*

Other bias	Low risk	None identified

Mitchell 1987

Study characteristics	
Methods	Randomised, double-blind, single-centre, parallel paediatric trial conducted in Los Angeles, USA 2 treatment arms: CBZ and PHB
Participants	Children with newly diagnosed epilepsy Number randomised: PHB = 18, CBZ = 15 20 boys (61%) 100% of participants had focal epilepsy. Mean age (range): PHB = 7.89 (2-12 years), CBZ = 6.07 (2-12 years)
Interventions	Monotherapy with PHB or CBZ Doses started and achieved not stated Trial duration: 12 months Range of follow-up: not reported
Outcomes	Change in cognitive, intelligence (IQ), behavioural, and psychometric scores between baseline, 6 months, and 12 months Compliance, drug changes, and withdrawal rates Seizure control at 6 and 12 months (excellent/good/fair/poor)
Notes	33 participants were randomised to PHB (18) and CBZ (15) in this trial; 6 children were enrolled into a 6-month pilot trial (PHB (4) CBZ (2)) prior to the randomised trial. The 6 children were included in 6-month follow-up psychometric data. Outcomes for this review were not reported; IPD were not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	33 children were "randomised using a scheme that balanced drug distribution by age and sex"; no further details were provided on the randomisation scheme. 6 non-randomised children were also used in some analyses.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial blinded participants (and parents); clinicians were unblinded for clinical follow-up.
Blinding of outcome assessment (detection bias)	High risk	The trial blinded participants (and parents); clinicians were unblinded for clinical follow-up.

Mitchell 1987 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were reported; results were reported for all children who completed each stage of follow-up.
Selective reporting (reporting bias)	Low risk	Cognitive/behavioural outcomes, seizure control outcomes, and adverse events were all well reported. No protocol was available; outcomes for this review were not reported.
Other bias	High risk	There was evidence that the trial may have been underpowered to detect differences (e.g. 55% power to find a 5-point difference in IQ score). The behavioural questionnaire was not fully validated. Non-randomised children from a pilot trial were included in the results for psychometric outcomes and medical outcomes.

Miura 1990

Study characteristics	
Methods	Prospective, randomised trial of participants newly referred to the paediatric clinic of Kitasato University School of Medicine, Japan 3 treatment arms: CBZ, PHT and VPS
Participants	Children aged 1-14 with previously untreated focal seizures and/or generalised tonic-clonic seizures Number randomised: CBZ = 66, PHT = 51, VPS = 46 116 participants with focal epilepsy (71%) No information on age and gender
Interventions	Monotherapy with PHT or CBZ Initial daily dose: CBZ = 13.0 +/- 1.6 mg/kg/d, PHT = 7.2 +/- 1.4 mg/kg/d, VPS = 22.9 +/- 4.9 mg/kg/d Range of follow-up: 6-66 months, mean follow-up: 34 months in CBZ group, 37 in PHT group and 40 in VPS group
Outcomes	Proportion of all randomised participants with seizure recurrence (by seizure type) Proportion of participants with optimum plasma levels with seizure recurrence (by seizure type)
Notes	Very limited information available, the trial was reported in a summary publication of 3 different studies (other 2 studies were not monotherapy designs). Outcomes chosen for this review were not reported; IPD not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Trial was described as "randomised" but no further details were provided.
Allocation concealment (selection bias)	Unclear risk	No information provided

Miura 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ranges of follow-up given for both treatment groups. Results reported "at the end of follow-up"; no withdrawals or exclusions mentioned, all participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Seizure recurrence outcomes described and well reported. No adverse events reported; no protocol available so unclear if adverse events were planned a priori. Outcomes for this review not available
Other bias	Low risk	None identified

Motamedi 2013

Study characteristics	
Methods	Double-blind randomised trial performed in a single centre in Tehran, Iran 2 treatment arms: LEV and LTG
Participants	Participants > 60 years who were referred to the neurologic clinic at Sina University Hospital, Iran in 2012 Participants must have had a diagnosis of epilepsy for at least 1 year and experienced a minimum of 1 unprovoked focal or generalised epileptic seizure over the last 6 months. Number randomised: LEV = 50, LTG = 50 55 male participants (58%) out of 95 participants who completed the trial 67 participants with focal epilepsy (71%) out of 95 participants who completed the trial Mean age (SD, range): 72.4 (5.87, 63-85) years for all randomised participants
Interventions	Monotherapy with LEV or LTG LEV was initiated with 250 mg twice daily and was increased to 500 mg twice daily, LTG was initiated with 25 mg daily and was increased up to a maximum dose of 100 mg twice daily Trial duration: 20 weeks, range of follow-up not stated
Outcomes	Seizure recurrence Abnormal laboratory values Adverse events
Notes	The trial was published in Persian; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Motamedi 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer-based table was generated by balanced block randomisation.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participant received a drug with a specific code and did not know the name of the drug. The physician in charge of the participant follow-up was unaware of the drug provided for the participant.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Only those who completed the trial were included in analyses; five participants excluded
Selective reporting (reporting bias)	Low risk	Seizure recurrence outcomes and adverse events were all well reported. No protocol was available; outcomes for this review were not reported.
Other bias	Low risk	None identified

NCT01954121

Study characteristics	
Methods	Phase 3, randomised, open-label, parallel-group trial conducted in China 2 treatment arms: CBZ and LEV
Participants	Chinese participants > 16 years, recent onset focal seizures, at least 2 unprovoked seizures in the year preceding randomisation, of which at least 1 unprovoked seizure occurred in the 3 months preceding randomisation Number enrolled: CBZ = 215, LEV = 218 233 male participants (54%) 100% of participants had focal epilepsy. Mean age (SD): CBZ = 33.3 (14.3), LEV = 37.8 (16.2)
Interventions	Monotherapy with CBZ or LEV Titration of 3 weeks to CBZ = 400 mg/d, LEV = 1000 mg/d Range of follow-up: not stated
Outcomes	Proportion of subjects remaining seizure-free during the 6-month evaluation period Proportion of subjects retained in the trial for the duration of the period covering the up-titration period, stabilisation period, and evaluation period Time to first seizure or discontinuation due to an adverse event (AE)/lack of efficacy (LOE) during the evaluation period Time to first seizure during the evaluation period

NCT01954121 *(Continued)*

	Time to first seizure during the period covering the up-titration period, stabilisation period, and evaluation period from the first dose of trial drug
Notes	Trial sponsored by UCB SA, request for IPD made via Vivli. Initially approved by the sponsor but due to a change in data sharing laws in China in late 2020, IPD could not be provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate reported; not all participants included in analysis which is not an ITT approach
Selective reporting (reporting bias)	High risk	Results reported online for only some of the outcomes; no statistical analysis reported for the time to first seizure outcomes
Other bias	Low risk	None identified

Nieto-Barrera 2001

Study characteristics	
Methods	Randomised, multicentre, open-label, parallel-group trial conducted in Europe and Mexico 2 treatment arms: LTG and CBZ randomised in a 2:1 ratio
Participants	Adults and children over the age of 2 years with newly diagnosed or currently untreated focal epilepsy with ≥ two seizures in the previous 6 months and with at least 1 seizure in the last 3 months Number randomised: LTG = 420, CBZ = 202 329 male participants (53%) 619 participants with focal epilepsy (99.5%) Not stated how many participants had received previous AED treatment Mean age (range): 27 (2-84) years
Interventions	Monotherapy with LTG or CBZ

Nieto-Barrera 2001 *(Continued)*

	6-week escalation phase leading to minimum of LTG: 2 mg/kg/d age range 2-12 years, 200 mg/d age range 13-64 years and 100 mg/d age > 65 years. CBZ: aged 2-12 years 5 mg/kg-40 mg/kg, age > 12 years 100 mg/d-1500 mg/d Range of follow-up: 0-245 days
Outcomes	Proportion of participants seizure-free during the last 16 weeks of treatment Efficacy success: proportion of participants who did not withdraw before the end of week 18 and were seizure-free in the last 16 weeks of the trial Time to withdrawal from the trial (proportion of participants completing the trial) Proportion of participants experiencing adverse events Withdrawals due to adverse events
Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment withdrawal and time to first seizure (plus seizure-freedom rates at 24 weeks) Dates of seizures during the first 4 weeks not provided with IPD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence. Participants randomised in a 2:1 ratio (LTG:CBZ), stratified by age group and country
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Protocol provided. Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Ogunrin 2005

Study characteristics

Methods	Double-blinded, parallel-group, randomised trial conducted in a single centre in Nigeria 3 treatment arms: CBZ, PHB, PHT

Ogunrin 2005 *(Continued)*

Participants	Consecutive newly diagnosed participants aged ≥ 14 years presenting at the outpatient neurology clinic of the University Teaching Hopsital, Benin City, Nigeria with recurrent, untreated afebrile seizures Number randomised: PHT = 18, PHB = 18, CBZ = 19 34 male participants (62%) 10 participants with focal epilepsy (18%) Mean age (range): 27.5 years (14-55 years)
Interventions	Monotherapy with PHT or CBZ Median daily dose (range): CBZ = 600 mg (400 mg-1200 mg), PHT = 200 mg (100 mg-300 mg), PHB = 120 mg (60 mg-180 mg) All participants followed up for 12 weeks
Outcomes	Cognitive measures (reaction times, mental speed, memory, attention)
Notes	IPD provided for all randomised participants by the trial author. Trial duration was 12 weeks; all participants completed the trial without withdrawing, therefore outcomes, time to treatment failure, time to six-month remission and time to 12-month remission could not be calculated. Time to first seizure calculated from IPD provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial randomised using simple randomisation. Each participant was asked to pick one from a table of numbers (1-60); numbers corresponded to allocation of 1 of 3 drugs (information provided by trial author).
Allocation concealment (selection bias)	Low risk	Recruitment/randomisation of participants and allocation of treatments took place on different sites (information provided by trial author).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants single-blinded. Research assistant recruiting participants and counselling on medication adherence was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators performing cognitive assessments were single-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants completed the trial. All randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. One outcome for this review calculated from IPD provided (see footnote 2). Other outcomes for this review not available due to short trial length. All cognitive outcomes from the trial well reported
Other bias	Low risk	None identified

Pal 1998

Study characteristics	
Methods	Randomised, parallel-group trial conducted in a rural district of West Bengal, India 2 treatment arms: PHB and PHT
Participants	Children from a rural district of a developing country (India) who had experienced 2 or more unprovoked seizures within the 12 months preceding the trial and had been untreated in the 3 months preceding the trial Number randomised: PHB = 47; PHT = 47 47 boys (50%) 60 children had focal epilepsy (64%) Mean age (range): 11 (2-18) years
Interventions	Monotherapy with PHB or PHT Maintenance doses: PHT = 5 mg/kg/d, PHB = 3 mg/kg/d. Daily dose achieved not stated Range of follow-up: 0.5-13 months
Outcomes	Time to first seizure Proportion seizure-free in each trial quarter Proportion of adverse events including behavioural side effects
Notes	IPD provided for remission and seizure outcomes of this review by the trial author. Treatment failure information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	First 10 participants randomised from a pre-prepared balanced random number list; following participants randomised by minimisation with stratification by age group and presence of cerebral impairment
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, parents and treating physicians unblinded for “practical and ethical reasons”. Withdrawal information from treatments not available, however lack of blinding may have influenced withdrawal rates.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors single-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)

Pal 1998 *(Continued)*

Other bias	Low risk	None identified

Placencia 1993

Study characteristics	
Methods	Randomised, parallel-group trial conducted in the context of existing community health care in a rural highland area of a developing country (Ecuador) 2 treatment arms: CBZ and PHB
Participants	Participants with a history of at least 2 afebrile seizures and no previous AED treatment in the 4 weeks preceding the trial were eligible. Number randomised: PHB = 97, CBZ = 95 67 male participants (35%) 133 participants with focal epilepsy (69%) Mean age (range): 29 (2-68) years
Interventions	Monotherapy with PHB or CBZ Minimum maintenance doses by age groups: 2-5 years: PHB: 15 mg/d, CBZ: 150 mg/d; 6-0 years: PHB: 30 mg/d, CBZ: 300 mg/d; 11-15 years: PHB: 45 mg/d, CBZ: 500 mg/d; > 16 years: PHB: 60 mg/d, CBZ: 600 mg/d. Doses gradually increased Doses achieved not stated
Outcomes	Proportion seizure-free at 3-, 6-, and 12-month follow-up Proportion seizure-free, with more than 50% seizure reduction and no change in seizure frequency in 6- to 12-month follow-up period Incidence of adverse effects Trial duration: 12 months Range of follow-up: 3.5-23 months
Notes	We received IPD for all outcomes used in this review from the trial author. Results in the published paper were given for 139 participants who completed 6 months' follow-up, but we received IPD for all 192 participants randomised.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised with random number list; no information provided on method of generating random list
Allocation concealment (selection bias)	High risk	Allocation concealed using sealed, opaque envelopes but method not used for all participants (information provided by trial author)
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided

Placencia 1993 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2).
Selective reporting (reporting bias)	Low risk	All outcomes were reported or calculated with the IPD provided (see footnote 2).
Other bias	High risk	Inconsistencies between number and reasons of treatment failures between the data and the published paper, which could not be resolved by the author

Privitera 2003

Study characteristics	
Methods	Multinational, randomised, double-blind trial was conducted at 115 centres across the USA, Canada, Europe and South America. Four treatments: CBZ, VPS and TPM (2 arms, 100 mg/d and 200 mg/d) - see Notes
Participants	Participants > 6 years and > 30 kg in weight, with a diagnosis of epilepsy within the 3 months before trial entry and no previous AED treatment except emergency treatment Number randomised (ITT population): CBZ = 126, TPM = 266 (CBZ branch), VPS = 78, TPM = 147 (VPS branch) 327 male participants (53%) 363 participants with focal epilepsy (59%) Mean age (range): 34 (6-84 years)
Interventions	Monotherapy with CBZ, VPS or TPM Starting doses: CBZ = 200 mg/d, VPS = 250 mg/d, TPM = 25 mg/d Target doses (after 4-week titration): CBZ = 600 mg/d, VPS = 1000 mg/d, TPM = 100 or 200 mg/d (see Notes) Range of follow-up: 0-29 months
Outcomes	Time to exit Time to first seizure Proportion of seizure-free participants during the last 6 months of double-blind treatment Safety assessment: most commonly occurring adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor, Johnson & Johnson. Trial designed in 2 strata based on whether recommended treatment would be CBZ or VPS. Within the 2 strata, participants were randomised to 10 mg/d TPM, 200 mg/d TPM or CBZ/VPS depending on the strata. Data analysed according to the separate strata in this review with the 2 TPM doses analysed together (see Data extraction and management)

Privitera 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was balanced using permuted blocks of size three and stratified by trial centre, according to a computer-generated randomisation schedule prepared by the trial sponsor.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial was double-blinded for the first 6 months, followed by an open-label phase.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants from the ITT population analysed from IPD provided (see footnote 2). Eight participants with no follow-up data were excluded from ITT population.
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Pulliainen 1994

Study characteristics	
Methods	Single-centre, randomised, parallel-group trial of participants, referrals to the outpatient department of neurology of the Central Hospital of Paijat-Hame, Finland 2 treatment arms: CBZ and PHT
Participants	Adults (eligible age range 15-57) with newly diagnosed epilepsy Number randomised: PHT = 20, CBZ = 23 20 male participants (47%) 10 participants with focal epilepsy (23%) Mean age (SD) years: PHT = 31.5 (11.3), CBZ = 26.8 (13.2)
Interventions	Monotherapy with PHT or CBZ Dose information not reported Trial duration: 6 months, range of follow-up not stated
Outcomes	Cognitive assessments (visual motor speed, co-ordination, attention and concentration, verbal and visuospatial learning, visual and recognition memory, reasoning, mood, handedness)

Pulliainen 1994 *(Continued)*

	Harmful side effects
Notes	59 participants were randomised but 16 were subsequently excluded. Results were presented only for the 43 participants who completed the entire trial. Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to treatment groups, method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cognitive outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	16/59 (27%) of participants excluded from analysis. Results presented only for participants who completed the trial
Selective reporting (reporting bias)	Unclear risk	Cognitive outcomes, described in methods section, well reported in results section. Adverse effects reported, no seizure outcomes reported and outcomes chosen for this review not reported. No protocol available so unclear if seizure outcomes were planned a priori
Other bias	Low risk	None identified

Ramsay 1983

Study characteristics

Methods	Randomised, 'two compartment' parallel-group trial, conducted in the USA 2 treatment arms: CBZ and PHT
Participants	Adults, previously untreated, with at least 2 seizures or at least 1 seizure and an EEG with paroxysmal features Number randomised: PHT = 45, CBZ = 42 60 male participants (69%) 55 participants with focal epilepsy (63%) Mean age (range) 37.4 (18-77) years
Interventions	Monotherapy with PHT or CBZ

Ramsay 1983 *(Continued)*

	Mean daily dose achieved (for the 54 participants with no major side effects): PHT = 5.35 mg/kg/d, CBZ = 9.32 mg/kg/d Trial duration: 2 years. Range of follow-up not reported
Outcomes	Laboratory measures Side effects (major and minor) Seizure control/treatment failure
Notes	7 participants on CBZ and 10 participants on PHT were “dropped for non-compliance” and excluded from analysis. Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned to treatment groups; method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participants and personnel) achieved with additional blank tablet
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	17/87 (19.5%) of participants excluded from analysis for "non-compliance". Results presented only for participants who completed the trial
Selective reporting (reporting bias)	Low risk	All efficacy and tolerability outcomes specified in the methods sections reported well in the results section. No protocol available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Ramsay 1992

Study characteristics

Methods	Open-label, parallel-design, multicentre RCT conducted at 16 centres in the USA 2 treatment arms: PHT and VPS randomised in a 2:1 ratio
Participants	Participants with at least 2 newly-diagnosed and previously untreated primary generalised tonic-clonic seizures within 14 days of starting the trial Number randomised: PHT = 50, VPS = 86

Ramsay 1992 *(Continued)*

	73 male participants (54%) 0% participants with focal epilepsy (all generalised epilepsy) Mean age (range): 21 (3-64 years)
Interventions	Monotherapy with PHT or VPS Starting doses PHT: 3 mg/kg/d- 5 mg/kg/d, VPS: 10 mg/kd/d-15 mg/kg/d; doses gradually increased Doses achieved not stated Range of follow-up: 0-11 months
Outcomes	Time to first generalised tonic-clonic seizure 6-month seizure recurrence rates Adverse events
Notes	IPD provided for 3/4 outcomes of this review by the Department of Veteran's Affairs (maximum follow-up 6 months, therefore trial could not contribute to outcome, 'time to 12-month remission')

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised on a 2:1 ratio VPS:PHT using randomisation tables in each centre (information provided by trial author)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial; trial authors stated that differences in adverse events of PHT and VPS would "quickly unblind" the trial anyway.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial; trial authors stated that differences in adverse events of PHT and VPS would "quickly unblind" the trial anyway.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Ramsay 2007

Study characteristics

Methods	Double-blind, multicentre RCT conducted in the USA 2 treatment arms: CBZ and LEV

Ramsay 2007 *(Continued)*

Participants	Adults > 60 years with new onset focal seizures (previously untreated or under treated) Interim results: 37 participants recruited (numbers recruited to each arm not stated) 28 male participants (76%) 100% of participants had focal epilepsy. Age: 20 participants aged 60-69 years and 17 participants > 70 years
Interventions	Monotherapy with CBZ or LEV Intitial doses: CBZ = 100 mg/d, LEV = 250 mg/d. Target doses: CBZ = 400 mg/d, LEV = 1000 mg/d Interim results; range of follow-up not stated
Outcomes	Discontinuations from the trial Treatment-emergent side effects Seizure control
Notes	Trial available as abstract only. Attempts to contact the principal investigator and trial sponsor for further information were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised, no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial - trial drugs were over-encapsulated and all participants received similar appearing active medication.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Interim report; 7/37 participants recruited had discontinued treatment. Unclear if an ITT approach would be taken to analysis
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to make a judgement
Other bias	Low risk	None identified

Ramsay 2010

Study characteristics

Methods	Randomised, multicentre, double-blind trial conducted in the USA

Ramsay 2010 *(Continued)*

	2 treatment arms: PHT and TPM
Participants	Participants 12–65 years (inclusive), weighed at least 50 kg and experienced 1–20 unprovoked, complex focal or primary/secondarily generalised tonic–clonic seizures within the past 3 months, either as newly diagnosed epilepsy or as epilepsy relapse from remission Number randomised: PHT = 128, TPM = 133 126 male participants (48%) 53 participants with focal epilepsy (20%) Mean age (range): 34 (12-78 years)
Interventions	Monotherapy with PHT or TPM Short titration (1 day) to target dose of PHT = 300 mg/d and TPM = 100 mg/d Range of follow-up: 0-2.5 months
Outcomes	Time to first complex focal seizure or generalised tonic-clonic seizure Participant retention (time to discontinuation of treatment) Incidence and summary of adverse events
Notes	IPD provided by trial sponsor Johnson & Johnson for time to treatment failure and time to first seizure; trial duration insufficient to measure remission outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessment of results and serum AED level
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Rastogi 1991

Study characteristics	
Methods	Parallel-design RCT conducted in Meerut, India 2 treatment arms: PHT and VPS
Participants	Participants with at least 2 focal or generalised tonic-clonic seizures per month Unclear if participants were newly diagnosed Number randomised: PHT = 45; VPS = 49 70 male participants (74%) 27 participants with focal epilepsy (29%) Age range: PHT: 12-42 years; VPS: 8-52 years
Interventions	Monotherapy with PHT or VPS Average daily dose achieved: PHT: 5.6 mg/kg/d, VPS: 18.8 mg/kg/d Participants were evaluated after 4, 12 and 24 weeks of treatment No information on range of follow-up
Outcomes	Reduction in frequency of seizures: • excellent (100% reduction); • good (75%-99% reduction); • fair (50%-74% reduction); • poor (< 50% reduction) Adverse effects Seizure control
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants "randomly allocated irrespective of seizure type"; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Unclear risk	Frequency of seizures reported for all randomised participants; no information provided on withdrawal rates/attrition rates etc.

Rastogi 1991 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Frequency of seizures during treatment well reported; most common adverse events reported No protocol available to compare with a priori analysis plan; outcomes for this review not reported
Other bias	Low risk	None identified

Ravi Sudhir 1995

Study characteristics	
Methods	Single-centre, randomised, parallel-group trial of participants referred to the Neurology Clinic of Nehru Hospital, Chandigarh, India 2 treatment arms: CBZ and PHT
Participants	Newly diagnosed and drug-naive adult participants > 14 attending the Neurology Clinic of Nehru Hospital, Chandigarh, India Number randomised: PHT = 20, CBZ = 20 28 male participants (70%) 11 participants with focal epilepsy (27.5%) Mean age (range): PHT group 23.4 (14-44 years), CBZ 24.4 (14-45 years)
Interventions	Monotherapy with PHT or CBZ Initial daily dose: PHT = 5 mg/kg/d, CBZ = 10 mg/kg/d Trial duration 10-12 weeks. Range of follow-up not reported
Outcomes	Cognitive measures before and after treatments (verbal, performance, memory, visuomotor, perceptomotor organisation, visual organisation, dysfunction)
Notes	6 participants on CBZ and 8 participants on PHT were excluded from final analysis of cognitive assessments who were lost to follow-up or who had uncontrolled seizures. Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were randomised to one of the two trial groups"; no further information given on methods of randomisation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided

Ravi Sudhir 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	14/40 (35%) of participants excluded from analysis who were lost to follow-up or experienced uncontrolled seizures. Results presented only for participants who completed the trial
Selective reporting (reporting bias)	Unclear risk	Cognitive outcomes described in methods section well reported in results section. No seizure outcomes or adverse events reported and outcomes chosen for this review not reported. No protocol available, so unclear if seizure outcomes were planned a priori
Other bias	Low risk	None identified

Resendiz 2004

Study characteristics	
Methods	Randomised, open-label trial conducted in several hospitals in Mexico 2 treatment arms: CBZ and TPM
Participants	Participants aged 2-18 years with newly diagnosed focal epilepsy with or without secondary generalisation with at least two unprovoked seizures > 24 hours apart and at least 1 seizure in the last 6 months. Participants must have had no established treatment and have had received no antiepileptic treatment within the past 30 days. Number randomised: CBZ = 42, TPM = 46. Number included in analysis: CBZ = 32, TPM = 33 100% focal epilepsy 33 male participants (60%) included in analysis Mean age (range): CBZ = 10 (5-17) years, TPM = 8 (2-16) years for participants included in analysis
Interventions	Monotherapy with CBZ or TPM Treatments titrated to a maximum of CBZ = 20 mg/kg/d-25 mg/kg/d, TPM = 9 mg/kg/d Follow-up assessments at 6 and 9 months; range of follow-up not stated
Outcomes	Seizure freedom and frequency of seizures during the trial Adverse events during the trial Laboratory results
Notes	The trial was published in Spanish; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD. Results presented only for those who completed the trial. Those with less than 35% reduction of seizures were excluded from analysis.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Resendiz 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number tables used to assign participants to treatment groups
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates reported (23 dropouts, 10 for CBZ and 13 for TPM). Only those who completed the trial were included in analysis (non-responders to treatment excluded); this is not an ITT approach.
Selective reporting (reporting bias)	Low risk	No protocol available. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

Reunanen 1996

Study characteristics	
Methods	Randomised, double-blind, parallel-group trial conducted in 56 centres in Europe and Australia 3 treatment arms: LTG (200 mg/d), LTG (100 mg/d) and CBZ
Participants	Adults and children > 12 years with newly diagnosed, currently untreated or recurrent epilepsy with ≥ two seizures in the previous 6 months and with at least 1 seizure in the last 3 months. Participants must not have taken AEDs in the previous 6 months. Number randomised: LTG (200 mg) = 115, LTG (100 mg) = 115, CBZ = 121 188 male participants (54%) 237 participants with focal epilepsy (68%) Not stated how many participants had received previous AED treatment Mean age (range): 32 (12-72) years
Interventions	Monotherapy with LTG or CBZ for 30 weeks 4-week escalation phase leading to LTG = 100 mg/d, LTG = 200 mg/d, CBZ = 600 mg/d Range of follow-up: 0-378 days
Outcomes	Proportion seizure-free after completing the first 6 weeks of treatment Time to first seizure Time to withdrawal

Reunanen 1996 *(Continued)*

	Frequency of adverse events with at least 5% incidence in any treatment group
Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment failure, time to first seizure and time to six-month remission. Participants considered to have completed the trial if they experienced a seizure after the first 6 weeks. In primary analysis, two arms of LTG pooled and compared to CBZ and separate doses of LTG compared to CBZ in sensitivity analysis (see Data extraction and management)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (information provided by drug manufacturer)
Allocation concealment (selection bias)	Low risk	Allocation concealed by individual, sealed, opaque envelopes (information provided by drug manufacturer)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Richens 1994

Study characteristics

Methods	Open-label, multicentre trial across 22 centres in the UK 2 treatment arms: CBZ and VPS
Participants	Adults with new onset primary generalised epilepsy or focal epilepsy with/without generalisation or with a recurrence of seizures following withdrawal of AED treatment were eligible given that no anticonvulsants had been received in the previous 6 months. Number randomised: CBZ = 151, VPS = 149 153 (51%) male participants (51%) 147 participants with focal epilepsy (49%) Mean age (range): 33 (16-79) years
Interventions	Monotherapy with CBZ or VPS Mean daily dose achieved by month 24: CBZ = 516 mg/d, VPS = 924 mg/d

Richens 1994 *(Continued)*

	Range of follow-up: 0.5-90 months
Outcomes	Remission analysis (time to 6-, 12- and 24-month remission) Retention analysis (time to treatment failure) Adverse event incidence Incidence of treatment failures due to poor seizure control and adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor Sanofi Participants with other generalised seizure types (e.g. myoclonic/absence) were included in the trial, but efficacy analyses were based solely on generalised tonic-clonic seizures. Results in the published paper were given for 181 participants out of 300 analysed by ITT (participants randomised and with data for at least 1 follow-up visit). IPD was provided for all 300 participants randomised and used for analyses in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment using a computerised minimisation programme with stratification for age, sex, seizure type and centre.
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed via central telephone allocation from the Trial Office at Sanofi Winthrop Ltd.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Rowan 2005

Study characteristics

Methods	Randomised, double-blind, parallel-group trial conducted in 18 Veterans Affairs medical centres in the USA 3 treatment arms: LTG, CBZ and GBP
Participants	Adults > 60 years with newly diagnosed seizures, untreated or treated with subtherapeutic AED levels, with at least 1 seizure in the previous 3 months

Rowan 2005 *(Continued)*

	Number randomised: CBZ = 198, GBP = 195, LTG = 200 570 male participants (96%) 446 participants with focal epilepsy (75%) Not stated how many participants had received previous AED treatment Mean age (years): CBZ = 71.9, GBP = 72.9, LTG = 71.9. Range not stated
Interventions	Monotherapy with CBZ, GBP, LTG 6-week escalation phase leading to CBZ = 600 mg/d, GBP = 1500 mg/d, LTG = 150 mg/d Trial duration: 12 months. Range of follow-up: not stated
Outcomes	Retention in the trial for 12 months Seizure freedom at 12 months Time to first, second, fifth and tenth seizure (time to seizures) Drug toxicity (incidence of systemic and neurologic toxicities) Serum drug levels and compliance Seizure-free retention rates
Notes	IPD requested from trial sponsor, the Department of Veterans Affairs, USA. IPD was not provided as the terms of a data sharing agreement could not be agreed upon. Aggregate data extracted from graphs in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (varying sizes) performed by site via a computer-generated list
Allocation concealment (selection bias)	Low risk	Telephone randomisation used and pharmacy dispensed a prescription of the allocated drug (part of a blinded drug kit) to participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved with double dummy tablets; doses of both increased and decreased simultaneously
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. Most of the randomised participants included in analysis; 3 excluded due to site closure (not related to treatment)
Selective reporting (reporting bias)	Low risk	No protocol available but case report forms of data collected provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

Saetre 2007

Study characteristics	
Methods	Randomised, double-blind, parallel-group trial conducted in 29 centres across Croatia, Finland, France, Finland and Norway 2 treatment arms: LTG and CBZ
Participants	Adults > 65 years with newly diagnosed seizures, with a history of at least 2 seizures and at least 1 seizure in the previous 6 months. Participants must not have taken AEDs for more than 2 weeks in the previous 6 months and never taken CBZ or LTG. Number randomised: LTG = 93, CBZ = 92 102 male participants (54%) Proportion with focal epilepsy not stated Not stated how many participants had received previous AED treatment Mean age: 74 (65-91) years
Interventions	Monotherapy with LTG or CBZ 4-week escalation phase leading to LTG = 100 mg/d, CBZ = 400 mg/d Trial duration: 40 weeks. Range of follow-up: not stated
Outcomes	Retention in the trial (time to treatment withdrawal for any cause) Seizure freedom after week 4 Seizure freedom after week 20 Time to first seizure Adverse event reports Tolerability according to the Liverpool Adverse Event profile (AEP)
Notes	IPD requested from trial sponsor Glaxo Smith Kline but data could not be located. Aggregate summary data extracted from the publication

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind achieved with double dummy tablets, packaged together
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided

Saetre 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all participants who received trial treatment were included in an ITT analysis.
Selective reporting (reporting bias)	Low risk	No protocol available but clinical trial summary provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

SANAD A 2007

Study characteristics	
Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the UK 5 treatment arms: LTG, CBZ, GBP, TPM and OXC
Participants	Adults and children > 4 years with newly diagnosed focal epilepsy, relapsed focal epilepsy or failed treatment with a previous drug not used in this trial Number randomised: CBZ = 378, LTG = 378, OXC = 210, TPM = 378, GBP = 377 944 male participants (55%) 1531 participants with focal epilepsy (89%) 309 had received previous AED treatment (18%). Mean age (range): 38 (5-86) years
Interventions	Monotherapy for LTG, CBZ, GBP, TPM or OXC Titration doses and maintenance doses decided by treating clinician Range of follow-up: 0-86 months
Outcomes	Time to treatment failure Time to 1-year (12-month) remission Time to 2-year remission Time to first seizure Health-related quality of life via the NEWQOL (Newly Diagnosed Epilepsy Quality of Life battery) Health economic assessment and cost-effectiveness of the drugs (cost per QALY gained and cost per seizure avoided) Frequency of clinically important adverse events
Notes	IPD provided for all outcomes of this review (trial conducted at our site)
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

SANAD A 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer minimisation programme stratified by centre, sex and treatment history
Allocation concealment (selection bias)	Low risk	Telephone randomisation to a central randomisation allocation service
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

SANAD B 2007

Study characteristics	
Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the UK 3 treatment arms: LTG, GBP, TPM
Participants	Adults and children > 4 years with newly diagnosed or relapsed generalised or unclassified epilepsy, or failed treatment with a previous drug not used in this trial Number randomised: LTG = 239, VPS = 238; TPM = 239 427 male participants (60%) 54 participants with focal epilepsy (8%) 108 had received previous AED treatment (15%) Mean age (range): 22.5 (5-77) years
Interventions	Monotherapy for LTG, GBP or TPM Titration doses and maintenance doses decided by treating clinician Range of follow-up: 0-83.5 months
Outcomes	Time to treatment failure Time to 1-year (12-month) remission Time to 2-year remission Time to first seizure

SANAD B 2007 *(Continued)*

	Health-related quality of life via the NEWQOL (Newly Diagnosed Epilepsy Quality of Life battery) Health economic assessment and cost-effectiveness of the drugs (cost per QALY gained and cost per seizure avoided) Frequency of clinically important adverse events
Notes	IPD provided for all outcomes of this review (trial conducted at our site)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer minimisation programme stratified by centre, sex and treatment history
Allocation concealment (selection bias)	Low risk	Telephone randomisation to a central randomisation allocation service
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

SANAD II A 2021

Study characteristics

Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the UK 3 treatment arms: LTG, LEV and ZNS
Participants	Adults and children > 5 years with two or more newly diagnosed, spontaneous and untreated focal seizures Number randomised: LTG = 330; LEV = 332; ZNS = 328 561 male participants (57%) 990 participants with focal epilepsy (100%) Mean age (range): 39 (5-91) years
Interventions	Monotherapy for LTG, LEV or ZNS

SANAD II A 2021 *(Continued)*

	LTG: starting dose of 25 mg (0.5 mg/kg for children < 12 years) once per day for two weeks titrated to target maintenance dose of 50 mg every morning and 100 mg every night (1.5 mg/kg for children < 12 years morning and night) LEV: starting dose of 250 mg once per day (10 mg/kg twice per day for children < 12 years) for two weeks titrated to target maintenance dose of 500 mg twice per day (40 mg/kg twice per day for children < 12 years) ZNS: starting dose of 50 mg (0.5-1 mg/kg for children < 12 years) once per day for two weeks titrated to target maintenance dose of 100 mg morning and night (5 mg/kg for children twice per day < 12 years) Range of follow-up: 0 to 72.8 months
Outcomes	Time to 12-month remission from seizures Time to treatment failure Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Adverse reactions QoL. Health economic outcomes
Notes	IPD provided for all outcomes of this review (trial conducted at our site)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation conducted via a centralised computer based minimisation system
Allocation concealment (selection bias)	Low risk	Randomisation centralised, therefore allocation concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

SANAD II B 2021

Study characteristics	
Methods	Randomised, multicentre, open-label, parallel-group trial conducted in the UK 2 treatment arms: LEV and VPS
Participants	Adults and children > 5 years with two or more newly diagnosed, spontaneous and untreated generalised tonic-clonic or unclassified seizures Number randomised: LEV = 260; VPS = 260 337 male participants (65.7%) 0 participants with focal epilepsy (0%) Mean age (range): 16.5 (5-94) years
Interventions	Monotherapy for LEV or VPS LEV: starting dose of 250 mg (10 mg/kg for children < 12 years) once per day for two weeks titrated to target maintenance dose of 500 mg twice per day (40 mg/kg for children < 12 years twice per day) VPS: starting dose of 500 mg once per day (10 mg/kg twice per day for children < 12 years) for two weeks titrated to target maintenance dose of 500 mg twice per day (25 mg/kg twice per day for children < 12 years) Range of follow-up: 0 to 67.9 months
Outcomes	Time to 12-month remission from seizures Time to treatment failure Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Adverse reactions QoL. Health economic outcomes
Notes	IPD provided for all outcomes of this review (trial conducted at our site)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation conducted via a centralised computer based minimisation system
Allocation concealment (selection bias)	Low risk	Randomisation centralised, therefore allocation concealed

SANAD II B 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Shakir 1981

Study characteristics	
Methods	Parallel-design RCT conducted at 2 centres (Glasgow, Scotland and Wellington, New Zealand) 2 treatment arms: PHT and VPS
Participants	21 (64%) of participants previously untreated, 12 (36%) of participants continued to have seizures on previous drug therapies. Original treatments gradually withdrawn before PHT or VPS treatment introduced Number randomised: PHT = 15, VPS = 18 12 male participants (36%) 19 participants with focal epilepsy (58%) Mean age (range): 23 (7-55 years)
Interventions	Monotherapy with PHT or VPS Starting doses: PHT: < 12 years 150 mg/d, older participants: 300 mg/d, VPS: < 12 years 300-400 mg/d, older participants: 800-1200 mg/d. Doses achieved not stated Mean follow-up (range): 30 (9-48 months)
Outcomes	Seizures during treatment Adverse events
Notes	Outcomes chosen for this review were not reported. IPD not available but could be constructed from the publication for the outcome 'time to treatment withdrawal.'
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Shakir 1981 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants "randomly divided", using telephone randomisation (information provided by trial author)
Allocation concealment (selection bias)	Low risk	Centralised telephone randomisation used (information provided by trial author)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomised participants; time on treatment reported for all randomised participants. No losses to follow-up reported
Selective reporting (reporting bias)	Low risk	No protocol available, outcomes chosen for this review not reported, Seizure and adverse event outcomes well reported
Other bias	Low risk	None identified

Sidhu 2018

Study characteristics	
Methods	Randomised open-label comparative study conducted within a single centre at the M.S. Ramaiah Memorial hospital, Bangalore, India between October 2004 and May 2006 2 treatment arms: LTG and VPS
Participants	Female participants aged between 12 and 40 years with newly diagnosed epilepsy who were untreated or who had received less than 2 weeks of an AED which must be tapered off before entry to the study. A negative pregnancy test was also required due to the objective of the trial to examine menstrual cycle and reproductive hormone outcomes. Number randomised: LTG = 45, VPS = 45. Number completing the study and included in analysis: LTG = 32, VPS = 34 0% male participants (all female participants) 41 had focal epilepsy of those completing the study (62%). Mean age (range) of those completing the study: LTG = 30 (15 to 42) years; VPS = 27 (14 to 40) years
Interventions	Monotherapy with LTG or VPS Titration over 4 weeks: LTG started at 25 mg/d and titrated to a maximum dose of 550 mg/d; VPS started at 750 mg/d in divided doses and titrated to a maximum dose of 1000-2000 mg/d Trial duration: 12 months
Outcomes	Anthropometric measures (weight, BMI) Clinical measures related to the menstrual cycle

Sidhu 2018 *(Continued)*

	Reproductive hormone levels: testosterone, dihyroepiandrosterone sulfate (DHEAS), androstenedione, sex hormone-binding globulin (SHBG), luteinising hormone (LH), follicle-stimulating hormone (FSH) Insulin resistance: homeostasis model assessment for insulin resistance (HOMA-IR) over 2.5 and fasting insulin levels (FIN)
Notes	Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD. 24 participants (27% of randomised participants) who withdrew prematurely from the study were excluded from analysis. It was stated that all participants should receive monotherapy for the duration of the study and could switch treatments at the end of the study. However, the characteristics table describes 'monotherapy at last visit' (27 out of 32 in the LTG group and 30 out of 34 in the VPS group), therefore it is unclear if all participants were receiving monotherapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were 'randomly allotted' into two groups. No further details provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	24 participants (27% of randomised participants) who withdrew prematurely from the study were excluded from analysis. This is not an ITT approach.
Selective reporting (reporting bias)	Unclear risk	No protocol available and outcomes chosen for this review not reported. Outcomes related to reproductive hormones and menstrual cycle well reported. No seizure or adverse event outcomes reported; unclear if data were collected on these outcomes
Other bias	Unclear risk	Unclear if all participants were receiving monotherapy (see notes) and unclear why a study which was conducted between 2004 and 2006 was not published until 2017

So 1992

Study characteristics

Methods	Randomised double-blind study conducted in the USA 2 treatment arms: CBZ and VPS
Participants	Participants between the ages of 10 and 70 who had experienced at least two complex focal seizures who were previously untreated or insufficiently treated

So 1992 *(Continued)*

	Number randomised: CBZ = 17, VPS = 16 15 male participants (45%) 100% of participants with focal epilepsy Mean age (range): CBZ = 32.5 (13-65), VPS = 31.3 (17-57)
Interventions	Monotherapy with CBZ or VPS Doses started or achieved not stated 4-week titration period followed by a 24-week maintenance period. Range of follow-up not stated
Outcomes	Proportion of participants free of complex focal seizures during the maintenance period Proportion of participants reporting specific adverse events
Notes	Outcomes for this review were not reported; IPD were not available due to time elapsed since the trial was conducted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised in a 1:1 ratio; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates reported. Only those who entered the maintenance period were included in analysis; this was not an ITT analysis.
Selective reporting (reporting bias)	Low risk	Efficacy and tolerability outcomes specified in the methods sections were reported well in the results section. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	Low risk	None identified

Steiner 1999

Study characteristics

Methods	Randomised, double-blind, multicentre trial conducted in the UK 2 treatment arms: LTG and PHT

Steiner 1999 *(Continued)*

Participants	Participants aged 14-75 years with two or more focal, secondarily generalised, or primary generalised tonic-clonic seizures Number randomised: PHT = 95, LTG = 86 101 male participants (56%) 90 participants with focal epilepsy (50%) Mean age (range): 34 (13-75 years)
Interventions	Monotherapy with LTG or PHT Titrated for 2 weeks to a target dose of LTG = 150 mg/d, PHT = 300 mg/d Range of follow-up: 0-15 months
Outcomes	Percentage of participants remaining on treatment Percentage of participants remaining seizure-free in the last 24 and last 16 weeks of treatment Number of seizures (percentage change from baseline) in the last 24 weeks and 16 weeks of treatment Time to first seizure after the first 6 weeks of treatment (dose-titration period) Time to discontinuation Incidence of adverse events and adverse events leading to discontinuation Quality of Life according to the Side Effects and Life Satisfaction (SEALS) inventory
Notes	IPD provided by trial sponsor Glaxo Smith Kline for time to treatment failure, time to first seizure and time to six-month remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to seizure type; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants, personnel and outcome assessors involved in the trial were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, personnel and outcome assessors involved in the trial were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Steinhoff 2005

Study characteristics	
Methods	Randomised, open-label, parallel-group trial conducted in 24 centres across Germany 4 treatment arms: LTG (two arms), CBZ and VPS Participants with focal and generalised epilepsy randomised separately to LTG or CBZ and LTG or VPS, respectively
Participants	Adults and children > 12 years with newly diagnosed epilepsy; at least 1 seizure and EEG imaging suggesting epilepsy Number randomised not stated; number included in analysis: LTG = 88, CBZ = 88 (focal); LTG = 33, VPS = 30 (generalised) 106 male participants (64%) in focal epilepsy group, 27 male participants (43%) in the generalised epilepsy group 166 out of 239 total included in analysis had focal epilepsy (69%). Not stated how many participants had received previous AED treatment Mean age (years): LTG (focal) = 46.6, CBZ = 43.1, LTG (generalised) = 22.3, VPS = 23.3. Range not stated
Interventions	Monotherapy with LTG, CBZ or VPS 4-week escalation phase leading to LTG = 100 mg/d-200 mg/d, CBZ = 600 mg/d-1200 mg/d in adults and 600 mg/d-1000 mg/d in children aged 11-15, VPS = 600 mg/d-1200 mg/d for children aged 6-14, 600 mg/d-1500 mg/d for adolescents over 14 years and 1200 mg/d-2100 mg/d for adults Trial duration: 26 weeks; range of follow-up: not stated
Outcomes	Number of seizure-free patients during trial weeks 17-24 "Leaving the study" (retention rates) Adverse event rates
Notes	IPD requested from trial sponsor Glaxo Smith Kline but data could not be provided due to restrictions over the de-identification of datasets from trials conducted in Germany Aggregate data extracted from graphs in the publication Data from participants with focal epilepsy were included in the randomised comparison of LTG and CBZ and data from participants with generalised epilepsy were included in the randomised comparison of LTG and VPS (see Data extraction and management).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	High risk	Open-label trial

Steinhoff 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants randomised to each group not reported (254 randomised and 239 analysed in the four arms of the trial). Reasons for exclusion stated but not to which drug these participants were randomised
Selective reporting (reporting bias)	Low risk	No protocol available but clinical trial summary provided by the sponsor. Seizure outcomes and adverse events well reported
Other bias	Low risk	None identified

Stephen 2007

Study characteristics	
Methods	Randomised, single-centre, open-label trial conducted in Scotland, UK 2 treatment arms LTG and VPS
Participants	Participants of at least 13 years with a minimum of 2 new onset unprovoked seizures of any type and no previous exposure to LTG or VPS Number randomised: LTG = 117, VPS =109 114 male participants (50%) 154 participants with focal epilepsy (68%) Mean age (range): 36 (13-80 years)
Interventions	Monotherapy with LTG or VPS Titration of 5-10 weeks to target doses of LTG = 200 mg/d and VPS = 1000 mg/d Range of follow-up: 0-51 months
Outcomes	Percentage of randomised participants achieving a minimum period of 12 months' seizure freedom Percentage of randomised participants withdrawing due to adverse events Percentage of randomised participants with lack of efficacy at maximum tolerated dose Changes in levels of androgenic hormone levels (testosterone, androstenedione and sex hormone-binding globulin levels) Changes in weight and BMI from baseline
Notes	IPD provided for all outcomes of this review by trial author
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Stephen 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants from the ITT population analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	High risk	There were inconsistencies between rates of seizure recurrence and reasons for withdrawal between the data provided and the published paper, which the authors could not resolve.

Suresh 2015

Study characteristics	
Methods	Randomised, single-centre, open-label trial conducted in Bengaluru, India 2 treatment arms: CBZ and LEV
Participants	Participants aged 18-60 years newly diagnosed with focal or focal seizures with or without secondary generalisation referred to the Department of Neurology at Vydehi Institute of Medical Sciences and Research Center Number randomised CBZ = 30, LEV = 30 30 male participants (50%) 100% participants with focal epilepsy Mean age (range): not provided for all randomised participants
Interventions	Monotherapy with CBZ or LEV Starting dose of CBZ = 200 mg/d, LEV = 500 mg/d titrated to a maximum dose of CBZ 1200 mg/d, LEV 300 mg/d Trial duration: 1 year; range of follow-up: not stated
Outcomes	Quality of Life by the QOLIE-10 questionnaire before and after 26 weeks of therapy Treatment efficacy (seizure freedom at 4 weeks, 12 weeks, 26 weeks and 6 months) Treatment safety (proportion of participants experiencing at least 1 adverse event)

Suresh 2015 *(Continued)*

Notes	Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised; no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates reported; two participants lost to follow-up in each group not included in analysis. This was not an ITT approach but unlikely that this small amount of missing data would influence the overall results
Selective reporting (reporting bias)	High risk	Only one outcome was predefined in the methods section (quality of life); other results reported were not predefined.
Other bias	Low risk	None identified

Thilothammal 1996

Study characteristics

Methods	Parallel-design RCT conducted in Madras (Chennai), India Three treatment arms: PHB, PHT, VPS
Participants	Children with more than 1 previously untreated generalised tonic-clonic (afebrile) seizure Number randomised: PHB group = 51, PHT = 52, VPS = 48 81 boys (54%) 0% focal epilepsy (all had generalised epilepsy) Age range: 4-12 years
Interventions	Monotherapy with PHT or VPS Starting doses: PHB: 3 mg/kg/d-5 mg/kg/d, PHT: 5 mg/kg/d-8 mg/kg/d, VPS: 15 mg/kg/d-50 mg/kg/d Dose achieved not stated Range of follow-up (months): 22-36
Outcomes	Proportion with recurrence of seizures

Thilothammal 1996 *(Continued)*

	Adverse events
Notes	Outcomes chosen for this review were not reported. IPD not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised via a computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double–blinded using additional placebo tablets; unclear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double–blinded using additional placebo tablets; unclear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed
Selective reporting (reporting bias)	Low risk	No protocol available; outcomes chosen for this review not reported, Seizure and adverse event outcomes well reported
Other bias	Low risk	None identified

Trinka 2013

Study characteristics

Methods	Multicentre, open-label, randomised, two parallel-group stratified trial carried out in a community setting between February 2005 and October 2007 in 269 centres across 23 European countries and Australia Four treatment arms: CBZ (controlled release), LEV (two arms) and VPS (extended release) - see notes
Participants	Patients aged ≥ 16 years were included if they had two or more unprovoked seizures in the previous 2 years with at least one during the previous 6 months. Participants must not have received one of the trial drugs previously or treated for epilepsy with any other AED in the previous 6 months. Number randomised (ITT population): CBZ = 503, LEV = 492 (CBZ branch), LEV = 349, VPS = 353 (VPS branch) 949 male participants (56%) 1048 participants with focal epilepsy (62%) Mean age (range): 40 (16-89 years)
Interventions	Monotherapy with CBZ, LEV or VPS Titration over two weeks to target doses CBZ-CR = 600 mg/d, LEV = 1000 mg/d, VPS-ER = 1000 mg/d

Trinka 2013 *(Continued)*

	Range of follow up: 0 to 28.5 months
Outcomes	Time to withdrawal from trial medication (treatment withdrawal) after randomisation Time to first seizure after randomisation Treatment withdrawal rates at 6 and 12 months Seizure-freedom rates at 6 and 12 months Change of baseline in quality of life measures (QOLIE-31-P and EQ-5D) Treatment-emergent adverse events (intensity and seriousness)
Notes	IPD provided for all outcomes of this review by trial sponsor UCB. Trial designed in 2 strata based on whether recommended treatment would be CBZ or VPS. Data analysed according to the separate strata in this review (see Data extraction and management)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified; no further information provided
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed by use of an interactive voice-response system via telephone to manage the randomisation process.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants from the ITT population analysed from IPD provided (see footnote 2). 8 randomised participants excluded from ITT population due to no informed consent or lack of compliance with good clinical practice
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Trinka 2018

Study characteristics

Methods	Randomised, multicentre, double-blind, non-inferiority trial conducted in 170 clinical centers across 31 countries using a stepwise design with three dose levels, conducted between January 2011 and September 2015 2 treatment arms: ESL and CBZ-CR

Trinka 2018 *(Continued)*

Participants	Adult patients (≥ 18 years old) with newly diagnosed focal epilepsy, at least two unprovoked seizures (with or without secondary generalisation) within 12 months of screening visit and at least 1 seizure during the previous 3 months Number randomised: ESL = 401, CBZ-CR = 414; number in the full analysis set: ESL = 401, CBZ-CR = 412; number in the per protocol set: ESL = 388, CBZ-CR = 397 448 male participants in the full analysis set (55%) 100% of participants had focal epilepsy. Mean age (SD) of the full analysis set: ESL = 37.6 (15.8) years, CBZ-CR = 38.7 (16.3) years
Interventions	Monotherapy with ESL or CBZ-CR Starting doses: ESL 400 mg/d, CBZ-CR 200 mg/d, before up titration to level A: ESL 800 mg/CBZ-CR 200 mg twice a day for participants who remained seizure-free throughout the 26-week evaluation period If a seizure occurred during the evaluation period, participants were titrated to level B (ESL 1200 mg/CBZ-CR 400 mg twice a day) or to level C (ESL 1600 mg/CBZ-CR 600 mg twice a day) and the evaluation period began again. Participants who remained seizure-free could undergo one dose reduction during the assessment period if they were unable to tolerate the increased dose. Participants who experienced a seizure on the third dose level or following dose reduction or during the extension phases were withdrawn from the study. Treatment duration: up to 121 weeks
Outcomes	Proportion of patients who were seizure-free for the entire evaluation phase at the last evaluated dose level Proportion of seizure-free patients during 1 year of treatment Time to first seizure at the last evaluated dose (treatment failure time) Seizure characteristics of the first seizure during the evaluation period Dose level at which patients reached 26-week seizure freedom Treatment retention time (defined as the time to withdrawal due to adverse events [AEs] or lack of efficacy) Changes in quality-of-life (Quality of Life in Epilepsy Inventory-31 (QOLIE-31) survey) Incidence of treatment-emergent adverse events
Notes	Two participants randomised to CBZ-CR did not receive treatment and were therefore excluded from the full analysis set. Initial contact made with manufacturers of ESL (Bial) to request IPD. At the time of updating the review, IPD had not been received. Published results were not within the correct format for inclusion in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in a 1:1 ratio to either ESL or CBZ-CR using randomisation schedule software (Rando; Accovion,Eschborn, Germany). A site-stratified block randomisation was used with a block size of 4 (block size not revealed to the sites).

Trinka 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation conducted centrally by the software and block side was not revealed to the sites
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To ensure blinding, both active treatments were identically over encapsulated and matching placebo capsules were provided so that the same numbers of oral capsules were taken in the double-blind setting. Patients, investigators, and clinical research and sponsor personnel, who administered medication, assessed outcomes, and analysed data, were masked to the allocation until all data for the primary analysis were collected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To ensure blinding, both active treatments were identically over encapsulated and matching placebo capsules were provided so that the same numbers of oral capsules were taken in the double-blind setting. Patients, investigators, and clinical research and sponsor personnel, who administered medication, assessed outcomes, and analysed data, were masked to the allocation until all data for the primary analysis were collected.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition clearly outlined, including reasons for withdrawal within a study flow diagram. Results provided for the full analysis set (i.e. ITT population) and per protocol set
Selective reporting (reporting bias)	Unclear risk	No protocol available; published results are not within the correct format for inclusion in the review. Seizure, adverse events and quality of life outcomes defined in the methods well described in the results section. Unclear why quality of life had not been compared across treatment groups (within-group comparisons only made)
Other bias	Low risk	None detected

Turnbull 1985

Study characteristics	
Methods	Single-centre, parallel-group design RCT conducted in Newcastle, UK 2 treatment arms: PHT and VPS
Participants	Participants with ≥ 2 focal or generalised tonic-clonic seizures in the past 3 years Participants were previously untreated but started on AED treatment within 3 months of their most recent seizure Number randomised: PHT = 70, VPS = 70 73 male participants (52%) 63 participants with focal epilepsy (45%) Mean age (range): 35 (14-70 years)
Interventions	Monotherapy with PHT or VPS Starting doses: PHT 300 mg/d, VPS 600 mg/d. Dose achieved not stated Range of follow-up: 3.5-52 months
Outcomes	Time to 2-year remission

Turnbull 1985 *(Continued)*

	Time to first seizure Adverse events
Notes	IPD provided for all outcomes included in this review by trial author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised with stratification for age group, gender and seizure type. Method of randomisation not stated or provided by author
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Verity 1995

Study characteristics

Methods	Open-label, multicentre trial across 63 centres in UK and Ireland 2 treatment arms: CBZ and VPS
Participants	Children with new onset primary generalised epilepsy or focal epilepsy with/without generalisation or with a recurrence of seizures following withdrawal of AED treatment were eligible given that no anticonvulsants had been received in the previous 6 months. Number randomised: CBZ = 130, VPS = 130 122 boys (47%) 108 participants with focal epilepsy (42%) Mean age (range): 10 (5-16) years
Interventions	Monotherapy with CBZ or VPS Mean daily dose achieved by month 24 CBZ = 450 mg/d, VPS = 700 mg/d

Verity 1995 *(Continued)*

	Range of follow-up: 2-59 months
Outcomes	Remission analysis (time to 6-, 12- and 24-month remission) Retention analysis (time to treatment failure) Adverse event incidence Incidence of treatment failures due to poor seizure control and adverse events
Notes	IPD provided for all outcomes of this review by trial sponsor Sanofi Results in the published paper were given for 244 children out of 260 analysed by "intention to treat" (children randomised and with data for at least one follow-up visit). IPD were provided for all 260 children randomised and used for analyses in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment using a computerised minimisation program with stratification for age, sex, seizure type and centre.
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed via central telephone allocation from the Trial Office at Sanofi Winthrop Ltd.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, ITT approach, all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Werhahn 2015

Study characteristics

Methods	Randomised, double-blind, parallel-group trial conducted in 47 centres across Germany, Austria and Switzerland 3 treatment arms: LTG, CBZ and LEV
Participants	Adults > 60 years with newly diagnosed focal seizures, with a history of at least 2 seizures and at least 1 seizure in the previous 6 months. Participants must not have taken AEDs for more than 4 weeks. Number randomised: LTG = 118, CBZ = 121, LEV = 122

Werhahn 2015 *(Continued)*

	215 male participants (60%) 100% of participants with focal epilepsy Not stated how many participants had received previous AED treatment Mean age (range): 71.5 (60-95) years
Interventions	Monotherapy with LEV, LTG or CBZ for 58 weeks 6-week escalation phase leading to CBZ = 400 mg/d, LEV = 1000 mg/d, LTG = 100 mg/d Range of follow-up: 0-54 months
Outcomes	Retention rate at week 58 Time to discontinuation from randomisation Seizure-freedom rates at week 30 and week 58 Time to first seizure from randomisation Time to first drug-related adverse event Adverse events (by severity)
Notes	IPD provided for all outcomes of this review by trial author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list for each centre (random permuted blocks) was prepared by the Interdisciplinary Centre for Clinical Trials (IZKS), Mainz, Germany.
Allocation concealment (selection bias)	Low risk	The pharmacy of the University Hospital Mainz encapsulated the trial drugs and labelled the blinded medication including the randomisation number.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and trial investigator blinded by the use of matching capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial investigator blinded; not stated if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported; all randomised participants analysed from IPD provided (see footnote 2)
Selective reporting (reporting bias)	Low risk	Protocol provided. All outcomes reported or calculated with IPD provided (see footnote 2)
Other bias	Low risk	None identified

Wu 2018

Study characteristics	
Methods	Randomised trial conducted at the Epilepsy Center Sichuan Provincial People's Hospital (China) from April 2015 to November 2016 3 treatment arms: OXC, LEV, LTG
Participants	Male participants with newly diagnosed focal or generalised epilepsy Number randomised: OXC = 16, LEV = 11, LTG = 11 100% male participants 18 (47%) with focal epilepsy Mean age (SD): OXC = 28.3 (4.65) years; LEV = 20.0 (6.12) years LTG = 27.0 (32.1) years
Interventions	Monotherapy with OXC, LEV or LTG Doses: OXC (300-900 mg/day), LEV (1000-1500 mg/day) or LTG (100-150 mg/day) Study duration: 6 months
Outcomes	Semen quality (the total number, the pH value, the fast forward movement rate (FFMR), and the survival rate of the sperm) Sexual function (International Index of Erectile Function Scale-5 and the Premature Ejaculation Diagnostic Tool Self-Assessment Scale) Levels of sex hormones (estradiol, testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin)
Notes	Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD. Results were reported in terms of before and after each drug; no differences between drugs reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were 'randomly divided into three subgroups'. No information provided on randomisation method and why the numbers across the groups were unbalanced
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated whether any randomised participants withdrew from treatment or from the study, or if an intention-to-treat approach was taken

Wu 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available and outcomes chosen for this review not reported. Semen quality, sexual function, and sex hormone outcomes well reported. No seizure or adverse event outcomes reported; unclear if data were collected on these outcomes
Other bias	Low risk	None identified

Xu 2012

Study characteristics	
Methods	Randomised trial conducted at the Sichuan Provincial Hospital, China from January 2009 to December 2010 4 treatment arms: LEV, LTG, OXC, TPM
Participants	Participants aged between 6 and 75 years with newly diagnosed focal epilepsy (diagnosed within the last 2 years), with 1 to 3 seizures per month and no previous treatment with AEDs Number randomised: 263 (10 lost to follow-up excluded but no details provided of groups to which these 10 were randomised); number included in statistical analysis: LEV = 68, LTG = 70, OXC = 57, TPM = 58 141 male participants randomised (53.6%) 100% of participants had focal epilepsy. Mean age (SD) of randomised patients: 26.4 (18.3) years
Interventions	Monotherapy with LEV, LTG, OXC or TPM No information provided on doses Trial duration: 1 year
Outcomes	Effective rate (at least 50% reduction in seizure frequency from baseline) at 1 year Retention rate at 1 year Reasons for drug withdrawal
Notes	The trial was published in Chinese; the characteristics and outcomes were translated. Outcomes chosen for this review were not reported; contact could not be made with trial author to provide IPD. Ten randomised participants lost to follow-up excluded from analyses; unclear to which group these participants were randomised. The trial design was 'initial monotherapy' and patients who did not achieve seizure control could add another drug to their monotherapy. Trial included as the effective rate was available for the monotherapy phase and adding on another drug was reflected in the retention rate

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were 'randomly' given one of four AEDs. No information provided on randomisation method and why the numbers across the groups were unbalanced

Xu 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Ten randomised participants lost to follow-up excluded from analyses; unclear to which group these participants were randomised. This was not an intention-to-treat approach. Reasons for drug withdrawal well reported for those included within analysis
Selective reporting (reporting bias)	Unclear risk	Seizure and retention outcomes described in the methods well reported. Very little detail reported on adverse events. No protocol was available. Outcomes chosen for this review were not reported.
Other bias	High risk	Design of the study unclear, particularly for how long patients received monotherapy

ADL: activities of daily living
AE: adverse event
AED: antiepileptic drug
AEP: adverse event profile
BMI: body mass index
CBCL: child behavior checklist
CBZ: carbamazepine
CR: controlled release
DHEAS: dihyroepiandrosterone sulfate
EEG: electroencephalography
EQ-5D:EuroQol- 5 Dimension
ER:extended release
ESL: eslicarbazepine acetate
FFMR: fast forward movement rate
FIN:fasting insulin levels
FSH: follicle-stimulating hormone
GBP: gabapentin
HOMA-IR: homeostasis model assessment for insulin resistance
IADL: instrumental activities of daily living
IPD: Iindividual participant data
IQ: intelligence quotient
ITT: intention-to-treat
LCM: lacosamide
LEV: levetiracetam
LH: luteinizing hormone
LOE: lack of efficacy
LTG: lamotrigine
NEWQOL: Newly Diagnosed Epilepsy Quality of Life Battery
NHS3: National Hospital Seizure Severity Scale
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin

PP: per protocol
PSG: polysomnography
QALY: quality of life adjusted year
QOLIE(-10)(-31)(-P):
RCT: randomised controlled trial
REM: rapid eye movement
SD: standard deviation
SEALS: Side Effects and Life Satisfaction
SHBG: sex hormone-binding globulin
TPM: topiramate
VPS: sodium valproate
vs: versus
WISC(-R)(-III): Wechsler Intelligence Scale for Children
ZNS: zonisamide

2. Attrition bias and reporting bias are reduced in trials for which IPD were provided, as attrition rates and unpublished outcome data were requested

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albani 2006	Conversion to monotherapy design; monotherapy comparison not possible
Alsaadi 2002	Conversion to monotherapy design; monotherapy comparison not possible
Alsaadi 2005	Conversion to monotherapy design; monotherapy comparison not possible
Baxter 1998	Participants randomised to LTG and physician's choice of CBZ or VPS. No fully randomised comparison between the drugs
Ben-Menachem 2003	Conversion to monotherapy design; monotherapy comparison not possible
Beydoun 1997	Conversion to monotherapy design; monotherapy comparison not possible
Beydoun 1998	Conversion to monotherapy design; monotherapy comparison not possible
Beydoun 2000	Conversion to monotherapy design; monotherapy comparison not possible
Bittencourt 1993	Conversion to monotherapy design; monotherapy comparison not possible
Canadian Group 1999	Conversion to monotherapy design; monotherapy comparison not possible
Cereghino 1974	Cross-over design is not appropriate for measuring long-term outcomes.
Chung 2012	Conversion to monotherapy design; monotherapy comparison not possible
DeToledo 2000	Conversion to monotherapy design; monotherapy comparison not possible
EUCTR2004-004053-26-SE	Trial terminated early; no results available
EUCTR2010-018284-42-NL	Trial terminated early; no results available
Fakhoury 2004	Conversion to monotherapy design; monotherapy comparison not possible
Foldvary-Schaefer 2017	LCM or placebo added to current treatments; monotherapy comparison not possible

Study	Reason for exclusion
French 2012	Conversion to monotherapy design; monotherapy comparison not possible
Gilliam 1998	Conversion to monotherapy design; monotherapy comparison not possible
Gruber 1962	Cross-over design is not appropriate for measuring long-term outcomes.
Hakami 2012	Conversion to monotherapy design; monotherapy comparison not possible
Hu 2012	Not a randomised study
ISRCTN73223855	Trial terminated early; no results available
Kaminow 2003	Participants randomised to LTG and physician's choice of CBZ, PHT or VPS. No fully randomised comparison between the drugs
Kerr 1999	Conversion to monotherapy design; monotherapy comparison not possible
Kerr 2001	Conversion to monotherapy design; monotherapy comparison not possible
Loiseau 1984	Cross-over design is not appropriate for measuring long-term outcomes.
Loring 2020	Ineligible unit of analysis: study randomised pairs of children and their parents and assessed only medication sensitivity.
NCT01891890	Trial terminated early; limited results for cognitive outcomes available. No results available for efficacy or safety outcomes considered within this review
Park 2001	Unclear if the study was randomised and children with ineligible seizure types for this review (generalised tonic, myoclonic and Lennox Gaustaut syndrome) appear to have been included.
Reinikainen 1984	Conversion to monotherapy design; monotherapy comparison not possible
Reinikainen 1987	Conversion to monotherapy design; monotherapy comparison not possible
Rosenow 2012	Conversion to monotherapy design; monotherapy comparison not possible
Rysz 1994	Not a randomised study (full-text article translated from Polish)
Simonsen 1975a	Conversion to monotherapy design; monotherapy comparison not possible
Simonsen 1975b	Conversion to monotherapy design; monotherapy comparison not possible
Tabrizi 2019	Study not randomised
Taragano 2003	Included participants primarily had dementia; only a subset had epilepsy

CBZ: carbamazepine
LCM; lacosamide
LTG: lamotrigine
PHT: phenytoin
VPS: sodium valproate

Characteristics of studies awaiting classification *[ordered by study ID]*

Ahadi 2020

Methods	Randomised, parallel-group design, open-label study conducted in Iran 2 treatment arms: LEV and CBZ
Participants	Children with rolandic epilepsy aged 4–12 years referred to the Pediatric Neurology Clinic at Imam Hossein Hospital, Isfahan, Iran, from April 2019 to January 2020 Number randomised LEV = 46; CBZ = 46
Interventions	Monotherapy with LEV or CBZ Doses: LEV, starting dose of 25-30 mg/kg per day; CBZ, starting dose of 15-20 mg/kg/day
Outcomes	Seizure frequency Adverse events Drug doses
Notes	Unclear if LEV and CBZ were monotherapy treatments We have attempted to contact the trial authors for more information.

Akhondian 2020

Methods	Randomised, parallel-group design, open-label study conducted in Iran 2 treatment arms: LEV and CBZ
Participants	Children with age over one year and less than sixteen years old with newly diagnosed focal epilepsy Number randomised LEV = 25; CBZ = 25
Interventions	Monotherapy with LEV or CBZ Doses: LEV, starting dose of 10 mg/kg per day, increasing by 10 mg/kg/week to target dose of 30 mg/kg/per day; CBZ, starting dose of 5 mg/kg/day, increasing by 5 mg/kg/week to a target dose of 15 mg/kg/per day
Outcomes	Occurence of seizures (from the start of the study to six months) Adverse events up to 6 months
Notes	Limited details on study design and participants available We have attempted to contact the trial authors for more information.

CTRI/2011/08/001959

Methods	Randomised, multicentre, international, double-blind trial 2 treatment arms: ESL and CBZ
Participants	Adults (above 18 years of age) with newly diagnosed focal epilepsy (with or without secondary generalisation) with at least 2 well documented, unprovoked seizures within the last 12 months

CTRI/2011/08/001959 *(Continued)*

Interventions	Monotherapy with ESL or controlled-release CBZ for 189 weeks Initial doses: ESL, 800 to 1600 mg per day; CBZ, 200 to 600 mg twice per day
Outcomes	Primary: Proportion of subjects remaining seizure-free for at least 6 months (excluding the titration period) on either drug during the evaluation period with maintenance of efficacy for at least 1 year Secondary: Other efficacy, safety, and pharmacokinetics outcomes
Notes	Trial registered as CTRI/2011/08/001959 on the International Clinical Trials Registry Platform and listed as completed Sponsored by Bial, further information and IPD requested

Du 2016

Methods	Randomised controlled trial conducted in Weifang Yidu Central Hospital, China
Participants	Children diagnosed with epilepsy based on their seizure history Number randomised: LTG = 102; VPS = 102 91 male participants (45%) Seizure types and how many participants had received previous AED treatment not stated Mean age (SD): LTG = 12.33 (6.13) years; VPS = 11.62 (7.69) years
Interventions	Treatment with LTG or VPS for at least 2 weeks Initial doses: LTG, at least 50 mg/day; VPS, 250-100 mg/kg/day
Outcomes	Mean monthly seizure frequency after VPS or LTG treatment was compared to that at 3 months before treatment. Effectiveness rate was computed as the number of patients with good efficacy (improved symptoms) normalised against the total number of patients. Influence of UGT2B7 and UGT1A4 polymorphisms on serum concentration and efficacy of LTG and VPS
Notes	Unclear if LTG and VPS were monotherapy treatments and if eligible seizure types were included We have attempted to contact the trial authors for more information.

Goyal 2016

Methods	Comparative blinded study conducted in India 4 treatment arms: CBZ, LEV, LTG, VPS
Participants	Adult epileptic participants
Interventions	Treatment with CBZ, LEV, LTG, VPS
Outcomes	Cognitive effects

Goyal 2016 *(Continued)*

Notes	Title only available; we could not find an abstract or full-text. Unclear if the study was randomised and if treatments were monotherapy. We have attempted to contact the trial authors for more information.

IRCT201202068943N1

Methods	Randomised, double-blind trial conducted at Neurology clinic of Ahvaz Golestan Hospital, Iran 2 treatment arms: OXC or PHT
Participants	Participants > 65 years with focal and secondary generalised epilepsy
Interventions	Monotherapy with PHT or OXC for 6 months Maximum dose: PHT = 600 mg/d, OXC = 600 mg/d
Outcomes	Seizure symptoms Adverse events
Notes	Trial registered as IRCT201202068943N1 on the Iranian Registry of Clinical Trials. We have attempted to contact the trial authors for more information.

NCT00154076

Methods	Phase 4, randomised, parallel-group design, open-label safety trial 2 treatment arms: TPM and ZNS
Participants	Participants > 13 years with at least 2 seizures and 1 in the 3 months prior to screening and no AEDs in the previous 4 months Estimated number enrolled = 140
Interventions	Monotherapy with TPM or ZNS Initial doses: TPM = 25 mg/d, ZNS = 100 mg/d. Maximum doses: TPM = 400 mg/d, ZNS = 600 mg/d
Outcomes	Cognitive function (change from baseline at 24 weeks)
Notes	Trial registered as NCT00154076 on ClincalTrials.gov and listed as completed with Results submitted but no results were posted on ClinicalTrials.gov. Trial sponsored by Eisai Korea; inquiries regarding this trial made to the sponsor via data sharing portal ClinicalStudyDataRequest.com but no data could be provided. If more information on this trial can be found, this trial will be included in future updates of the review.

Shi 2020

Methods	Randomised controlled trial conducted in Shanxi Children's Hospital, China

Shi 2020 *(Continued)*

Participants	Children aged 4 to 13 years with at least two unprovoked focal seizures Number randomised: LEV = 25, OXC = 26
Interventions	LEV = starting dose 10 mg/kg/day, maintenance dose 30–40 mg/kg. OXC = starting dose 5–10 mg/kg/day, maintenance dose 20–40 mg/kg
Outcomes	Thyroid hormone levels, bone metabolic markers and bone mineral density
Notes	Unclear if any efficacy (i.e. seizure outcomes) or adverse event data had been recorded We have attempted to contact the trial authors for more information.

Suo 2021

Methods	Randomised single-centre trial conducted at Affiliated Hospital of Nantong University, China
Participants	Children diagnosed with benign epilepsy with centrotemporal spikes Number randomised: LEV = 35, OXC = 35
Interventions	LEV: starting dose 10 mg/kg/day, maintenance dose 20–60 mg/kg. OXC; starting dose 8–10 mg/kg/day, maintenance dose 20–46 mg/kg
Outcomes	Seizure frequency Epileptiform activity Cognitive function
Notes	Unclear if seizure type was eligible We have attempted to contact the trial authors for more information.

Wang 2016

Methods	Randomised study conducted in Xuzhou Children's Hospital, China between August 2010 and August 2013 Two treatment arms: TPM and PHB
Participants	Children with epilepsy Number randomised: TPM = 100, PHB = 100 111 male participants (56%) 33% of participants with focal epilepsy Not stated how many participants had received previous AED treatment Mean age (SD): TPM = 4.1 ± 2.5; PB = 4.3 ± 1.9
Interventions	Treatment with TPM or PHB
Outcomes	Seizure frequency and efficiency

Wang 2016 *(Continued)*

	Epileptiform discharges
	Adverse reactions
Notes	Unclear if TPM and PB were monotherapy treatments
	We have attempted to contact the trial authors for more information.

Zhou 2019

Methods	Randomised comparative study
Participants	Children with epilepsy
Interventions	Treatment with LEV or VPS
Outcomes	Cognitive function
	Seizure frequency
Notes	Abstract only available; unclear if LEV and VPS were monotherapy treatments and if eligible seizure types were included
	We have attempted to contact the trial authors for more information.

AED: antiepileptic drug
CBZ: carbamazepine
CR: control released
ESL: eslicarbazepine acetate
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHT: phenytoin
PHB: phenobarbitone
SD: standard deviation
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2017/11/010605

Study name	Open-label randomised comparison of levetiracetam and sodium valproate monotherapy in childhood epilepsy
Methods	Open-label, parallel-group, randomised trial conducted in Delhi
	2 treatment arms: LEV and VPS
Participants	Children with newly diagnosed focal motor or generalised epilepsy
	Target enrolment = 100
Interventions	Treatment with LEV or VPS

CTRI/2017/11/010605 *(Continued)*

Outcomes	Primary outcome: Repeat seizure activity (seizure freedom) for 6 months Secondary outcomes: Side effect profile of the patients in each group Achievement of therapeutic drug levels at steady state at 6 months Time to first seizure after steady state of drug at 6 months
Starting date	01 January 2017
Contact information	Dr Anju Aggarwal and Swati Bhayana (swatibh1312@gmail.com)
Notes	Trial registered as CTRI/2017/11/010605 on the International Clinical Trials Registry Platform and listed as open to recruitment

CTRI/2019/04/018520

Study name	Comparison of the efficacy of sodium valproate with levetiracetam in controlling seizure in the age group of 2 to 18 years, a randomised control trial
Methods	Open-label, parallel-group, randomised trial conducted in Pondicherry, India 2 treatment arms: LEV and VPS
Participants	Children aged between 2 and 18 years with new onset epilepsy
Interventions	LEV: 1 to 20 mg/kg/day increased by 10 mg/kg/day every 1-2 weeks up to 40-60 mg/kg/day and VPS: 20 to 60 mg/kg/day for 6 months
Outcomes	Percentage of children seizure-free for 3 continuous months Seizure reduction by 50% Number of patients with relapse status Adverse effect and toxicity profile
Starting date	09 April 2019
Contact information	Dr Kalyanaprabhakaran B (prabha146167@gmail.com)
Notes	Trial registered as CTRI/2019/04/018520 on the International Clinical Trials Registry Platform and listed as open to recruitment

CTRI/2019/05/018990

Study name	Comparison of the seizure drug levetiracetam with controlled release carbamazepine in new focal seizure patients
Methods	Open-label, parallel-group, randomised trial conducted in Himachal Pradesh, India 2 treatment arms: LEV and CBZ
Participants	Adults aged 18 years or over with newly diagnosed focal seizures
Interventions	LEV: 500 mg twice daily and titrated up to 3000 mg per day depending upon seizure control.

CTRI/2019/05/018990 *(Continued)*

	Controlled release CBZ: 300 mg twice daily after adequate buildup and titrated up to 1200 mg per day depending upon seizure control
Outcomes	Adverse drug reactions Seizure freedom at 6 months Quality of life at 6 months Pharmacoeconomics
Starting date	08 May 2019
Contact information	Dr Nitin Patiyal (nitin.jadu@gmail.com)
Notes	Trial registered as CTRI/2019/05/018990 on the International Clinical Trials Registry Platform and listed as completed with post marketing surveillance ongoing

CTRI/2020/09/027792

Study name	Open-label randomised controlled trial comparing efficacy of oral levetiracetam v/s sodium valproate as first-line monotherapy in newly diagnosed generalised epilepsy in children
Methods	Open-label, parallel-group, randomised trial conducted in Aurangabad, India 2 treatment arms: LEV and VPS
Participants	Children aged between 2 and 18 years diagnosed with generalised epilepsy attending a tertiary care hospital in Aurangabad, India
Interventions	LEV: 20 to 70 mg/kg/day and VPS: 15 to 35 mg/kg/day for 1 year
Outcomes	'Effect' (i.e. efficacy) Side effects
Starting date	15 September 2020
Contact information	Dr Pritamkumar Bhagwan Chimane (pritamkumar.chimane@gmail.com)
Notes	Trial registered as CTRI/2020/09/027792 on the International Clinical Trials Registry Platform and listed as 'Not Yet Recruiting'

EpiNet-First Trial 1

Study name	EpiNet-First Trial 1: Comparison of efficacy of levetiracetam, lamotrigine and carbamazepine in people with previously untreated epilepsy who have focal seizures
Methods	Phase 4 randomised, open-label, pragmatic trial conducted across sites in New Zealand and Europe 3 treatment arms: CBZ, LEV and LTG
Participants	Individuals > 5 years with ≥ 2 spontaneous generalised seizures that require AED treatment (provided all seizures have not been absence seizures)

EpiNet-First Trial 1 *(Continued)*

	Target sample size = 1467
Interventions	Monotherapy with CBZ, LEV or LTG Target doses CBZ: 250 mg-4000 mg, LEV: 250 mg-4000 mg, LTG: 250 mg-400 mg
Outcomes	Time to 12-month remission from seizures Proportion of participants who achieve a seizure-free 12-month remission by 18 months AND who have not changed to a different AED Time to treatment failure due to either inadequate seizure control, or due to unacceptable adverse events Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Serious adverse events attributed to the trial medication or other antiepileptic medication Quality of life as assessed by the QOLIE-31 and QOLIE-48 questionnaires
Starting date	May 2015
Contact information	Dr Peter Bergin (pbergin@adhb.govt.nz)
Notes	Trial was registered as ACTRN12615000643572 on the Australian New Zealand Clinical Trials Registry and is listed as currently recruiting participants. Principal investigator confirmed (January 2020) that recruitment will be reviewed in late 2020.

EpiNet-First Trial 2

Study name	EpiNet-First Trial 2: Comparison of efficacy of levetiracetam and sodium valproate in people with previously untreated epilepsy who have generalised seizures
Methods	Phase 4 randomised, open-label, pragmatic trial conducted across sites in New Zealand and Europe 2 treatment arms: LEV and VPS
Participants	Individuals > 5 years with ≥ 2 spontaneous generalised seizures that require AED treatment (provided all seizures have not been absence seizures) Target sample size = 506
Interventions	Monotherapy with LEV or VPS Target doses LEV: 250 mg-4000 mg, VPS: 250 mg-400 mg
Outcomes	Time to 12-month remission from seizures Proportion of participants who achieve a seizure-free 12-month remission by 18 months AND who have not changed to a different AED Time to treatment failure due to either inadequate seizure control, or due to unacceptable adverse events

EpiNet-First Trial 2 *(Continued)*

	Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission. Serious adverse events attributed to the trial medication or other AED Quality of life as assessed by the QOLIE-31 and QOLIE-48 questionnaires
Starting date	May 2015
Contact information	Dr Peter Bergin (pbergin@adhb.govt.nz)
Notes	Trial was registered as ACTRN12615000556549 on the Australian New Zealand Clinical Trials Registry and is listed as currently recruiting participants. Principal investigator confirmed (January 2020) that recruitment will be reviewed in late 2020.

EpiNet-First Trial 3

Study name	EpiNet-First Trial 3: Comparison of efficacy of levetiracetam and lamotrigine in people with previously untreated epilepsy who have generalised seizures, and for whom sodium valproate is not deemed an acceptable antiepileptic drug
Methods	Phase 4 randomised, open-label, pragmatic trial conducted across sites in New Zealand and Europe 2 treatment arms: LEV and LTG
Participants	Individuals > 5 years with ≥ 2 spontaneous generalised seizures that require AED treatment (provided all seizures have not been absence seizures) Target sample size = 664
Interventions	Monotherapy with LEV or LTG Target doses LEV: 250 mg-4000 mg, LTG: 250 mg-400 mg
Outcomes	Time to 12-month remission from seizures Proportion of participants who achieve a seizure-free 12-month remission by 18 months AND who have not changed to a different AED Time to treatment failure due to either inadequate seizure control, or due to unacceptable adverse events Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Serious adverse events attributed to the trial medication or other antiepileptic medication Quality of life as assessed by the QOLIE-31 and QOLIE-48 questionnaires

EpiNet-First Trial 3 *(Continued)*

Starting date	May 2015
Contact information	Dr Peter Bergin (pbergin@adhb.govt.nz)
Notes	Trial was registered as ACTRN12615000639527 on the Australian New Zealand Clinical Trials Registry and is listed as currently recruiting participants. Principal investigator confirmed (January 2020) that recruitment will be reviewed in late 2020.

EpiNet-First Trial 4

Study name	EpiNet-First Trial 4: Comparison of efficacy of levetiracetam, lamotrigine and sodium valproate in people with previously untreated epilepsy who have unclassified seizures
Methods	Phase 4 randomised, open-label, pragmatic trial conducted across sites in New Zealand and Europe Three treatment arms: LEV, LTG and VPS
Participants	Individuals > 5 years with ≥ 2 spontaneous generalised seizures that require AED treatment (provided all seizures have not been absence seizures) Target sample size = 1176
Interventions	Monotherapy with LEV, LTG or VPS Target doses LEV: 250 mg-4000 mg, LTG 250 mg-400 mg, VPS: 250 mg-400 mg
Outcomes	Time to 12-month remission from seizures Proportion of participants who achieve a seizure-free 12-month remission by 18 months AND who have not changed to a different AED Time to treatment failure due to either inadequate seizure control, or due to unacceptable adverse events Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Serious adverse events attributed to the trial medication or other AED Quality of life as assessed by the QOLIE-31 and QOLIE-48 questionnaires
Starting date	May 2015
Contact information	Dr Peter Bergin (pbergin@adhb.govt.nz)
Notes	Trial was registered as ACTRN12615000640505 on the Australian New Zealand Clinical Trials Registry and is listed as currently recruiting participants. Principal investigator confirmed (January 2020) that recruitment will be reviewed in late 2020.

EpiNet-First Trial 5

Study name	EpiNet-First Trial 5: Comparison of efficacy of levetiracetam and lamotrigine in people with previously untreated epilepsy who have unclassified seizures, and for whom sodium valproate is not deemed an acceptable AED
Methods	Phase 4 randomised, open-label, pragmatic trial conducted across sites in New Zealand and Europe 2 treatment arms: LEV and LTG
Participants	Individuals > 5 years with ≥ 2 spontaneous generalised seizures that require AED treatment (provided all seizures have not been absence seizures) Target sample size = 664
Interventions	Monotherapy with LEV or LTG Target doses LEV: 250 mg-4000 mg, LTG: 250 mg-400 mg
Outcomes	Time to 12-month remission from seizures Proportion of participants who achieve a seizure-free 12-month remission by 18 months AND who have not changed to a different AED Time to treatment failure due to either inadequate seizure control, or due to unacceptable adverse events Time to treatment failure due to inadequate seizure control Time to treatment failure due to unacceptable adverse events Time to first seizure Time to 24-month remission Serious adverse events attributed to the trial medication or other antiepileptic medication Quality of life as assessed by the QOLIE-31 and QOLIE-48 questionnaires
Starting date	May 2015
Contact information	Dr Peter Bergin (pbergin@adhb.govt.nz)
Notes	Trial was registered as ACTRN12615000641594 on the Australian New Zealand Clinical Trials Registry and is listed as currently recruiting participants. Principal investigator confirmed (January 2020) that recruitment will be reviewed in late 2020.

IRCT20120215009014N351

Study name	Effect of levetiracetam monotherapy versus sodium valproate on treatment of children with generalized or focal epilepsy
Methods	Randomised, phase II, clinical trial 2 treatment arms: LEV and VPS
Participants	Children aged 2 to 18 years old with a diagnosis of focal or generalised epilepsy
Interventions	LEV: 30 mg/kg every 12 hours or VPS: 30 mg/kg every 12 hours for 18 months

IRCT20120215009014N351 *(Continued)*

Outcomes	Seizure frequency Blood complication
Starting date	23 July 2019
Contact information	Jalal Poorolajal (poorolajal@umsha.ac.ir)
Notes	Trial registered as IRCT20120215009014N351 on the Iranian Registry of Clinical Trials and listed as 'recruitment complete'. We have attempted to contact the trial authors for more information.

IRCT20170216032603N2

Study name	Analysis of the efficacy and side effects of levetiracetam and carbamazepine on treatment of children's epilepsy
Methods	Randomised, open-label, clinical trial 2 treatment arms: LEV and CBZ
Participants	Children aged 2 to 14 years old with a diagnosis of focal epilepsy
Interventions	LEV: starting dose 10 mg/kg twice a day, increasing by 10 mg/kg per week to reach a dose of 30 mg/kg per day CBZ: starting dose of 5 mg/kg twice a day, increasing by 5 kg/kg per week to reach a dose of 15 mg/kg per day
Outcomes	Efficacy (no specific outcomes listed) Side effects
Starting date	02 February 2020
Contact information	Hadi Montazer Lotf Elahi (h-mlotfelahi@razi.tums.ac.ir)
Notes	Trial registered as IRCT20170216032603N2 on the Iranian Registry of Clinical Trials and listed as 'recruitment complete'. We have attempted to contact the trial authors for more information.

NCT02201251

Study name	A study to investigate the safety of the drugs topiramate and levetiracetam in treating children recently diagnosed with epilepsy
Methods	Phase 3, randomised, open-label, parallel-group trial conducted in multiple centres in the USA, South America, Asia and Europe 2 treatment arms: LEV and TPM

NCT02201251 *(Continued)*

Participants	Participants with a clinical diagnosis of new-onset or recent-onset epilepsy characterised by focal-onset seizures (with or without secondary generalisation) or primary generalised tonic-clonic seizures with no previous treatment for epilepsy (except emergency treatment) Estimated enrolment = 282
Interventions	Monotherapy with LEV or TPM Maximum recommended doses: LEV, 3000 mg/d; TPM, 400 mg/d
Outcomes	Percentage of participants with kidney stones Change from baseline in weight Z-score at month 12 Change from baseline in height at month 12 Change from baseline in bone mineral density (BMD) at month 12 (other measures of weight, height and bone density specified on trial registration page)
Starting date	October 2014
Contact information	Janssen Research & Development
Notes	Trial registered as NCT02201251 on ClincalTrials.gov and listed as completed. Estimated finishing date is November 2021.

AED: antiepileptic drug
BMD: bone mineral density
CBZ: carbamazepine
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
QOLIE(-31)(-48): quality of life in epilepsy (31 item and 48 item)
TPM: topiramate
VPS: sodium valproate

ADDITIONAL TABLES

Table 1. Number of participants randomised to each drug

Trial\Drug	CBZ	PHB	PHT	VPS	LTG	OXC	LEV	TPM	GBP	ZNS	LCM	ESL	Total	Total randomised[a]
Trials providing individual participant data														
Banu 2007	54	54	0	0	0	0	0	0	0	0	0	0	108	108
Baulac 2012	301	0	0	0	0	0	0	0	0	282	0	0	583	583
Baulac 2017	443	0	0	0	0	0	0	0	0	0	445	0	888	888
Bill 1997	0	0	144	0	0	143	0	0	0	0	0	0	287	287
Biton 2001	0	0	0	69	66	0	0	0	0	0	0	0	135	136
Brodie 1995a	66	0	0	0	70	0	0	0	0	0	0	0	136	136
Brodie 1995b	63	0	0	0	61	0	0	0	0	0	0	0	124	124
Brodie 1999	48	0	0	0	102	0	0	0	0	0	0	0	150	150
Brodie 2007	291	0	0	0	0	0	288	0	0	0	0	0	579	579
Chadwick 1998	74	0	0	0	0	0	0	0	218	0	0	0	292	292
Craig 1994	0	0	81	85	0	0	0	0	0	0	0	0	166	166
De Silva 1996	54	10	54	49	0	0	0	0	0	0	0	0	167	173
Dizdarer 2000	26	0	0	0	0	26	0	0	0	0	0	0	52	52
Eun 2012	41	0	0	0	43	0	0	0	0	0	0	0	84	84
Guerreiro 1997	0	0	94	0	0	99	0	0	0	0	0	0	193	193
Heller 1995	61	58	63	61	0	0	0	0	0	0	0	0	243	243
Kwan 2009	0	0	0	44	37	0	0	0	0	0	0	0	81	81

Table 1. Number of participants randomised to each drug *(Continued)*

Lee 2011	53	0	0	0	57	0	0	0	0	0	0	0	110	110
Mattson 1985	155	155	165	0	0	0	0	0	0	0	0	0	475	475
Mattson 1992	236	0	0	244	0	0	0	0	0	0	0	0	480	480
Nieto-Barrera 2001	202	0	0	0	420	0	0	0	0	0	0	0	622	622
Ogunrin 2005	19	18	18	0	0	0	0	0	0	0	0	0	55	55
Pal 1998	0	47	47	0	0	0	0	0	0	0	0	0	94	94
Placencia 1993	95	97	0	0	0	0	0	0	0	0	0	0	192	192
Privitera 2003 (CBZ branch)[b]	129	0	0	0	0	0	0	266	0	0	0	0	395	395
Privitera 2003 (VPS branch)[b]	0	0	0	78	0	0	0	147	0	0	0	0	225	225
Ramsay 1992	0	0	50	86	0	0	0	0	0	0	0	0	136	136
Ramsay 2010	0	0	128	0	0	0	0	133	0	0	0	0	261	261
Reunanen 1996	121	0	0	0	230	0	0	0	0	0	0	0	351	351
Richens 1994	151	0	0	149	0	0	0	0	0	0	0	0	300	300
SANAD A 2007	378	0	0	0	378	210	0	378	377	0	0	0	1721	1721
SANAD II A 2021	0	0	0	0	330	0	330	0	0	330	0	0	990	990
SANAD B 2007	0	0	0	238	239	0	0	239	0	0	0	0	716	716
SANAD II B 2021	0	0	0	260	0	0	260	0	0	0	0	0	520	520
Steiner 1999	0	0	95	0	86	0	0	0	0	0	0	0	181	181
Stephen 2007	0	0	0	109	117	0	0	0	0	0	0	0	226	227
Trinka 2013 (CBZ branch)[b]	503	0	0	0	0	0	493	0	0	0	0	0	996	999

Table 1. Number of participants randomised to each drug *(Continued)*

Trinka 2013 (VPS branch)[b]	0	0	0	353	0	0	350	0	0	0	0	0	703	703
Turnbull 1985	0	0	70	70	0	0	0	0	0	0	0	0	140	140
Verity 1995	130	0	0	130	0	0	0	0	0	0	0	0	260	260
Werhahn 2015	121	0	0	0	118	0	122	0	0	0	0	0	361	361
Total	***3815***	***439***	***1009***	***2025***	***2354***	***478***	***1843***	***1163***	***595***	***612***	***445***	***0***	***14,778***	***14,789***
Trials not providing individual participant data														
Trial\Drug	**CBZ**	**PHB**	**PHT**	**VPS**	**LTG**	**OXC**	**LEV**	**TPM**	**GBP**	**ZNS**	**LCM**	**ESL**	**Total**	**Total randomised[a]**
Aikia 1992	0	0	18	0	0	19	0	0	0	0	0	0	37	37
Akter 2018	0	68	0	0	0	0	50	0	0	0	0	0	118	118
Bidabadi 2009	36	35	0	0	0	0	0	0	0	0	0	0	71	71
Brodie 2002	0	0	0	0	151	0	0	0	158	0	0	0	309	309
Callaghan 1985	59	0	58	64	0	0	0	0	0	0	0	0	181	181
Capone 2008	17	0	0	0	0	0	18	0	0	0	0	0	35	35
Castriota 2008	14	0	0	0	0	0	13	0	0	0	0	0	27	27
Chen 1996	26	25	0	25	0	0	0	0	0	0	0	0	76	76
Chen 2013	60	0	0	0	0	58	0	0	0	0	0	0	118	118
Cho 2011	15	0	0	0	0	0	16	0	0	0	0	0	31	31
Christe 1997	0	0	0	121	0	128	0	0	0	0	0	0	249	249
Consoli 2012	66	0	0	0	0	0	62	0	0	0	0	0	128	128

Table 1. Number of participants randomised to each drug *(Continued)*

Cossu 1984	6	6	0	0	0	0	0	0	0	0	0	0	12	12
Czapinski 1997	30	30	30	30	0	0	0	0	0	0	0	0	120	120
Dam 1989	100	0	0	0	0	94	0	0	0	0	0	0	194	194
Donati 2007	28	0	0	29	0	55	0	0	0	0	0	0	112	112
Feksi 1991	152	150	0	0	0	0	0	0	0	0	0	0	302	302
Forsythe 1991	23	0	20	21	0	0	0	0	0	0	0	0	64	64
Fritz 2006	0	0	0	0	21	27	0	0	0	0	0	0	48	48
Gilad 2007	32	0	0	0	32	0	0	0	0	0	0	0	64	64
Giri 2016	0	0	0	30	30	0	0	0	0	0	0	0	60	60
Jung 2015	64	0	0	0	0	0	57	0	0	0	0	0	121	121
Kalviainen 2002	70	0	0	0	73	0	0	0	0	0	0	0	143	143
Kim 2017	0	0	0	0	0	178	175	0	0	0	0	0	353	353
Kopp 2007	6	0	0	3	0	0	6	0	0	0	0	0	15	15
Korean Lamotrigine Study Group 2008	129	0	0	0	264	0	0	0	0	0	0	0	393	393
Korean Zonisamide Study 1999	82	0	0	0	0	0	0	0	0	73	0	0	155	155
Lukic 2005	0	0	0	38	35	0	0	0	0	0	0	0	73	73
Maiti 2018	30	0	0	0	0	30	0	0	0	0	0	0	60	60
Mitchell 1987	15	18	0	0	0	0	0	0	0	0	0	0	33	33
Miura 1990	66	0	51	46	0	0	0	0	0	0	0	0	163	163
Motamedi 2013	0	0	0	0	50	0	50	0	0	0	0	0	100	100

Table 1. Number of participants randomised to each drug *(Continued)*

NCT01954121	215	0	0	0	0	0	218	0	0	0	0	0	433	433
Pulliainen 1994	23	0	20	0	0	0	0	0	0	0	0	0	43	43
Ramsay 1983	42	0	45	0	0	0	0	0	0	0	0	0	87	87
Ramsay 2007 [c]	?	0	0	0	0	0	?	0	0	0	0	0	37	37
Rastogi 1991	0	0	45	49	0	0	0	0	0	0	0	0	94	94
Ravi Sudhir 1995	20	0	20	0	0	0	0	0	0	0	0	0	40	40
Resendiz 2004	42	0	0	0	0	0	0	46	0	0	0	0	88	88
Rowan 2005	198	0	0	0	200	0	0	0	195	0	0	0	593	593
Saetre 2007	92	0	0	0	93	0	0	0	0	0	0	0	185	185
Shakir 1981	0	0	15	18	0	0	0	0	0	0	0	0	33	33
Sidhu 2018	0	0	0	34	32	0	0	0	0	0	0	0	66	66
So 1992	17	0	0	16	0	0	0	0	0	0	0	0	33	33
Suresh 2015	30	0	0	0	0	0	30	0	0	0	0	0	60	60
Steinhoff 2005	88	0	0	30	121	0	0	0	0	0	0	0	239	239
Thilothammal 1996	0	51	52	48	0	0	0	0	0	0	0	0	151	151
Trinka 2018	412	0	0	0	0	0	0	0	0	0	0	401	813	813
Wu 2018	0	0	0	0	11	16	11	0	0	0	0	0	38	38
Xu 2012	0	0	0	0	70	57	68	58	0	0	0	0	253	253
Total[c]	***2305***	***383***	***374***	***602***	***1183***	***662***	***774***	***104***	***353***	***73***	***0***	***401***	***7251***	***7251***
Grand total[c]	**6120**	**822**	**1383**	**2627**	**3537**	**1140**	**2617**	**1267**	**948**	**685**	**445**	**401**	***22,029***	***22,040***
Proportion of IPD	**62%**	**53%**	**73%**	**77%**	**67%**	**42%**	**70%**	**92%**	**63%**	**89%**	**100%**	**0%**	**67%**	**67%**

CBZ: carbamazepine
ESL: eslicarbazepine acetate
GBP: gabapentin
IPD: individual participant data
ITT: intention-to-treat
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

[a]Drug allocated missing for 11 participants provided in the IPD

[b]Trials designed in two strata based on whether recommended treatment would be CBZ or VPS. Within the two strata, participants were randomised to TPM in Privitera 2003/LEV in Trinka 2013 or CBZ/VPS depending on the strata. Data analysed according to the separate strata (CBZ branch or VPS branch) in this review

[c]One trial provided the total number randomised but not the numbers randomised to each group. The 37 participants randomised were counted in the overall totals.

Table 2. Characteristics of participants providing individual participant data (categorical variables)

Trial	Gender			Epilepsy type			Epilepsy type reclassified[c]		
	Male	Female	Missing	Gen[b]	Focal	Missing	Gen[b]	Focal	Unclassified[d]
Banu 2007	61 (56%)	47 (44%)	0 (0%)	49 (45%)	59 (55%)	0 (0%)	49 (45%)	59 (55%)	0 (0%)
Baulac 2012	347 (60%)	236 (40%)	0 (0%)	0 (0%)	583 (100%)	0 (0%)	0 (0%)	583 (100%)	0 (0%)
Baulac 2017	475 (53%)	413 (47%)	0 (0%)	80 (9%)	808 (91%)	0 (0%)	0 (0%)	822 (93%)	66 (7%)
Bill 1997	174 (61%)	113 (39%)	0 (0%)	105 (37%)	182 (63%)	0 (0%)	78 (27%)	182 (63%)	27 (9%)
Biton 2001	60 (44%)	75 (55%)	1 (1%)	46 (34%)	82 (60%)	8 (6%)	33 (24%)	82 (60%)	21 (15%)
Brodie 1995a	56 (41%)	80 (59%)	0 (0%)	54 (40%)	82 (60%)	0 (0%)	35 (26%)	82 (60%)	19 (14%)
Brodie 1995b	56 (45%)	68 (55%)	0 (0%)	62 (50%)	62 (50%)	0 (0%)	40 (32%)	62 (50%)	22 (18%)
Brodie 1999	83 (55%)	67 (45%)	0 (0%)	45 (30%)	105 (70%)	0 (0%)	0 (0%)	105 (70%)	45 (30%)
Brodie 2007	319 (55%)	260 (45%)	0 (0%)	113 (20%)	466 (80%)	0 (0%)	46 (8%)	466 (80%)	67 (12%)

Table 2. Characteristics of participants providing individual participant data (categorical variables) *(Continued)*

Chadwick 1998	157 (54%)	135 (46%)	0 (0%)	0 (0%)	292 (100%)	0 (0%)	0 (0%)	292 (100%)	0 (0%)
Craig 1994	71 (43%)	92 (55%)	3 (2%)	86 (52%)	80 (48%)	0 (0%)	2 (1%)	80 (48%)	84 (51%)
De Silva 1996	86 (50%)	81 (47%)	6 (3%)	84 (49%)	89 (51%)	0 (0%)	84 (49%)	89 (51%)	0 (0%)
Dizdarer 2000	21 (40%)	31 (60%)	0 (0%)	0 (0%)	52 (100%)	0 (0%)	0 (0%)	52 (100%)	0 (0%)
Eun 2012	48 (57%)	36 (43%)	0 (0%)	0 (0%)	84 (100%)	0 (0%)	0 (0%)	84 (100%)	0 (0%)
Guerreiro 1997	100 (52%)	93 (48%)	0 (0%)	50 (26%)	143 (74%)	0 (0%)	45 (23%)	143 (74%)	5 (3%)
Heller 1995	117 (48%)	126 (52%)	0 (0%)	141 (58%)	102 (42%)	0 (0%)	97 (40%)	102 (42%)	44 (18%)
Kwan 2009	40 (49%)	41 (51%)	0 (0%)	48 (59%)	29 (36%)	4 (5%)	22 (27%)	29 (36%)	30 (37%)
Lee 2011	57 (52%)	53 (48%)	0 (0%)	15 (14%)	95 (86%)	0 (0%)	6 (5%)	95 (86%)	9 (8%)
Mattson 1985	413 (87%)	58 (12%)	4 (1%)	1 (0%)	474 (100%)	0 (0%)	1 (0%)	474 (100%)	0 (0%)
Mattson 1992	445 (93%)	35 (7%)	0 (0%)	0 (0%)	480 (100%)	0 (0%)	0 (0%)	480 (100%)	0 (0%)
Nieto-Barrera 2001	329 (53%)	293 (47%)	0 (0%)	3 (1%)	619 (99%)	0 (0%)	1 (0%)	619 (100%)	2 (0%)
Ogunrin 2005	34 (62%)	21 (38%)	0 (0%)	45 (82%)	10 (18%)	0 (0%)	30 (55%)	10 (18%)	15 (27%)
Pal 1998	47 (50%)	45 (48%)	2 (2%)	34 (36%)	60 (64%)	0 (0%)	34 (36%)	60 (64%)	0 (0%)
Placencia 1993	67 (35%)	125 (65%)	0 (0%)	59 (31%)	133 (69%)	0 (0%)	50 (26%)	133 (69%)	9 (5%)
Privitera 2003 (CBZ branch)[a]	215 (54%)	180 (46%)	0 (0%)	88 (22%)	285 (72%)	22 (6%)	50 (13%)	285 (72%)	60 (15%)
Privitera 2003 (VPS branch)[a]	112 (50%)	113 (50%)	0 (0%)	131 (58%)	78 (35%)	16 (7%)	85 (38%)	78 (35%)	62 (27%)
Ramsay 1992	73 (54%)	63 (46%)	0 (0%)	136 (100%)	0 (0%)	0 (0%)	111 (82%)	0 (0%)	25 (18%)
Ramsay 2010	126 (48%)	135 (52%)	0 (0%)	150 (57%)	53 (20%)	58 (22%)	78 (30%)	53 (20%)	130 (50%)

Table 2. Characteristics of participants providing individual participant data (categorical variables) *(Continued)*

Reunanen 1996	188 (54%)	163 (46%)	0 (0%)	114 (32%)	237 (68%)	0 (0%)	76 (22%)	237 (67%)	38 (11%)
Richens 1994	153 (51%)	147 (49%)	0 (0%)	154 (51%)	146 (49%)	0 (0%)	86 (29%)	146 (49%)	68 (22%)
SANAD A 2007	944 (55%)	777 (45%)	0 (0%)	190 (11%)	1531 (89%)	0 (0%)	36 (2%)	1531 (89%)	154 (9%)
SANAD B 2007	427 (60%)	289 (40%)	0 (0%)	661 (92%)	54 (8%)	0 (0%)	469 (65%)	54 (8%)	193 (27%)
SANAD II A 2021	561 (57%)	429 (43%)	0 (0%)	0 (0%)	990 (100%)	0 (0%)	0 (0%)	984 (99%)	9 (1%)
SANAD II B 2021	337 (65%)	183 (35%)	0 (0%)	520 (100%)	0 (0%)	0 (0%)	385 (74%)	0 (0%)	135 (26%)
Steiner 1999	101 (56%)	80 (44%)	0 (0%)	91 (50%)	90 (50%)	0 (0%)	57 (31%)	90 (50%)	34 (19%)
Stephen 2007	114 (50%)	112 (49%)	1 (0%)	32 (14%)	154 (68%)	41 (18%)	29 (13%)	154 (68%)	44 (19%)
Trinka 2013 (CBZ branch)[a]	551 (55%)	448 (45%)	0 (0%)	141 (14%)	858 (86%)	0 (0%)	46 (5%)	858 (86%)	95 (9%)
Trinka 2013 (VPS branch)[a]	398 (57%)	305 (43%)	0 (0%)	513 (73%)	190 (27%)	0 (0%)	274 (39%)	190 (27%)	239 (34%)
Turnbull 1985	73 (52%)	67 (48%)	0 (0%)	77 (55%)	63 (45%)	0 (0%)	45 (32%)	63 (45%)	32 (23%)
Verity 1995	122 (47%)	138 (53%)	0 (0%)	152 (58%)	108 (42%)	0 (0%)	152 (58%)	108 (42%)	0 (0%)
Werhahn 2015	215 (60%)	146 (40%)	0 (0%)	0 (0%)	361 (100%)	0 (0%)	0 (0%)	361 (100%)	0 (0%)
Total	**8373 (57%)**	**6399 (43%)**	**17 (< 1%)**	**4270 (29%)**	**10,369 (70%)**	**150 (1%)**	**2632 (18%)**	**10,377 (70%)**	**1780 (12%)**

CBZ: carbamazepine
LEV: levetiracetam
TPM: topiramate
VPS: sodium valproate

[a]Trials designed in two strata based on whether recommended treatment would be CBZ or VPS. Within the two strata, participants were randomised to TPM in Privitera 2003/LEV in Trinka 2013 or CBZ/VPS depending on the strata. Data analysed according to the separate strata (CBZ branch or VPS branch) in this review
[b]Gen: Generalised tonic-clonic seizures with or without other seizure types
[c]See Sensitivity analysis for further details of misclassification of epilepsy type
[d]Unclassified seizures defined as missing seizure type or generalised onset seizures and age of onset of seizures over the age of 30 years (see Sensitivity analysis for further details)

Table 3. Characteristics of participants providing individual participant data (continuous variables)

Trial	Age (years)				Epilepsy duration (years)			Number of seizures in the last 6 months		
	Mean	SD	Range	Missing	Median	Range	Missing	Median	Range	Missing
Banu 2007	5.7	3.5	1 to 15	0	1.2	0 to 11.5	0	24	1 to 7200	5
Baulac 2012	36.4	15.9	18 to 75	0	0.2	0 to 17.7	30	2	1 to 30	1
Baulac 2017	41.9[b]	17.5[b]	16 to 73[b]	2	0.8	0 to 40.3	2	4	1 to 1930	12
Bill 1997	26.8	10.7	15 to 91	1	0.4	0 to 25	0	3	0 to 252	0
Biton 2001	32.0	14.5	12 to 76	0	1	0 to 53	27	2	0 to 100	2
Brodie 1995a	34.0	15.8	13 to 70	0	1	0 to 17.9	0	4	1 to 960	0
Brodie 1995b	30.0	14.1	14 to 81	0	0.5	0 to 19.4	0	3	1 to 1020	0
Brodie 1999	76.9	6.0	65 to 94	0	NA	NA	150	3	0 to 163	0
Brodie 2007	39.0	16.2	15 to 82	0	NA	NA	579	3	1 to 1410	4
Chadwick 1998	35.7	16.6	12 to 86	0	0.3	0 to 7.7	5	4	1 to 146	6
Craig 1994	78.2	7.1	61 to 95	3	NA	NA	166	3	0 to 99	3
De Silva 1996	9.9	3.6	2 to 15	6	0.5	0 to 13.7	6	3	1 to 900	6
Dizdarer 2000	10.8	2.3	4 to 15	0	NA	NA	52	3	1 to 60	0
Eun 2012	8.8	2.1	5 to 13	0	0.4	0 to 4.5	0	3	2 to 11	0
Guerreiro 1997	18.6	9.7	5 to 53	1	0.4	0 to 20	0	2	0 to 157	0
Heller 1995	32.3	14.8	13 to 77	3	1	0 to 39.8	4	2	1 to 579	3
Kwan 2009	33.9	10.9	16 to 56	0	NA	NA	81	1	0 to 540	0

Table 3. Characteristics of participants providing individual participant data (continuous variables) *(Continued)*

Lee 2011	35.8	12.2	16 to 60	0	NA	NA	110	2	0 to 200	0
Mattson 1985	41.0	15.5	18 to 82	4	2	0.5 to 59	5	1	1 to 100	7
Mattson 1992	47.1	16.1	18 to 83	0	3	1 to 68	19	12	1 to 2248	38
Nieto-Barrera 2001	27.2	21.4	2 to 83	1	NA	NA	622	3	1 to 9000	0
Ogunrin 2005	27.5	8.5	14 to 55	0	7	3 to 11.5	18	12	6 to 42	0
Pal 1998	11.4	5.0	2 to 18	0	2.5	0.5 to 17	2	NA	NA	94
Placencia 1993	29.0	17.6	2 to 68	0	5	0.5 to 44	0	2	0 to 100	0
Privitera 2003 (CBZ branch)[a]	34.4	18.4	6 to 80	0	NA	NA	395	4	0 to 2400	0
Privitera 2003 (VPS branch)[a]	32.8	19.4	6 to 84	0	NA	NA	225	4	0 to 20000	0
Ramsay 1992	20.9	14.2	3 to 64	0	0	0 to 3	15	NA	NA	136
Ramsay 2010	34.1	14.8	12 to 78	0	NA	NA	261	4	0 to 570	0
Reunanen 1996	32.1	14.2	12 to 72	2	0.7	0 to 26.8	3	3	1 to 145	1
Richens 1994	33.0	14.9	16 to 79	2	NA	NA	300	4	2 to 101	5
SANAD A 2007	38.3	18.2	5 to 86	0	1.4	0 to 68.6	1	4	0 to 1184	5
SANAD B 2007	22.5	14.0	5 to 77	0	1.3	0 to 60.8	0	3	0 to 2812	3
SANAD II A 2021	38.8	21.2	5 to 91	0	1	0 to 59.3	7	6	1 to 99[c]	1
SANAD II B 2021	16.5	12.3	5 to 94	0	0.7	0 to 54.0	10	10	1 to 99[c]	6
Steiner 1999	34.1	16.7	13 to 74	1	1.3	0 to 28.5	1	3	1 to 600	0
Stephen 2007	36.0	16.9	13 to 80	2	NA	NA	227	18	6 to 1080	37
Trinka 2013	42.8	17.2	16 to 89	0	NA	NA	999	NA	NA	999

Table 3. Characteristics of participants providing individual participant data (continuous variables) *(Continued)*

(CBZ branch)[a]										
Trinka 2013	36.5	17.8	16 to 85	1	NA	NA	703	NA	NA	703
(VPS branch)[a]										
Turnbull 1985	35.2	16.1	14 to 70	0	0.8	0.1 to 30	0	2	0 to 60	0
Verity 1995	10.1	2.9	4 to 15	13	0.3	0 to 5.9	32	3	1 to 104	12
Werhahn 2015	71.5	7.2	60 to 95	0	NA	NA	361	2	1 to 96	7
Total (missing)				**42 (< 1%)**			**7820 (47%)**			**2096 (14%)**

CBZ: carbamazepine
IPD: individual participant data
LEV: levetiracetam
NA: not available (i.e. data not provided)
SD: standard deviation
TPM: topiramate
VPS: sodium valproate

[a]Trials designed in two strata based on whether recommended treatment would be CBZ or VPS. Within the two strata, participants were randomised to TPM in Privitera 2003/LEV in Trinka 2013 or CBZ/VPS depending on the strata. Data analysed according to the separate strata (CBZ branch or VPS branch) in this review
[b]Exact age not provided in IPD; age intervals only provided (largest age interval > 73 years). Mean age and SD calculated from aggregate data taken from Baulac 2017 journal article

Table 4. Characteristics of participants providing individual participant data (baseline investigations)

Trial	EEG results			CT or MRI scan results			Neurological assessment		
	Normal	Abnormal	Missing	Normal	Abnormal	Missing	Normal	Abnormal	Missing
Banu 2007	49 (45%)	54 (50%)	5 (5%)	21 (19%)	5 (5%)	82 (76%)	0 (0%)	0 (0%)	108 (100%)
Baulac 2012	0 (0%)	0 (0%)	583 (100%)	0 (0%)	0 (0%)	583 (100%)	478 (82%)	103 (18%)	2 (0%)
Baulac 2017	262 (29%)	624 (70%)	2 (1%)	508 (57%)	379 (43%)	1 (0%)	452 (51%)	436 (49%)	0 (0%)
Bill 1997	126 (44%)	152 (53%)	9 (3%)	173 (60%)	69 (24%)	45 (16%)	0 (0%)	0 (0%)	287 (100%)
Biton 2001	0 (0%)	0 (0%)	136 (100%)	0 (0%)	0 (0%)	136 (100%)	89 (65%)	46 (34%)	1 (1%)

Table 4. Characteristics of participants providing individual participant data (baseline investigations) *(Continued)*

Brodie 1995a	62 (46%)	72 (53%)	2 (1%)	82 (60%)	12 (9%)	42 (31%)	123 (90%)	13 (10%)	0 (0%)
Brodie 1995b	76 (61%)	42 (34%)	6 (5%)	72 (58%)	20 (16%)	32 (26%)	108 (87%)	16 (13%)	0 (0%)
Brodie 1999	0 (0%)	0 (0%)	150 (100%)	62 (41%)	87 (58%)	1 (1%)	90 (60%)	60 (40%)	0 (0%)
Brodie 2007	0 (0%)	0 (0%)	579 (100%)	0 (0%)	0 (0%)	579 (100%)	493 (85%)	86 (15%)	0 (0%)
Chadwick 1998	107 (37%)	179 (61%)	6 (2%)	0 (0%)	0 (0%)	292 (100%)	0 (0%)	0 (0%)	292 (100%)
Craig 1994	28 (17%)	74 (45%)	64 (39%)	0 (0%)	0 (0%)	166 (100%)	0 (0%)	0 (0%)	166 (100%)
De Silva 1996	0 (0%)	0 (0%)	173 (100%)	0 (0%)	0 (0%)	173 (100%)	152 (88%)	15 (9%)	6 (3%)
Dizdarer 2000	18 (35%)	34 (65%)	0 (0%)	50 (96%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	52 (100%)
Eun 2012	6 (7%)	78 (93%)	0 (0%)	75 (89%)	9 (11%)	0 (0%)	83 (99%)	1 (1%)	0 (0%)
Guerreiro 1997	92 (48%)	99 (51%)	2 (1%)	126 (65%)	12 (6%)	55 (28%)	0 (0%)	0 (0%)	193 (100%)
Heller 1995	0 (0%)	0 (0%)	243 (100%)	0 (0%)	0 (0%)	243 (100%)	222 (91%)	19 (8%)	2 (1%)
Kwan 2009	0 (0%)	0 (0%)	81 (100%)	0 (0%)	0 (0%)	81 (100%)	0 (0%)	0 (0%)	81 (100%)
Lee 2011	58 (53%)	52 (47%)	0 (0%)	74 (67%)	36 (33%)	0 (0%)	110 (100%)	0 (0%)	0 (0%)
Mattson 1985	0 (0%)	0 (0%)	475 (100%)	0 (0%)	0 (0%)	475 (100%)	0 (0%)	0 (0%)	475 (100%)
Mattson 1992	0 (0%)	0 (0%)	480 (100%)	0 (0%)	0 (0%)	480 (100%)	0 (0%)	0 (0%)	480 (100%)
Nieto-Barrera 2001	0 (0%)	0 (0%)	622 (100%)	0 (0%)	0 (0%)	622 (100%)	0 (0%)	0 (0%)	622 (100%)
Ogunrin 2005	0 (0%)	0 (0%)	55 (100%)	37 (67%)	0 (0%)	18 (33%)	55 (100%)	0 (0%)	0 (0%)
Pal 1998	0 (0%)	0 (0%)	94 (100%)	0 (0%)	0 (0%)	94 (100%)	24 (26%)	70 (74%)	0 (0%)
Placencia 1993	180 (94%)	12 (6%)	0 (0%)	0 (0%)	0 (0%)	192 (100%)	0 (0%)	0 (0%)	192 (100%)
Privitera 2003 (CBZ branch)[a]	0 (0%)	0 (0%)	395 (100%)	0 (0%)	0 (0%)	395 (100%)	0 (0%)	0 (0%)	395 (100%)
Privitera 2003	0 (0%)	0 (0%)	225 (100%)	0 (0%)	0 (0%)	225 (100%)	0 (0%)	0 (0%)	225 (100%)

Table 4. Characteristics of participants providing individual participant data (baseline investigations) *(Continued)*

(VPS branch)[a]									
Ramsay 1992	0 (0%)	0 (0%)	136 (100%)	0 (0%)	0 (0%)	136 (100%)	0 (0%)	0 (0%)	136 (100%)
Ramsay 2010	0 (0%)	0 (0%)	261 (100%)	0 (0%)	0 (0%)	261 (100%)	0 (0%)	0 (0%)	261 (100%)
Reunanen 1996	13 (4%)	13 (4%)	325 (93%)	16 (5%)	5 (1%)	330 (94%)	305 (87%)	46 (13%)	0 (0%)
Richens 1994	0 (0%)	0 (0%)	300 (100%)	0 (0%)	0 (0%)	300 (100%)	0 (0%)	0 (0%)	300 (100%)
SANAD A 2007	770 (45%)	773 (45%)	178 (10%)	1000 (58%)	437 (25%)	287 (17%)	1302 (76%)	419 (24%)	0 (0%)
SANAD B 2007	187 (26%)	494 (69%)	35 (5%)	322 (45%)	44 (6%)	350 (49%)	605 (85%)	111 (15%)	0 (0%)
SANAD II A 2021	598 (60%)	293 (30%)	99 (10%)	643 (65%)	347 (35%)	0 (0%)	823 (83%)	167 (17%)	0 (0%)
SANAD II B 2021	210 (40%)	44 (8%)	266 (52%)	153 (29%)	367 (71%)	0 (0%)	485 (93%)	35 (7%)	0 (0%)
Steiner 1999	103 (57%)	71 (39%)	7 (4%)	111 (61%)	33 (18%)	37 (20%)	165 (91%)	16 (9%)	0 (0%)
Stephen 2007	51 (22%)	121 (53%)	55 (24%)	0 (0%)	0 (0%)	227 (100%)	0 (0%)	0 (0%)	227 (100%)
Trinka 2013 (CBZ branch)[1]	0 (0%)	0 (0%)	999 (100%)	0 (0%)	0 (0%)	999 (100%)	0 (0%)	0 (0%)	999 (100%)
Trinka 2013 (VPS branch)[1]	0 (0%)	0 (0%)	703 (100%)	0 (0%)	0 (0%)	703 (100%)	0 (0%)	0 (0%)	703 (100%)
Turnbull 1985	70 (50%)	70 (50%)	0 (0%)	17 (12%)	10 (7%)	113 (81%)	0 (0%)	0 (0%)	140 (100%)
Verity 1995	0 (0%)	0 (0%)	260 (100%)	0 (0%)	0 (0%)	260 (100%)	0 (0%)	0 (0%)	260 (100%)
Werhahn 2015	117 (32%)	242 (67%)	2 (1%)	78 (22%)	282 (78%)	1 (0%)	0 (0%)	0 (0%)	361 (100%)
Total	**3183 (22%)**	**3593 (24%)**	**8013 (54%)**	**3620 (24%)**	**2156 (15%)**	**9013 (61%)**	**6164 (42%)**	**1659 (11%)**	**6966 (47%)**

CBZ: carbamazepine
CT: computerised tomography
EEG: electroencephalogram
LEV: levetiracetam

MRI: magnetic resonance imaging

TPM: topiramate

VPS: sodium valproate

[a]Trials designed in two strata based on whether recommended treatment would be CBZ or VPS. Within the two strata, participants were randomised to TPM in Privitera 2003/LEV in Trinka 2013 or CBZ/VPS depending on the strata. Data analysed according to the separate strata (CBZ branch or VPS branch) in this review

Table 5. Summary of results of trials without individual participant data

Trial	Outcomes	Summary of results[b]
Aikia 1992	Neuropsychological assessment and cognitive functioning at baseline, 6 months' and 12 months' follow-up	MANOVA revealed no significant interaction effect of group and time in the assessments of neurological and psychological functioning.
Akter 2018	1. Seizure remission of at least 50%	1. 3 months: PHB = 25/68 (37%), LEV = 31/50 (62%); 6 months: PHB = 42/51 (82%), LEV = 40/45 (89%); 9 months: PHB = 49/51 (96%), LEV = 45/45 (100%); 12 months: PHB = 49/51 (96%), LEV = 45/45 (100%).
	2. Psychological assessments	2. "No significant influence" on psychological function in both group after 12 months
	3. EEG abnormalities	3. EEG abnormalities were reduced in both groups at 12 months.
	4. Side effects	4. Most common side effect of PHB was behavioural problems; most common side effect of LEV was irritability or sleep disturbance.
Bidabadi 2009	1. Proportion seizure-free	1. CBZ: 64%, PHB: 63%
	2. Response rate and rate of side-effects	2. No statistically significant differences between groups
	3. Seizure frequency	3. Mean seizure frequency: CBZ: 0.66, PHB: 0.8
	4. Seizure duration	4. Mean duration (seconds): CBZ: 12.63; PHB: 15
Brodie 2002	1. Time to exit	1. Median time to exit: GBP: 69 days, LTG: 48 days; HR: 1.043 (95% CI 0.602 to 1.809)
	2. Percentage of completers	2. Proportion of population completing the study – GBP: 71.6%, LTG: 67.1%
	3. Time to withdrawal for any reason	3. No difference between groups
	4. Time to first seizure	4. No difference between groups
	5. Percentage who remained seizure-free during the final 12 weeks of the 30-week evaluation period	5. GBP: 76.1%, LTG: 76.8% (ITT population)
	6. Withdrawal rate due to adverse events	6. Withdrawals during titration: GBP: 7, LTG: 10; Withdrawals after titration: GBP: 10, LTG: 13.
Callaghan 1985	1. Seizure control: • excellent (complete freedom of seizures)	1. Excellent: PHT: 67%; CBZ: 37%; VPS: 53% Good: PHT: 12%; CBZ: 37%; VPS: 25% Poor: PHT: 21%; CBZ: 25%; VPS: 22%

Table 5. Summary of results of trials without individual participant data *(Continued)*

	• good (> 50% reduction in seizure frequency) • poor (< 50% reduction in seizure frequency or no response)	
	2. Side effects	2. PHT: 10%; CBZ: 8%; VPS:11%
Capone 2008	1. Seizure freedom	1. CBZ: 76%, LEV: 76%
	2. Proportion with adverse events	2. CBZ: 65%, LEV: 50%
	3. Discontinuations of the trial drug	3. CBZ: 2 discontinuations due to failure to control seizures and interactions with other medications LEV: 3 discontinuations – 1 death from stroke and 2 due to AEs
Castriota 2008	Event-related potential recordings and neuropsychological assessments	No significant difference between groups
Chen 1996	1. Cognitive/psychometric outcomes	1. No significant difference between groups
	2. Auditory event-related potentials (neurophysiological outcome)	2. No significant difference between groups
	3.Incidence of allergic reactions	3. 2 children from PHB group, 1 child from CBZ group and no children from VPS group withdrew from the study because of allergic reactions.
	4. Seizure control	4. No significant difference between groups
Chen 2013	1. Response rate at 13 weeks and at 26 weeks	1. 13 weeks: CBZ = 41/58 (71%), OXC = 45/60 (75%); 26 weeks: CBZ = 38/58 (66%), OXC = 43/60 (72%).
	2. Seizure-free rate at 13 weeks and at 26 weeks	2. 13 weeks: CBZ = 29/58 (50%), OXC = 32/60 (53%); 26 weeks: CBZ = 25/58 (43%), OXC = 30/60 (50%).
	3. Adverse events at 26 weeks	3. CBZ = 23/58 (40%); OXC = 11/60 (18%) (P < 0.05)
Cho 2011	1. Change in overnight sleep parameters from baseline after 4-6 weeks of treatment	1. Overall effect on sleep parameters was comparable between groups. LEV group PSG significant increase post-treatment compared to baseline in sleep efficiency (P = 0.039) and in decrease of wake time after sleep onset (P = 0.047); no significant change in other sleep parameters. CBZ group post-treatment compared to baseline: significant increases in the percentage of slow wave sleep (P = 0.038); no significant change in other sleep parameters
	2. Change in sleep questionnaires and National Hospital Seizure Severity Scale (NHS3) from baseline after 4-6 weeks of treatment	2. No significant difference between baseline and post-treatment between the 2 groups
Christe 1997	1. The proportion of seizure-free participants who had at least 1	1. OXC 56.6%; VPS 53.8%

Table 5. Summary of results of trials without individual participant data *(Continued)*

	seizure during the maintenance period	
	2. Time to premature discontinuation due to adverse experiences	2. No significant difference between groups
	3. Rate of premature discontinuations for any reason	3. OXC 40.6% ; VPS 33.9%
	4. Overall assessments of efficacy and tolerability and therapeutic effect	4. No significant difference between groups
	5. Individual adverse experiences	5. Proportion of participants experiencing at least 1 AE regardless of relationship to trial drug: OXC 89.8%; VPS 87.6%
	6. Seizure frequency during maintenance	6. Seizure frequency per week: OXC (n = 106) mean 0.17 median 0, VPS (n = 106) mean 0.40, median 0
Consoli 2012	1. Frequency of seizures during the treatment period	1. No significant difference between groups
	2. Retention of treatment from the first intake	2. Completed study: LEV 52/62, CBZ 54/66 Withdrawals: 8 poor compliance (LEV 4, CBZ 4); 7 severe adverse effects (LEV 3, CBZ 4); 7 unknown cause (LEV 3, CBZ 4)
	3. Changes in cognitive measures and quality-of-life measures at the end of the treatment period	3. Attention deficit on digital span end of follow up greater in CBZ group than LEV (P = 0.03) Stroop test worse in CBZ than LEV (P = 0.02) No significant difference between groups for other scales. Impairment of activities of daily living greater CBZ than LEV (P = 0.05)
	4. Changes in EEG assessments at the end of the treatment period	4. 4 participants (LEV 2, CBZ 2) had abnormal EEG at baseline, normal at end of treatment. Drug dose reduction (LEV 4, CBZ 2). Remaining participants unmodified versus baseline
	5. Tolerability of treatment	5. No significant difference between groups
Cossu 1984	Changes in memory function from baseline after 3 weeks of treatment	Significant decrease in visual-verbal memory for CBZ and acoustic memory for PHB. No significant differences for other tests
Czapinski 1997	1. Proportion achieving 24-month remission at 3 years	1. PHB: 60%, PHT: 59%; CBZ: 62%; VPS: 64%
	2. Exclusions after randomisation due to adverse effects or no efficacy	2. PHB: 33%, PHT: 23%; CBZ: 30%; VPS: 23%
Dam 1989	1.Changes in seizure frequency between baseline and the end of each maintenance period	1. Baseline: OXC mean 2.9 (SD 7.0), median 1, range 0-60; CBZ mean 5.8 (SD 14.7) median 1, range 0-99 Maintenance phases: OXC mean 0.4 (SD 3.0) median 0, range 0-27; CBZ mean 0.3 (SD 1.4) median 0, range 0-12

Table 5. Summary of results of trials without individual participant data *(Continued)*

	2. Side effects observed by participants and investigators at each visit	2. Severe side effects: CBZ 25, OXC 13, statistically significant difference favouring OXC (P = 0.04) Participants without any side effects: CBZ 25, OXC 29 no significant difference between groups (P = 0.22) Nature of side effects same between groups, included tiredness, headache, dizziness, ataxia. Participants withdrawn due to severe side effects: CBZ 16, OXC 9
	3.Global evaluation of therapeutic efficacy and tolerability by the investigator at the end of each maintenance period	3. Global efficacy: no significant difference between groups (P = 0.77); global tolerability (P = 0.11) Participants very good/good: CBZ 69 (73%), OXC 76 (84%) Participants poor/very poor: CBZ 26 (27%), OXC 15 (16%)
	4. Changes in EEG tracings between baseline and the end of each maintenance period	4. Clinically relevant changes observed in 2 participants only, both CBZ group, both stopped treatment
Donati 2007	1. Cognitive testing	1. No significant difference between treatment groups
	2. Percentage of participants remaining seizure-free throughout treatment	2. OXC 58%; CBZ 46%; VPS 54%
	3. Most common adverse events	3. Most common (> 10% reported) side effects OXC fatigue and headache; CBZ fatigue and rash; VPS headache, increased appetite, alopecia
	4. Treatment satisfaction on a 4-point scale from poor to very good	4. Good/very good: OXC investigators 84%, participants 82%, parents/carers 86%; Combined CBZ/VPS investigators 77%, participants 73%, parents/carers 80%
Feksi 1991	1. Adverse effects	1. Minor adverse effects reported in PHB: 58 participants (39%) reported 86 AEs, CBZ: 46 participants (30%) reported 68 AEs
	2. Withdrawals from allocated treatment	2. All withdrawals: PHB: 18%, CBZ: 17%; withdrawals due to side-effects: PHB: 5%, CBZ: 3%
	3. Seizure frequency (during second 6 months of trial)	3. Seizure-free: PHB: 54%, CBZ: 52%; > 50% reduction of seizures: PHB: 23%, CBZ: 29% 50% reduction to 50% increase in seizures: PHB: 15%, CBZ: 13%; > 50% increase in seizures: PHB: 8%, CBZ: 6%
Forsythe 1991	1. Cognitive assessments	1. Significant difference favouring VPS test of speed of information processing No significant differences between treatment groups for any other cognitive tests
	2. Withdrawals from randomised drug	2. PHT: 30%; CBZ: 39%; VPS: 33%

Table 5. Summary of results of trials without individual participant data *(Continued)*

Fritz 2006	1.Seizure reduction	1. Seizure freedom: LTG: 38%, OXC: 44%; > 50% seizure reduction: LTG: 48%, OXC: 55%
	2. Cognition, mood and health-related quality of life	2. Both groups showed improvement in verbal learning and in 1/4 measures of attention. In addition, participants under OXC improved in word fluency. Improved mood was reported with OXC only.
Gilad 2007	1.The appearance of a second seizure under treatment or by finishing the 12-month follow-up without seizures	1. Number of participants experiencing early seizures as first event: LTG 2/32, CBZ 3/32 Number of participants remaining seizure-free in the follow-up period: LTG 23/32 (72%), CBZ 14/32 (44%), P = 0.05
	2. Tolerability: incidence of adverse events	2. LTG 2/32 (6.25%), CBZ 12/32 (37.5%), P = 0.05
	3. Withdrawals due to adverse events	3. LTG 1/32 (3%), CBZ 10/32 (31%), P = 0.02
Giri 2016	1. Seizure-free	1. 3 months: LTG = 8/30 (26.7%), VPS = 16/30 (53.3%); 6 months: LTG = 14/30 (46.7%), VPS = 19/30 (63.3%); 12 months: LTG = 17/30 (56.7%), VPS = 23/30 (76.7%).
	2. At least 50% reduction in seizure frequency (not seizure-free)	2. 3 months: LTG = 2/30 (6.7%), VPS = 3/30 (10%); 6 months: LTG = 3/30 (10%), VPS = 3/30 (10%); 12 months: LTG= 3/30 (10%), VPS = 1/30 (3.3%).
	3. Number of seizures per month (at 12 months)	3. Mean (SD): LTG = 2.43 (1.87), VPS =1.70 (1.82)
	4. Adverse events	4. Adverse effects were recorded in 9 (30.0%) patients of VPS group and 17 (56.7%) in LTG group patients. Sedation, ataxia and tremor were recorded in patients taking VPS but these symptoms responded to a decrease in dosage. Skin rash developed within three months in 3 (10.00%) patients taking LTG; they withdrew from the study.
Jung 2015	1. Neuropsychological outcomes	1. No difference between groups in terms of social competence; school competence; internalising behaviour problems; externalising behaviour problems; total behaviour problems and anxiety. Significant decrease in depression in LEV group compared to CBZ group (P = 0.027)
	2. Mean percentage change in seizure frequency from baseline	2. LEV 95.7%, CBZ 97.1%, P = 0.686
	3. Seizure-freedom rates	3. LEV 66.7%, CBZ 57.8%, P = 0.317
	4. Incidence of adverse events	4. LEV 33.3%, CBZ 46.9%. Number of AEs not significantly different between groups
Kalviainen 2002	1. Seizure freedom	1.CBZ: 53% LTG: 56%
	2. Cognitive assessments	2. No significant difference between groups in overall cognitive score. In terms of individual assessments; only Stroop test B showed a statistically significant advantage for LTG.

Table 5. Summary of results of trials without individual participant data *(Continued)*

Kim 2017	1. Percentage of participants with a treatment failure after 50 weeks	1. LEV = 19/173 (11.0%), OXC = 31/171 (18.1%) (full analysis set)
	2. Time to treatment failure	2. Hazard ratio (LEV vs OXC): 0.6 (0.3 to 1.0), log rank P = 0.0658
	3. Time to the first seizure defined as the time from the first dose of medication to the occurrence of the first seizure during the 48 weeks' treatment period	3. Median months: LEV: 7.6, OXC: NA (fewer than 50% of participants in the OXC group had seizure recurrence)
	4. Percentage of subjects who achieved seizure freedom for 24 consecutive weeks during the 48 weeks' treatment period at any time	4. LEV = 93/173 (53.8%), OXC = 100/171 (58.5%) (full analysis set)
	5. Percentage of subjects who achieved seizure freedom during the 48 weeks' treatment period	5. LEV = 60/173 (34.7%), OXC = 70/171 (40.9%) (full analysis set)
Kopp 2007	Cognitive performance and neuropsychological assessments	No significant difference between groups
Korean Lamotrigine Study Group 2008	1. Retention rate at study end	1. LTG: 65%, CBZ: 70%
	2. Terminal 24-week seizure-free rate and time interval from the end of dose titration phase to the first seizure	2. Total seizure-free rate LTG: 62%, CBZ: 63% Time to first seizure, mean (SD): weeks: LTG: 10 (5.09), CBZ: 10.82 (6.44)
Korean Zonisamide Study 1999	1. Seizure remission rate at 24 weeks	1. The 24-week terminal remission rate was 51 out of 73 (69.9%) in ZNS group compared with 62 out of 82 (75.6%) in CBZ group (P = 0.9).
	2. Time interval to first seizure recurrence (after the dose-escalation period).	2. The time interval to the first seizure recurrence was 40.9 ± 31.7 days in ZNS group (n = 13) and 47.8 ± 30.8 days in CBZ group (P = 0.75).
	3. Incidence of adverse events	3. The incidence of adverse events (AEs) was 67.1% in ZNS group and 53.7% in CBZ group (P = 0.088) (entire treatment period).
Lukic 2005	1. Seizure freedom	1. LTG: 54%, VPS: 55%, no difference by seizure type
	2. Retention on treatment	2. LTG: 69%, VPS: 68 %
Maiti 2018	1. Serum S100B levels	1. Decrease in serum S100B was significantly higher with CBZ group (0.004; 95% CI 0.001 to 0.006; P = 0.01) against OXC group
	2. Quality of life (by the QOLIE-31)	2. An improvement in quality of life was seen in both groups for all domains.
	3. Chalfont-National Hospital seizure severity scale (NHS3)	3. No difference in mean change of NHS3 between groups

Table 5. Summary of results of trials without individual participant data *(Continued)*

	4. Adverse events	4. No adverse events reported on OXC. On CBZ, sedation and dizziness (n = 4) and vertigo (n = 3). All adverse drug reactions were mild, and the drug was not discontinued.
Mitchell 1987	Change in cognitive, intelligence (IQ), behavioural, and psychometric scores between baseline, 6 months, and 12 months	1. No significant differences between treatment groups
	2. Compliance, drug changes, and withdrawal rates	2. Compliance: trend towards better compliance in CBZ group (not significant). Trend towards higher rate withdrawal from treatment in PHB group (not significant). More mild systemic side effects in CBZ group (significant). 3 children switched from CBZ to PHB and 1 from PHB to CB following adverse reactions.
	Seizure control at 6 and 12 months (excellent/good/fair/poor)	3. 6 months: excellent/good: PHB = 15, CBZ = 13 12 months: excellent/good: PHB = 13, CBZ = 9
Miura 1990	1. Proportion of all randomised participants with seizure recurrence (by seizure type)	1. Focal seizures - PHT: 32%; CBZ: 40%; VPS: 41% Generalised seizures - PHT: 35%; CBZ: 15%; VPS: 7%
	2. Proportion of participants with optimum plasma levels with seizure recurrence (by seizure type)	2. Focal seizures - PHT: 24%; CBZ: 24%; VPS: 25% Generalised seizures - PHT: 13%; CBZ: 0%; VPS: 0%
Motamedi 2013	1. Seizure recurrence	1. Seizure recurrence at 2 weeks - LTG: 43%, LEV: 35%, P = 0.42 Seizure recurrence at 4 weeks - LTG: 39%, LEV: 33%, P = 0.53 Seizure recurrence at 8 weeks - LTG: 35%, LEV: 28%, P = 0.50 Seizure recurrence at 12 weeks - LTG: 33%, LEV: 24%, P = 0.35 Seizure recurrence at 20 weeks - LTG: 31%, LEV: 13%, P = 0.03
	2. Abnormal laboratory values	2. No significant difference between groups
	3. Adverse events	3. Proportion with AEs - LTG: 53%, LEV: 67%
NCT01954121	1. Proportion of subjects remaining seizure-free during the 6-month evaluation period	1. LEV: 47.3%, CBZ: 68.4%
	2. Proportion of subjects retained in the trial for the duration of the period covering the up-titration period, stabilisation period, and evaluation period	2. LEV: 48.4%, CBZ: 70.2%
	3. Time to first seizure or discontinuation due to an adverse	3. Number of events: LEV: 88, CBZ: 45 (times not reported)

Table 5. Summary of results of trials without individual participant data *(Continued)*

	event /lack of efficacy during the evaluation period	
	4. Time to first seizure during the evaluation period	4. Number of events: LEV: 87, CBZ: 39 (times not reported)
	5. Time to first seizure during the period covering the up-titration period, stabilisation period, and evaluation period from the first dose of trial drug	5. Number of events: LEV: 97, CBZ: 57 (times not reported)
Pulliainen 1994	1. Cognitive assessments	1. Compared to CBZ, participants on PHT became slower (motor speed of the hand) and their visual memory decreased. There was an equal decrease in negative mood (helplessness, irritability, depression) on PHT and CBZ.
	2. Harmful side effects	2. 3 participants taking PHT complained of tiredness, and 1 participant taking CBZ complained of facial skin problems, another tiredness and memory problems
Ramsay 1983	1. Side effects (major and minor)	1. Incidence of major side effects (proportion of analysed participants): PHT 23%; CBZ: 23% Minor side effects: cognitive impairment and sedation twice as likely on CBZ compared to PHT. Other minor side effects similar between groups
	2. Treatment failure	2. Treatment failures among analysed participants: PHT 4/35 (11%); CBZ: 5/35 (14%)
	3. Seizure control	3. Seizure control (among analysed participants with no major side effects): PHT: 86%; CBZ: 82%
	4. Laboratory assessments	4. Significantly lower mean LDH level at 24 weeks in CBZ participants than PHT participants. Other laboratory results similar across treatment groups
Ramsay 2007 [c]	1. Discontinuations from the trial	1. 8 discontinuations; due to generalised rash (n = 1), excessive tiredness (n = 1), withdrew consent (n = 2), renal transplant (n = 1), lost to follow-up (n = 2), died (n = 1)
	2. Treatment-emergent side effects	2. 6 participants reported treatment-emergent side effects.
	3. Seizure control	3. No participants withdrew due to lack of seizure control.
Rastogi 1991	1. Reduction in frequency of seizures: • excellent (100% reduction); • good (75%-99% reduction); • fair (50%-74% reduction); • poor (< 50% reduction)	1. Excellent: PHT: 51%, VPS: 49% Good: PHT: 24%, VPS: 35% Fair: PHT: 18%, VPS: 10% Poor PHT: 2%, VPS: 6%
	2. Adverse effects	2. All reported AEs were minor and similar rates between groups.

Table 5. Summary of results of trials without individual participant data *(Continued)*

Ravi Sudhir 1995	Cognitive measures before and after treatments	No significant differences between any tests of cognitive function taken before treatment and after 10-12 weeks for both treatment groups
Resendiz 2004	1. Seizure freedom and frequency of seizures during the trial	1. Six months of seizure freedom: CBZ: 81%, TPM: 91% 50% reduction of seizures: CBZ: 84% TPM: 97% The average number of seizures was significantly less in the TPM group compared to the CBZ group at 6 and 9 months.
	2. Adverse events during the trial	2. AEs were mild and similar between groups.
	3. Laboratory results	3. No significant differences between groups
Rowan 2005	1. Retention in the trial for 12 months	1. Significant difference between 3 treatment groups (P = 0.00022) CBZ more early terminators than GBP (P = 0.008) or LTG (P < 0.0001)
	2. Seizure freedom at 12 months	2. LTG 51.4%, GBP 47.4%, CBZ 64.3%, no significant difference between groups, P = 0.09
	3. Time to first, second, fifth and tenth seizure (time to seizures)	3. No difference between groups for time to first, second, fifth and tenth seizure (P = 0.18, 0.13, 0.74, 0.95, respectively)
	4. Drug toxicity (incidence of systemic and neurologic toxicities)	4. More systemic toxicities on GBP than CBZ or LTG No significant differences in neurotoxicities between treatment groups over 12 months
	5. Serum drug levels and compliance	5. Mean serum levels: 6 weeks: GBP 8.67 ± 4.83; µg/mL, CBZ 6.79 ± 2.92 µg/mL and LTG 2.87 ± 1.60 µg/mL 52 weeks: GBP 8.54 ± 5.57 µg/mL, CBZ 6.48 ± 3.72 µg/mL and LTG 3.46 ± 1.68 µg/mL Overall medical compliance: 89% without significant group differences
	6. Seizure-free retention rates	6. 3 months: LTG 49.7%, GBP 43.3%, CBZ 36.0%, significant difference between groups, P = 0.02 6 months: LTG 37.2%, GBP 33.0%, CBZ 28.9%, no significant difference between groups, P = 0.22 12 months: LTG 28.6%, GBP 23.2%, CBZ 22.8%, no significant difference between groups, P = 0.33
Saetre 2007	1. Retention in the trial (time to treatment withdrawal for any cause)	1. LTG 68 (73%), CBZ 61 (67%), no significant difference between groups
	2. Seizure freedom after week 4	2. LTG 59 (63%), CBZ 69 (76%), no significant difference, P = 0.068 (ITT analysis)
	3. Seizure freedom after week 20	3. LTG 71 (76%), CBZ 81 (89%), significant difference, P = 0.0234 (ITT analysis)
	4. Time to first seizure	4. Hazard ratio (LTG/CBZ) 1.50, 95% CI 0.94 to 2.40, P = 0.092

Table 5. Summary of results of trials without individual participant data *(Continued)*

	5. Adverse event reports	5. During treatment period, LTG 82 (88%) reported 378 AEs, CBZ 79 (86%) reported 310 AEs. No significant differences between groups for any AEs except for immune system Withdrew due to AE: LTG 13 (14%), CBZ 23 (25%), P = 0.078
	6. Tolerability according to the Liverpool Adverse Event profile (AEP)	6. No difference between groups even when changes over time corrected for age, gender and baseline score
Shakir 1981	1. Seizures during treatment	1. PHT: 33%; VPS: 39%
	2. Adverse events	2. All reported AEs were minor and similar rates between groups.
Sidhu 2018	1. Anthropometric measures (weight, BMI)	1. The mean weight and BMI were significantly higher in VPS group in LTG group at 12 months.
	2. Clinical measures related to the menstrual cycle	2. Menstrual disturbances were found in 11 women; among them nine (30%) received VPS and two (6%) received LTG
	3. Reproductive hormone levels	3. Mean testosterone level was significantly higher in the VPS group than in the LTG group at 6 and 12 months. There were no differences between groups in terms of other hormone levels.
	4. Insulin resistance	4. 11 (37%) of VPS group, and 2 (6%) of LTG group developed insulin resistance during the course of therapy.
So 1992	1. Proportion of participants free of complex focal seizures during the maintenance period	1. VPS 7/11 (64%), CBZ 9/14 (64%)
	2. Proportion of participants reporting specific adverse events	2. At least one AE reported VPS 15/16 (94%), CBZ 16/17 (94%)
Steinhoff 2005	1. Number of seizure-free patients during trial weeks 17-24	1. Focal: CBZ group 83/88 (94.3%), LTG group 78/88 (88.6%), no significant difference between groups Generalised: VPS group 25/30 (83.3%) LTG group 20/33 (60.6%), no significant difference between groups
	2. “Leaving the study” (retention rates)	2. Focal: CBZ group 81%, LTG group 91%, no significant difference between groups Generalised: VPS group 97%, LTG group 88%, not stated as significant or non-significant difference
	3. Adverse event rates	3. At least 1 AE: Focal: CBZ 81 participants (91%), LTG 68 participants (77.3%) Generalised: VPS 25 participants (83.3%), LTG 24 participants (72.7%) Serious AEs: Focal: CBZ 8 participants (9%), LTG 6 participants (7%) Generalised: VPS 1 participant (3%), LTG 5 participants (15%) AEs considered related to study drug: Focal: CBZ 65 participants (74%), LTG 38 participants (43%)

Table 5. Summary of results of trials without individual participant data *(Continued)*

		Generalised: VPS 16 participants (53%), LTG 15 participants (45.5%)
Suresh 2015	1. Quality of life by the QOLIE-10 questionnaire before and after 26 weeks of therapy	1. Mean quality of life score at baseline: CBZ group 31.14 ± 1.83, LEV group 29.76 ± 1.71 (P = 0.5861) Mean quality of life score after 26 weeks of treatment: CBZ group 58.41 ± 1.89, LEV 64.58 ± 2.02 (P = 0.0302)
	2. Seizure freedom at 4 weeks, 12 weeks, 26 weeks and 6 months	2. 4 weeks: CBZ group 85.72%, LEV group 85.72% (P = 1); 12 weeks: CBZ group 89.29%, LEV group 93.34% (P = 0.4595); 26 weeks: CBZ group 96.43%, LEV group 100% (P = 0.1212); 6 months: CBZ group 71.42% (20 participants), LEV group 78.57% (22 participants) (P = 0.2529)
	3. Proportion of participants experiencing at least 1 adverse event)	3. CBZ group 36.66%, LEV group 40% (P = 0.77)
Thilothammal 1996	1. Proportion with recurrence of seizures	1. PHB: 31%, PHT: 27%, VPS: 21%
	2. Adverse events	2. PHB: 33%, PHT: 63%, VPS: 31%
Trinka 2018	1. Proportion of patients who were seizure-free for the entire evaluation phase at the last evaluated dose level.	1. Per protocol set: 71.1% of ESL group and 75.6% of the CBZ-CR group Full analysis set: 70.8% of ESL group and 74.0% of CBZ group seizure-free at the last evaluated dose level
	2. Proportion of seizure-free patients during 1-year of treatment	2. Per protocol set: 64.7% of ESL group and 70.3% of the CBZ-CR group Full analysis set: 63.8% of ESL group and 68.7% of CBZ group seizure-free at 1 year of treatment
	3. Time to first seizure at the last evaluated dose (treatment failure time)	3. Treatment failure (i.e. first seizure) was higher in the ESL group (12%) than in the CBZ-CR group (6%). Treatment failure based on withdrawal from the study (post hoc) was also higher in the ESL group (7%) than in the CBZ-CR group (3%).
	4. Seizure characteristics of the first seizure during the evaluation period	4. A similar proportion between treatment groups was found for seizure-free patients during the evaluation period by most frequent baseline seizure type.
	5. Dose level at which patients reached 26-week seizure freedom	5. The overall proportion of seizure-free patients at each dose level was similar.
	6. Treatment retention time (defined as the time to withdrawal due to adverse events [AEs] or lack of efficacy)	6. The probability of patients withdrawing due to either AEs or lack of efficacy (ESL vs CBZ-CR) was 26% vs 21% at 1 year. Retention time was similar across the drugs.
	7. Changes in quality of life (Quality of Life in Epilepsy Inventory-31 (QOLIE-31) survey)	7. Comparable improvements from baseline in the QOLIE-31 scores were observed at the maintenance period visit and the final endpoint visit (between group differences not calculated).

Table 5. Summary of results of trials without individual participant data *(Continued)*

	8. Incidence of treatment-emergent adverse events	8. The percentage of patients who experienced at least 1 TEAE was similar (ESL: 76.3%, CBZ-CR: 79.6%)
Wu 2018	1. Semen quality	1. OXC can improve the sperm quality in fast forward movement rate and survival rate. LEV and LTG have no effect on semen quality.
	2. Sexual function and sex hormones	2. OXC, LEV and LTG have no significant effect on sexual function or sex hormones.
Xu 2012	1. Effective rate at 1 year	1. OXC = 43/57 (75.4%), TPM = 49/58 (84.5%); LEV = 58/68 (85.5%), LTG = 61/70 (87.1%)
	2. Retention rate at 1 year	2. OXC = 35/57 (61.4%), TPM = 40/58 (68.9%); LEV = 50/68 (73.5%), LTG = 62/70 (88.6%)
	3. Reasons for drug withdrawal	3. The primary cause of drug withdrawal was seizure-control ineffectiveness (28, 42.4%), adverse effects (13, 19.7%) and price (10, 15.2%).

AE: adverse event
AEP: adverse event profile
BMI: body mass index
CBZ: carbamazepine
CR: controlled release
EEG: electroencephalogram
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
IQ: intelligence quotient
ITT: intention-to-treat
LDH: lactic acid dehydrogenase
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
MANOVA: repeated measures analysis of variance
NA: not applicable
NHS3: National Hospital Seizure Severity Scale
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
PSG: polysomnography
QOLIE(-10)(-31): quality of life
SD: standard deviation
TEAE: treatment emergent adverse event
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

[a] For further details of adverse events, see Table 20 and Table 21.
[b] See Table 1 for details of treatment arms in each trial and number of participants randomised to each arm.
[c] Results not split by treatment arm for Ramsay 2007.

Table 6. Number of participants contributing individual participant data to analyses

Trial	Time to treatment failure[c]				Time to first seizure				Time to 12-month remission[d]				Time to six-month remission[d]			
	Cens	Event	Total	Miss-ing	Cens	Event	Total	Miss-ing	Cens	Event	Total	Miss-ing	Cens	Event	Total	Miss-ing
Banu 2007 [a]	0	0	0	108	38	66	104	4	0	0	0	108	0	0	0	108
Baulac 2012	392	191	583	0	396	186	582	1	234	348	582	1	151	431	582	1
Baulac 2017	562	325	887	1	481	403	884	4	343	541	884	4	224	660	884	4
Bill 1997	207	80	287	0	137	145	282	5	190	92	282	5	136	146	282	5
Biton 2001	99	36	135	1	64	71	135	1	0	0	0	136	90	45	135	1
Brodie 1995a	79	57	136	0	69	67	136	0	0	0	0	136	122	14	136	0
Brodie 1995b	79	45	124	0	52	72	124	0	0	0	0	124	96	28	124	0
Brodie 1999	95	55	150	0	70	80	150	0	0	0	0	150	0	0	0	150
Brodie 2007	323	256	579	0	350	229	579	0	260	319	579	0	177	402	579	0
Chadwick 1998	100	191	291	1	102	190	292	0	0	0	0	292	193	99	292	0
Craig 1994	0	0	0	166	66	81	147	19	117	30	147	19	58	89	147	19
De Silva 1996	100	63	163	10	18	149	167	6	22	145	167	6	19	148	167	6
Dizdarer 2000	44	8	52	0	40	12	52	0	11	41	52	0	8	44	52	0
Eun 2012	75	9	84	0	52	32	84	0	0	0	0	84	35	49	84	0
Guerreiro 1997	153	40	193	0	106	84	190	3	112	78	190	3	84	106	190	3
Heller 1995	164	69	233	10	66	177	243	0	78	165	243	0	49	194	243	0
Kwan 2009	58	23	81	0	38	29	67	14	68	13	81	0	30	50	80	1
Lee 2011	82	28	110	0	79	31	110	0	0	0	0	110	39	71	110	0
Mattson 1985	266	208	474	1	226	238	464	11	325	149	474	1	281	193	474	1

Table 6. Number of participants contributing individual participant data to analyses *(Continued)*

Mattson 1992	302	168	470	10	165	299	464	16	334	133	467	13	242	225	467	13
Nieto-Barrera 2001	510	111	621	1	309	312	621	1	0	0	0	622	0	0	0	622
Ogunrin 2005 [a]	0	0	0	55	29	26	55	0	0	0	0	55	0	0	0	55
Pal 1998	0	0	0	94	41	49	90	4	82	8	90	4	63	27	90	4
Placencia 1993	157	32	189	3	121	71	192	0	131	60	191	1	68	123	191	1
Privitera 2003 (CBZ branch)[b]	221	174	395	0	208	187	395	0	316	79	395	0	194	201	395	0
Privitera 2003 (VPS branch)[b]	111	114	225	0	119	106	225	0	180	45	225	0	106	119	225	0
Ramsay 1992	113	23	136	0	81	44	125	11	0	0	0	136	78	47	125	11
Ramsay 2010	230	31	261	0	197	64	261	0	0	0	0	261	0	0	0	261
Reunanen 1996	288	63	351	0	216	135	351	0	0	0	0	351	328	23	351	0
Richens 1994	210	76	286	14	91	198	289	11	92	198	290	10	77	213	290	10
SANAD A 2007	881	835	1716	5	389	1292	1681	40	596	1085	1681	40	355	1326	1681	40
SANAD B 2007	410	302	712	4	185	521	706	10	174	532	706	10	96	610	706	10
SANAD II A 2021	567	423	990	0	300	690	990	0	341	649	990	0	203	787	990	0
SANAD II B 2021	290	230	520	0	162	358	520	0	195	325	520	0	104	416	520	0
Steiner 1999	108	73	181	0	100	81	181	0	0	0	0	181	157	24	181	0
Stephen 2007	163	64	227	0	81	140	221	6	172	55	227	0	137	90	227	0
Trinka 2013 (CBZ branch)[b]	760	239	999	0	572	427	999	0	780	219	999	0	336	663	999	0
Trinka 2013	582	120	702	1	455	247	702	1	484	218	702	1	191	511	702	1

Table 6. Number of participants contributing individual participant data to analyses *(Continued)*

(VPS branch)[b]																
Turnbull 1985	111	29	140	0	75	65	140	0	47	93	140	0	36	104	140	0
Verity 1995	187	59	246	14	59	187	246	14	84	162	246	14	19	227	246	14
Werhahn 2015	195	166	361	0	249	96	345	16	211	150	361	0	178	183	361	0
Total	**9274**	**5016**	**14290**	**499**	**6654**	**7937**	**14591**	**198**	**5979**	**5932**	**11911**	**2878**	**4760**	**8688**	**13,448**	**1341**

CBZ: carbamazepine
cens: censored
VPS: sodium valproate
[a]For two studies, we could only calculate 'time to first seizure'; the study duration of Ogunrin 2005 was 12 weeks, and all randomised participants completed the study without withdrawing; and Banu 2007 did not record the dates of all seizures after randomisation and dates of withdrawal for allocated treatment for all participants.
[b]Trials designed in two strata based on whether recommended treatment would be CBZ or VPS. Within the two strata, participants were randomised to TPM in Privitera 2003/LEV in Trinka 2013 or CBZ/VPS depending on the strata. Data analysed according to the separate strata (CBZ branch or VPS branch) in this review
[c]Withdrawal information was not available for two trials so we could not calculate 'time to withdrawal of allocated treatment' (Craig 1994; Pal 1998).
[d]We could not calculate 'time to 12-month remission' for nine trials as the duration of the study was less than 12 months (Biton 2001; Brodie 1995a; Brodie 1995b; Chadwick 1998; Eun 2012; Lee 2011; Ramsay 1992; Reunanen 1996; Steiner 1999) and we could not calculate 'time to 12-month remission' or 'time to six-month remission' for three trials as the duration of the study was less than six months (Brodie 1999; Nieto-Barrera 2001; Ramsay 2010).

Table 7. Reasons for treatment failure / withdrawal from allocated treatment

Reason for treatment failure/withdrawal	Classification for analysis	Randomised drug[b]											
		CBZ	PHB	PHT	VPS	LTG	OXC	TPM	GBP	LEV	ZNS	LCM	Total
Adverse events	Event	588 (45%)	24 (19%)	94 (38%)	169 (29%)	302 (41%)	60 (38%)	262 (50%)	73 (21%)	240 (40%)	94 (39%)	48 (29%)	1954 (39%)
Inadequate response	Event	258 (20%)	20 (16%)	28 (11%)	157 (27%)	192 (26%)	39 (25%)	123 (24%)	205 (58%)	159 (27%)	58 (24%)	47 (29%)	1286 (26%)
Both adverse events and inadequate response	Event	145 (11%)	53 (42%)	42 (17%)	107 (18%)	18 (2%)	11 (7%)	46 (9%)	32 (9%)	0 (0%)	0 (0%)	0 (0%)	454 (9%)

Table 7. Reasons for treatment failure / withdrawal from allocated treatment *(Continued)*

Protocol violation/non compliance	Event	94 (7%)	6 (5%)	57 (23%)	20 (3%)	68 (9%)	40 (26%)	39 (8%)	17 (5%)	21 (4%)	3 (1%)	11 (7%)	376 (8%)
Withdrew consent	Event	146 (11%)	16 (13%)	17 (7%)	60 (10%)	93 (13%)	2 (1%)	5 (1%)	2 (1%)	95 (16%)	48 (20%)	47 (29%)	531 (11%)
Other[a]	Event	66 (5%)	6 (5%)	9 (4%)	66 (11%)	60 (8%)	4 (3%)	45 (9%)	23 (7%)	81 (14%)	35 (15%)	11 (7%)	406 (8%)
Total events[b]		**1297 (35%)**	**125 (40%)**	**247 (29%)**	**579 (30%)**	**733 (31%)**	**156 (33%)**	**520 (45%)**	**352 (59%)**	**596 (32%)**	**238 (39%)**	**164 (37%)**	**5007 (35%)**
Illness or death	Censored	31 (1%)	14 (7%)	16 (3%)	12 (1%)	19 (1%)	2 (1%)	16 (3%)	10 (4%)	0 (0%)	0 (0%)	0 (0%)	120 (1%)
Remission of seizures	Censored	49 (2%)	4 (2%)	37 (6%)	91 (7%)	65 (4%)	12 (4%)	44 (7%)	21 (9%)	52 (4%)	23 (6%)	0 (0%)	398 (4%)
Lost to follow-up	Censored	103 (4%)	31 (16%)	58 (9%)	69 (5%)	47 (3%)	28 (9%)	18 (3%)	0 (0%)	41 (3%)	0 (0%)	15 (5%)	410 (4%)
Other[c]	Censored	33 (1%)	2 (1%)	22 (4%)	14 (1%)	36 (2%)	11 (3%)	28 (4%)	10 (4%)	7 (1%)	27 (7%)	0 (0%)	190 (2%)
Completed study	Censored	2208 (91%)	139 (73%)	480 (78%)	1146 (86%)	1451 (90%)	269 (84%)	531 (83%)	201 (83%)	1149 (92%)	322 (87%)	265 (95%)	8161 (88%)
Total censored[b]		**2424 (65%)**	**190 (60%)**	**613 (71%)**	**1332 (70%)**	**1618 (69%)**	**322 (67%)**	**637 (55%)**	**242 (41%)**	**1249 (68%)**	**372 (61%)**	**280 (63%)**	**9279 (65%)**
Total[d]		**3271**	**315**	**860**	**1911**	**2351**	**478**	**1157**	**594**	**1845**	**610**	**444**	**14,286**

CBZ: carbamazepine
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate

VPS: sodium valproate
ZNS: zonisamide
[a]Other treatment-related reasons included: physician's decision, drug-related death, pregnancy or perceived remission, or nonspecific (drug-related) reason.
[b]Proportions for specific reasons indicated proportion of total events or total censored. Proportion for total events and total censored indicated the proportion of total participants.
[c]Other non treatment-related reasons included: epilepsy diagnosis changed, participants developed other medical disorders including neurological and psychiatric disorders or nonspecific (non drug-related) reason.
[d]Four studies did not contribute to analysis of time to treatment failure (Banu 2007; Craig 1994; Ogunrin 2005; Pal 1998). Reason for treatment failure missing for 4 participants; we treated those with missing reasons for withdrawal as censored in analysis and performed a sensitivity analysis treating these individuals as having withdrawal 'events.' Results of sensitivity analysis were practically identical and conclusions unchanged so we have presented the results treating these individuals as censored.

Table 8. Pairwise and network meta-analysis results - Time to treatment failure (for any reason) for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	520	4	**1.55 (1.16 to 2.07)**	68%	18.5%	**1.56 (1.18 to 2.07)**
CBZ vs PHT	428	3	**1.19 (0.87 to 1.61)**	0%	24.4%	1.14 (0.90 to 1.44)
CBZ vs VPS	814	5	1.02 (0.80 to 1.29)	0%	23.8%	1.08 (0.88 to 1.31)
CBZ vs LTG	2203	9	**0.75 (0.65 to 0.88)**	0%	27.7%	**0.79 (0.69 to 0.91)**
CBZ vs OXC	599	2	1.10 (0.85 to 1.43)	66%	0.4%	1.03 (0.82 to 1.30)
CBZ vs TPM	976	2	**1.23 (1.03 to 1.48)**	0%	24.2%	1.19 (0.99 to 1.43)
CBZ vs GBP	681	2	**1.22 (1.02 to 1.45)**	0%	26.6%	**1.21 (1.01 to 1.45)**
CBZ vs LEV	1567	3	0.85 (0.71 to 1.01)	50%	15.8%	**0.80 (0.69 to 0.93)**
CBZ vs ZNS	583	1	1.08 (0.81 to 1.44)	NA	15.7%	0.93 (0.77 to 1.14)
CBZ vs LCM	807	1	0.94 (0.75 to 1.19)	NA	100.0%	0.95 (0.74 to 1.22)
PHB vs PHT	404	3	**0.68 (0.51 to 0.91)**	56%	22.4%	**0.73 (0.55 to 0.97)**
PHB vs VPS	75	2	**0.36 (0.17 to 0.76)**	18%	11.2%	**0.69 (0.50 to 0.95)**
PHB vs LTG	No direct evidence				0.0%	**0.51 (0.37 to 0.69)**
PHB vs OXC	No direct evidence				0.0%	**0.66 (0.47 to 0.93)**
PHB vs TPM	No direct evidence				0.0%	0.76 (0.55 to 1.05)
PHB vs GBP	No direct evidence				0.0%	0.78 (0.56 to 1.08)
PHB vs LEV	No direct evidence				0.0%	**0.51 (0.38 to 0.70)**
PHB vs ZNS	No direct evidence				0.0%	**0.60 (0.43 to 0.84)**
PHB vs LCM	No direct evidence				0.0%	**0.60 (0.42 to 0.88)**
PHT vs VPS	168	3	0.75 (0.49 to 1.15)	0%	13.2%	0.94 (0.71 to 1.25)
PHT vs LTG	90	1	1.22 (0.61 to 2.48)	NA	3.9%	**0.70 (0.54 to 0.90)**

Table 8. Pairwise and network meta-analysis results - Time to treatment failure (for any reason) for individuals with focal seizures *(Continued)*

PHT vs OXC	325	2	0.80 (0.51 to 1.23)	0%	11.3%	0.90 (0.68 to 1.20)
PHT vs TPM	111	1	1.45 (0.27 to 7.92)	NA	0.7%	1.04 (0.79 to 1.38)
PHT vs GBP	No direct evidence				0.0%	1.06 (0.80 to 1.41)
PHT vs LEV	No direct evidence				0.0%	**0.70 (0.54 to 0.92)**
PHT vs ZNS	No direct evidence				0.0%	0.82 (0.61 to 1.10)
PHT vs LCM	No direct evidence				0.0%	0.83 (0.59 to 1.17)
VPS vs LTG	267	3	0.48 (0.29 to 0.79)	0%	5.1%	**0.74 (0.59 to 0.92)**
VPS vs OXC	No direct evidence				0.0%	0.96 (0.72 to 1.28)
VPS vs TPM	129	2	0.79 (0.45 to 1.40)	0%	4.0%	1.10 (0.86 to 1.42)
VPS vs GBP	No direct evidence				0.0%	1.13 (0.87 to 1.46)
VPS vs LEV	190	2	1.08 (0.84 to 1.38)	0%	24.3%	0.75 (0.59 to 0.95)
VPS vs ZNS	No direct evidence				0.0%	0.87 (0.66 to 1.14)
VPS vs LCM	No direct evidence				0.0%	0.88 (0.64 to 1.21)
LTG vs OXC	521	1	**1.37 (1.05 to 1.81)**	NA	17.1%	**1.30 (1.02 to 1.66)**
LTG vs TPM	699	2	**1.62 (1.30 to 2.02)**	0%	17.4%	**1.50 (1.23 to 1.81)**
LTG vs GBP	676	1	**1.64 (1.32 to 2.04)**	NA	17.8%	**1.53 (1.26 to 1.85)**
LTG vs LEV	902	2	0.87 (0.71 to 1.07)	0%	23.3%	1.01 (0.86 to 1.20)
LTG vs ZNS	658	1	1.01 (0.80 to 1.28)	NA	25.0%	1.18 (0.96 to 1.44)
LTG vs LCM	No direct evidence				0.0%	1.19 (0.90 to 1.58)
OXC vs TPM	509	1	1.18 (0.91 to 1.53)	NA	20.9%	1.15 (0.89 to 1.49)
OXC vs GBP	521	1	1.19 (0.92 to 1.55)	NA	21.2%	1.18 (0.91 to 1.52)
OXC vs LEV	No direct evidence				0.0%	0.78 (0.60 to 1.02)
OXC vs ZNS	No direct evidence				0.0%	0.91 (0.67 to 1.22)
OXC vs LCM	No direct evidence				0.0%	0.92 (0.65 to 1.29)
TPM vs GBP	664	1	1.02 (0.83 to 1.24)	NA	25.7%	1.02 (0.83 to 1.26)
TPM vs LEV	No direct evidence				0.0%	**0.68 (0.54 to 0.85)**

Table 8. Pairwise and network meta-analysis results - Time to treatment failure (for any reason) for individuals with focal seizures *(Continued)*

TPM vs ZNS	No direct evidence				0.0%	0.79 (0.61 to 1.02)
TPM vs LCM	No direct evidence				0.0%	0.80 (0.58 to 1.09)
GBP vs LEV	No direct evidence				0.0%	**0.66 (0.53 to 0.83)**
GBP vs ZNS	No direct evidence				0.0%	**0.77 (0.59 to 1.00)**
GBP vs LCM	No direct evidence				0.0%	0.78 (0.57 to 1.06)
LEV vs ZNS	660	1	1.16 (0.91 to 1.48)	NA	27.6%	1.16 (0.94 to 1.43)
LEV vs LCM	No direct evidence				0.0%	1.18 (0.88 to 1.58)
ZNS vs LCM	No direct evidence				0.0%	1.01 (0.74 to 1.39)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 9. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	520	4	**1.52 (1.06 to 2.19)**	73%	31.7%	**1.99 (1.21 to 3.27)**
CBZ vs PHT	428	3	0.83 (0.56 to 1.24)	0%	35.3%	1.00 (0.66 to 1.53)
CBZ vs VPS	570	3	0.94 (0.70 to 1.26)	0%	40.3%	0.88 (0.59 to 1.29)
CBZ vs LTG	2203	9	**0.57 (0.47 to 0.70)**	0%	32.9%	**0.56 (0.44 to 0.73)**

Table 9. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with focal seizures *(Continued)*

CBZ vs OXC	599	2	1.01 (0.73 to 1.38)	0%	18.4%	0.75 (0.46 to 1.22)
CBZ vs TPM	976	2	1.10 (0.88 to 1.39)	0%	29.6%	0.99 (0.69 to 1.43)
CBZ vs GBP	681	2	**0.68 (0.53 to 0.89)**	88%	1.7%	**0.58 (0.37 to 0.91)**
CBZ vs LEV	1567	3	**0.60 (0.47 to 0.77)**	35%	28.8%	**0.65 (0.47 to 0.90)**
CBZ vs ZNS	583	1	0.96 (0.59 to 1.55)	NA	17.9%	0.70 (0.43 to 1.13)
CBZ vs LCM	807	1	1.22 (0.84 to 1.79)	NA	100.0%	1.24 (0.65 to 2.37)
PHB vs PHT	404	3	**0.52 (0.36 to 0.77)**	80%	15.1%	**0.50 (0.30 to 0.86)**
PHB vs VPS	75	2	**0.15 (0.05 to 0.44)**	58%	10.0%	**0.44 (0.24 to 0.80)**
PHB vs LTG	No direct evidence				0.0%	**0.28 (0.16 to 0.49)**
PHB vs OXC	No direct evidence				0.0%	**0.38 (0.19 to 0.75)**
PHB vs TPM	No direct evidence				0.0%	**0.50 (0.27 to 0.92)**
PHB vs GBP	No direct evidence				0.0%	**0.29 (0.15 to 0.58)**
PHB vs LEV	No direct evidence				0.0%	**0.33 (0.18 to 0.58)**
PHB vs ZNS	No direct evidence				0.0%	**0.35 (0.18 to 0.69)**
PHB vs LCM	No direct evidence				0.0%	0.63 (0.28 to 1.41)
PHT vs VPS	168	3	0.58 (0.30 to 1.10)	0%	14.2%	0.87 (0.53 to 1.45)
PHT vs LTG	90	1	1.12 (0.42 to 2.99)	NA	4.4%	**0.56 (0.36 to 0.89)**
PHT vs OXC	325	2	0.35 (0.15 to 0.82)	0%	5.8%	0.75 (0.43 to 1.31)
PHT vs TPM	111	1	1.07 (0.18 to 6.40)	NA	1.3%	0.98 (0.59 to 1.65)
PHT vs GBP	No direct evidence				0.0%	0.58 (0.32 to 1.04)
PHT vs LEV	No direct evidence				0.0%	0.65 (0.39 to 1.09)
PHT vs ZNS	No direct evidence				0.0%	0.70 (0.37 to 1.30)
PHT vs LCM	No direct evidence				0.0%	1.24 (0.57 to 2.68)
VPS vs LTG	267	3	**0.33 (0.15 to 0.74)**	0%	4.3%	**0.64 (0.42 to 0.98)**
VPS vs OXC	No direct evidence				0.0%	0.85 (0.48 to 1.53)

Table 9. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with focal seizures *(Continued)*

VPS vs TPM	129	2	0.94 (0.41 to 2.16)	0%	4.0%	1.13 (0.70 to 1.82)
VPS vs GBP	No direct evidence				0.0%	0.66 (0.37 to 1.16)
VPS vs LEV	190	2	**1.93 (1.12 to 3.33)**	0%	12.9%	0.75 (0.46 to 1.21)
VPS vs ZNS	No direct evidence				0.0%	0.80 (0.44 to 1.45)
VPS vs LCM	No direct evidence				0.0%	1.42 (0.67 to 3.01)
LTG vs OXC	521	1	**1.91 (1.33 to 2.73)**	NA	15.3%	1.33 (0.80 to 2.20)
LTG vs TPM	699	2	**2.20 (1.63 to 2.99)**	0%	17.6%	**1.75 (1.17 to 2.62)**
LTG vs GBP	676	1	**1.50 (1.09 to 2.08)**	NA	21.1%	1.02 (0.63 to 1.65)
LTG vs LEV	902	2	0.84 (0.60 to 1.19)	32%	14.6%	1.16 (0.81 to 1.66)
LTG vs ZNS	658	1	0.90 (0.57 to 1.41)	NA	20.3%	1.24 (0.75 to 2.03)
LTG vs LCM	No direct evidence				0.0%	**2.21 (1.10 to 4.41)**
OXC vs TPM	509	1	1.16 (0.84 to 1.59)	NA	21.6%	1.32 (0.78 to 2.23)
OXC vs GBP	521	1	0.79 (0.56 to 1.11)	NA	22.7%	0.77 (0.44 to 1.35)
OXC vs LEV	No direct evidence				0.0%	0.87 (0.49 to 1.56)
OXC vs ZNS	No direct evidence				0.0%	0.93 (0.48 to 1.82)
OXC vs LCM	No direct evidence				0.0%	1.66 (0.74 to 3.73)
TPM vs GBP	664	1	**0.68 (0.52 to 0.90)**	NA	29.8%	**0.58 (0.35 to 0.97)**
TPM vs LEV	No direct evidence				0.0%	0.66 (0.41 to 1.07)
TPM vs ZNS	No direct evidence				0.0%	0.71 (0.39 to 1.28)
TPM vs LCM	No direct evidence				0.0%	1.26 (0.60 to 2.65)
GBP vs LEV	No direct evidence				0.0%	1.13 (0.65 to 1.97)
GBP vs ZNS	No direct evidence				0.0%	1.21 (0.63 to 2.32)
GBP vs LCM	No direct evidence				0.0%	2.16 (0.98 to 4.75)
LEV vs ZNS	660	1	0.90 (0.57 to 1.42)	NA	24.8%	1.07 (0.64 to 1.78)
LEV vs LCM	No direct evidence				0.0%	1.90 (0.93 to 3.91)

Table 9. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with focal seizures *(Continued)*

ZNS vs LCM	No direct evidence	0.0%	1.78 (0.80 to 3.98)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 10. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	388	3	**1.86 (1.26 to 2.75)**	0%	37.2%	**1.88 (1.25 to 2.81)**
CBZ vs PHT	428	3	1.12 (0.76 to 1.64)	0%	33.2%	1.14 (0.78 to 1.68)
CBZ vs VPS	814	5	1.04 (0.82 to 1.33)	0%	52.9%	1.16 (0.88 to 1.52)
CBZ vs LTG	2098	8	1.00 (0.72 to 1.39)	0%	17.7%	1.02 (0.78 to 1.33)
CBZ vs OXC	599	2	1.17 (0.76 to 1.81)	0%	0.0%	1.14 (0.73 to 1.77)
CBZ vs TPM	976	2	**1.48 (1.08 to 2.03)**	0%	21.9%	1.32 (0.95 to 1.83)
CBZ vs GBP	681	2	**2.05 (1.59 to 2.66)**	0%	30.5%	**2.07 (1.56 to 2.75)**
CBZ vs LEV	1567	3	1.44 (0.98 to 2.12)	0%	23.0%	1.07 (0.78 to 1.45)
CBZ vs ZNS	583	1	1.07 (0.60 to 1.92)	NA	10.3%	1.23 (0.86 to 1.77)
CBZ vs LCM	807	1	0.79 (0.49 to 1.26)	NA	100.0%	0.79 (0.47 to 1.33)

Table 10. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with focal seizures *(Continued)*

PHB vs PHT	404	3	**0.58 (0.40 to 0.85)**	0%	43.7%	**0.61 (0.41 to 0.91)**
PHB vs VPS	75	2	0.74 (0.29 to 1.86)	28%	4.1%	**0.62 (0.39 to 0.97)**
PHB vs LTG	No direct evidence				0.0%	**0.54 (0.34 to 0.88)**
PHB vs OXC	No direct evidence				0.0%	0.61 (0.33 to 1.10)
PHB vs TPM	No direct evidence				0.0%	0.71 (0.42 to 1.19)
PHB vs GBP	No direct evidence				0.0%	1.11 (0.67 to 1.81)
PHB vs LEV	No direct evidence				0.0%	**0.57 (0.34 to 0.94)**
PHB vs ZNS	No direct evidence				0.0%	0.66 (0.38 to 1.13)
PHB vs LCM	No direct evidence				0.0%	**0.42 (0.22 to 0.82)**
PHT vs VPS	168	3	0.93 (0.52 to 1.68)	0%	13.8%	1.02 (0.67 to 1.53)
PHT vs LTG	No direct evidence				0.0%	0.89 (0.56 to 1.41)
PHT vs OXC	325	2	1.00 (0.06 to 16.0)	0%	0.6%	1.00 (0.55 to 1.79)
PHT vs TPM	No direct evidence				6.0%	1.16 (0.69 to 1.94)
PHT vs GBP	No direct evidence				0.0%	**1.82 (1.12 to 2.94)**
PHT vs LEV	No direct evidence				0.0%	0.93 (0.57 to 1.52)
PHT vs ZNS	No direct evidence				0.0%	1.08 (0.64 to 1.82)
PHT vs LCM	No direct evidence				0.0%	0.70 (0.37 to 1.32)
VPS vs LTG	267	3	0.65 (0.33 to 1.26)	0%	2.3%	0.88 (0.62 to 1.24)
VPS vs OXC	No direct evidence				0.0%	0.98 (0.59 to 1.64)
VPS vs TPM	129	2	0.33 (0.11 to 1.01)	0%	3.5%	1.14 (0.74 to 1.75)
VPS vs GBP	No direct evidence				0.0%	**1.79 (1.20 to 2.66)**
VPS vs LEV	190	2	1.09 (0.76 to 1.56)	49%	19.9%	0.92 (0.62 to 1.36)
VPS vs ZNS	No direct evidence				0.0%	1.06 (0.69 to 1.64)
VPS vs LCM	No direct evidence				0.0%	0.68 (0.38 to 1.23)
LTG vs OXC	521	1	1.21 (0.79 to 1.85)	NA	20.6%	1.12 (0.71 to 1.76)
LTG vs TPM	699	2	**1.49 (1.07 to 2.08)**	0%	22.8%	1.30 (0.92 to 1.85)

Table 10. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with focal seizures *(Continued)*

LTG vs GBP	676	1	**2.30 (1.70 to 3.11)**	NA	18.0%	**2.04 (1.48 to 2.80)**
LTG vs LEV	902	2	0.83 (0.57 to 1.21)	3%	30.9%	1.05 (0.76 to 1.46)
LTG vs ZNS	658	1	1.12 (0.78 to 1.59)	NA	22.2%	1.22 (0.86 to 1.72)
LTG vs LCM	No direct evidence				0.0%	0.78 (0.44 to 1.40)
OXC vs TPM	509	1	1.24 (0.81 to 1.88)	NA	24.0%	1.16 (0.73 to 1.84)
OXC vs GBP	521	1	**1.91 (1.28 to 2.83)**	NA	28.7%	**1.82 (1.17 to 2.82)**
OXC vs LEV	No direct evidence				0.0%	0.94 (0.56 to 1.57)
OXC vs ZNS	No direct evidence				0.0%	1.08 (0.63 to 1.86)
OXC vs LCM	No direct evidence				0.0%	0.70 (0.35 to 1.38)
TPM vs GBP	664	1	**1.54 (1.15 to 2.06)**	NA	32.8%	**1.57 (1.13 to 2.18)**
TPM vs LEV	No direct evidence				0.0%	0.81 (0.52 to 1.24)
TPM vs ZNS	No direct evidence				0.0%	0.93 (0.59 to 1.47)
TPM vs LCM	No direct evidence				0.0%	0.60 (0.33 to 1.11)
GBP vs LEV	No direct evidence				0.0%	**0.51 (0.35 to 0.77)**
GBP vs ZNS	No direct evidence				0.0%	**0.60 (0.39 to 0.91)**
GBP vs LCM	No direct evidence				0.0%	**0.38 (0.21 to 0.69)**
LEV vs ZNS	660	1	1.40 (0.96 to 2.05)	NA	0.3%	1.16 (0.80 to 1.67)
LEV vs LCM	No direct evidence				0.0%	0.74 (0.41 to 1.36)
ZNS vs LCM	No direct evidence				0.0%	0.64 (0.34 to 1.21)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 11. Pairwise and network meta-analysis results - Time to treatment failure (for any reason) for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	156	3	0.83 (0.35 to 1.95)	12%	23.5%	1.40 (0.79 to 2.48)
CBZ vs PHT	118	2	0.37 (0.13 to 1.05)	0%	10.9%	0.77 (0.51 to 1.17)
CBZ vs VPS	405	4	0.79 (0.46 to 1.38)	7%	23.3%	**0.66 (0.51 to 0.85)**
CBZ vs LTG	365	6	0.88 (0.57 to 1.38)	0%	31.9%	**0.70 (0.53 to 0.92)**
CBZ vs OXC	62	1	0.90 (0.39 to 2.13)	NA	12.6%	0.82 (0.47 to 1.42)
CBZ vs TPM	193	2	0.84 (0.49 to 1.44)	0%	25.1%	0.90 (0.67 to 1.22)
CBZ vs GBP	73	1	0.71 (0.33 to 1.52)	NA	16.5%	0.75 (0.40 to 1.39)
CBZ vs LEV	251	2	0.82 (0.49 to 1.35)	0%	55.9%	**0.74 (0.55 to 1.00)**
CBZ vs LCM	80	1	1.84 (0.82 to 4.13)	NA	100.0%	1.74 (0.78 to 3.86)
PHB vs PHT	95	2	0.64 (0.20 to 2.04)	0%	15.9%	0.55 (0.29 to 1.06)
PHB vs VPS	94	2	1.80 (0.65 to 4.95)	0%	19.7%	**0.47 (0.26 to 0.84)**
PHB vs LTG	No direct evidence				0.0%	**0.50 (0.27 to 0.91)**
PHB vs OXC	No direct evidence				0.0%	0.58 (0.27 to 1.25)
PHB vs TPM	No direct evidence				0.0%	0.65 (0.35 to 1.19)
PHB vs GBP	No direct evidence				0.0%	0.53 (0.23 to 1.21)
PHB vs LEV	No direct evidence				0.0%	**0.53 (0.29 to 0.98)**
PHB vs LCM	No direct evidence				0.0%	1.24 (0.47 to 3.31)
PHT vs VPS	326	4	1.53 (0.61 to 3.83)	22%	10.4%	0.85 (0.58 to 1.25)
PHT vs LTG	91	1	0.90 (0.34 to 2.37)	NA	12.8%	0.90 (0.61 to 1.33)
PHT vs OXC	155	2	1.38 (0.60 to 3.16)	0%	19.7%	1.05 (0.62 to 1.78)
PHT vs TPM	208	1	0.23 (0.03 to 1.78)	NA	3.0%	1.17 (0.78 to 1.76)

Table 11. Pairwise and network meta-analysis results - Time to treatment failure (for any reason) for individuals with generalised seizures *(Continued)*

PHT vs GBP	No direct evidence				0.0%	0.96 (0.49 to 1.90)
PHT vs LEV	No direct evidence				0.0%	0.96 (0.62 to 1.49)
PHT vs LCM	No direct evidence				0.0%	2.25 (0.92 to 5.51)
VPS vs LTG	560	3	1.91 (0.93 to 3.90)	0%	15.9%	1.06 (0.81 to 1.37)
VPS vs OXC	No direct evidence				0.0%	1.24 (0.72 to 2.14)
VPS vs TPM	588	2	1.81 (0.91 to 3.60)	36%	11.0%	**1.37 (1.06 to 1.77)**
VPS vs GBP	No direct evidence				0.0%	1.13 (0.61 to 2.11)
VPS vs LEV	1032	2	1.46 (0.63 to 3.38)	0%	17.8%	1.13 (0.89 to 1.42)
VPS vs LCM	No direct evidence				0.0%	**2.64 (1.14 to 6.09)**
LTG vs OXC	67	1	0.69 (0.03 to 1.60)	NA	14.1%	1.17 (0.68 to 2.02)
LTG vs TPM	528	2	0.66 (0.33 to 1.31)	0%	17.1%	**1.30 (1.01 to 1.67)**
LTG vs GBP	78	1	0.55 (0.26 to 1.14)	NA	18.4%	1.07 (0.59 to 1.96)
LTG vs LEV	No direct evidence				0.0%	1.07 (0.77 to 1.48)
LTG vs LCM	No direct evidence				0.0%	**2.50 (1.07 to 5.81)**
OXC vs TPM	75	1	0.95 (0.43 to 2.11)	NA	16.8%	1.11 (0.64 to 1.92)
OXC vs GBP	65	1	0.79 (0.34 to 1.82)	NA	18.1%	0.92 (0.44 to 1.89)
OXC vs LEV	No direct evidence				0.0%	0.91 (0.51 to 1.63)
OXC vs LCM	No direct evidence				0.0%	2.13 (0.81 to 5.63)
TPM vs GBP	86	1	0.83 (0.41 to 1.65)	NA	22.7%	0.83 (0.45 to 1.51)
TPM vs LEV	No direct evidence			NA	0.0%	0.82 (0.59 to 1.14)
TPM vs LCM	No direct evidence			NA	0.0%	1.92 (0.82 to 4.50)
GBP vs LEV	No direct evidence			NA	0.0%	1.00 (0.52 to 1.90)
GBP vs LCM	No direct evidence			NA	0.0%	2.33 (0.85 to 6.39)
LEV vs LCM	No direct evidence			NA	0.0%	**2.34 (1.00 to 5.48)**

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam

LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant
c. Proportion of the NMA estimate contributed by direct evidence

Table 12. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	156	3	0.33 (0.09 to 1.16)	0%	25.2%	1.09 (0.42 to 2.87)
CBZ vs PHT	118	2	0.62 (0.13 to 3.08)	0%	13.6%	0.79 (0.37 to 1.73)
CBZ vs VPS	117	2	1.36 (0.34 to 5.49)	0%	10.3%	**0.51 (0.29 to 0.88)**
CBZ vs LTG	368	7	1.03 (0.57 to 1.87)	0%	35.5%	**0.44 (0.26 to 0.73)**
CBZ vs OXC	62	1	0.59 (0.19 to 1.77)	NA	17.8%	0.51 (0.17 to 1.50)
CBZ vs TPM	193	2	0.75 (0.37 to 1.49)	0%	30.1%	0.72 (0.40 to 1.31)
CBZ vs GBP	73	1	0.60 (0.21 to 1.68)	NA	18.9%	0.33 (0.11 to 1.02)
CBZ vs LEV	251	2	0.62 (0.29 to 1.36)	0%	58.9%	0.62 (0.32 to 1.19)
CBZ vs LCM	80	1	3.51 (0.69 to 17.9)	NA	100%	4.39 (0.71 to 27.1)
PHB vs PHT	95	2	1.82 (0.33 to 10.1)	0%	18.1%	0.73 (0.25 to 2.15)
PHB vs VPS	94	2	3.86 (0.95 to 15.7)	0%	21.5%	0.47 (0.18 to 1.21)
PHB vs LTG	No direct evidence				0.0%	0.40 (0.14 to 1.11)
PHB vs OXC	No direct evidence				0.0%	0.47 (0.12 to 1.86)
PHB vs TPM	No direct evidence				0.0%	0.66 (0.23 to 1.86)
PHB vs GBP	No direct evidence				0.0%	0.31 (0.07 to 1.27)
PHB vs LEV	No direct evidence				0.0%	0.56 (0.19 to 1.66)
PHB vs LCM	No direct evidence				0.0%	4.01 (0.51 to 31.5)
PHT vs VPS	326	4	2.71 (0.47 to 15.7)	0%	13.8%	0.64 (0.31 to 1.34)

Table 12. Pairwise and network meta-analysis results - Time to treatment failure due to adverse events for individuals with generalised seizures *(Continued)*

PHT vs LTG	91	1	0.58 (0.14 to 2.50)	NA	16.6%	0.55 (0.26 to 1.17)
PHT vs OXC	155	2	7.99 (0.51 to 124)	0%	0.0%	0.64 (0.20 to 2.07)
PHT vs TPM	208	1	0.10 (0.01 to 1.61)	NA	4.5%	0.91 (0.41 to 2.03)
PHT vs GBP	No direct evidence				0.0%	0.42 (0.12 to 1.49)
PHT vs LEV	No direct evidence				0.0%	0.78 (0.32 to 1.91)
PHT vs LCM	No direct evidence				0.0%	5.53 (0.77 to 39.9)
VPS vs LTG	560	3	1.88 (0.68 to 5.21)	0%	20.3%	0.86 (0.50 to 1.48)
VPS vs OXC	No direct evidence				0.0%	1.00 (0.33 to 3.02)
VPS vs TPM	588	2	1.53 (0.59 to 3.97)	54%	10.8%	1.42 (0.82 to 2.46)
VPS vs GBP	No direct evidence				0.0%	0.66 (0.21 to 2.08)
VPS vs LEV	1032	2	0.79 (0.19 to 3.39)	0%	14.7%	1.21 (0.66 to 2.21)
VPS vs LCM	No direct evidence				0.0%	8.61 (1.29 to 57.5)
LTG vs OXC	67	1	0.48 (0.15 to 1.54)	NA	16.1%	1.17 (0.40 to 3.42)
LTG vs TPM	528	2	0.55 (0.21 to 1.42)	0%	17.5%	1.65 (0.92 to 2.95)
LTG vs GBP	78	1	0.49 (0.16 to 1.47)	NA	16.9%	0.76 (0.25 to 2.34)
LTG vs LEV	No direct evidence				0.0%	1.41 (0.67 to 2.93)
LTG vs LCM	No direct evidence				0.0%	10.0 (1.51 to 66.4)
OXC vs TPM	75	1	1.16 (0.39 to 3.45)	NA	20.2%	1.42 (0.49 to 4.12)
OXC vs GBP	65	1	1.02 (0.30 to 3.50)	NA	20.5%	0.65 (0.17 to 2.49)
OXC vs LEV	No direct evidence				0.0%	1.21 (0.37 to 3.98)
OXC vs LCM	No direct evidence				0.0%	8.60 (1.04 to 71.2)
TPM vs GBP	86	1	0.88 (0.32 to 2.43)	NA	21.6%	0.46 (0.15 to 1.39)
TPM vs LEV	No direct evidence				0.0%	0.85 (0.41 to 1.79)
TPM vs LCM	No direct evidence				0.0%	6.07 (0.90 to 41.2)
GBP vs LEV	No direct evidence				0.0%	1.84 (0.54 to 6.30)
GBP vs LCM	No direct evidence				0.0%	**13.1 (1.55 to 111)**
LEV vs LCM	No direct evidence				0.0%	**7.13 (1.03 to 49.4)**

CBZ: carbamazepine

CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 13. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	99	2	0.78 (0.21 to 2.95)	0%	22.7%	1.63 (0.72 to 3.69)
CBZ vs PHT	118	2	0.40 (0.13 to 1.30)	0%	26.5%	0.62 (0.27 to 1.41)
CBZ vs VPS	405	4	0.76 (0.41 to 1.40)	0%	51.3%	1.04 (0.67 to 1.59)
CBZ vs LTG	323	6	0.00 (0.00 to 0.02)	98%	0.1%	**1.92 (1.04 to 3.52)**
CBZ vs OXC	62	1	1.62 (0.34 to 7.70)	NA	15.3%	1.57 (0.51 to 4.81)
CBZ vs TPM	193	2	1.16 (0.39 to 3.49)	0%	24.9%	**1.84 (1.03 to 3.28)**
CBZ vs GBP	73	1	1.35 (0.36 to 5.04)	NA	19.0%	**2.86 (1.15 to 7.12)**
CBZ vs LEV	251	2	6.11 (0.75 to 50.0)	0%	28.2%	1.29 (0.70 to 2.37)
CBZ vs LCM	80	1	0.52 (0.09 to 2.86)	NA	99.9%	0.41 (0.08 to 2.22)
PHB vs PHT	95	2	0.47 (0.11 to 1.95)	0%	27.0%	0.38 (0.14 to 1.02)
PHB vs VPS	94	2	1.14 (0.33 to 3.98)	0%	25.8%	0.64 (0.29 to 1.42)
PHB vs LTG	No direct evidence				0.0%	1.18 (0.46 to 3.01)
PHB vs OXC	No direct evidence				0.0%	0.96 (0.26 to 3.63)
PHB vs TPM	No direct evidence				0.0%	1.13 (0.45 to 2.82)
PHB vs GBP	No direct evidence				0.0%	1.76 (0.55 to 5.65)

Table 13. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with generalised seizures *(Continued)*

PHB vs LEV	No direct evidence				0.0%	0.79 (0.32 to 1.96)
PHB vs LCM	No direct evidence				0.0%	0.25 (0.04 to 1.65)
PHT vs VPS	326	4	2.05 (0.64 to 6.54)	0%	26.8%	1.66 (0.75 to 3.70)
PHT vs LTG	No direct evidence				0.0%	**3.08 (1.22 to 7.76)**
PHT vs OXC	No direct evidence				0.0%	2.52 (0.71 to 8.95)
PHT vs TPM	No direct evidence				0.0%	**2.96 (1.20 to 7.29)**
PHT vs GBP	No direct evidence				0.0%	**4.60 (1.46 to 14.5)**
PHT vs LEV	No direct evidence				0.0%	2.07 (0.83 to 5.15)
PHT vs LCM	No direct evidence				0.0%	0.66 (0.10 to 4.31)
VPS vs LTG	560	3	1.98 (0.60 to 6.49)	0%	14.1%	**1.85 (1.11 to 3.11)**
VPS vs OXC	No direct evidence				0.0%	1.51 (0.50 to 4.54)
VPS vs TPM	588	2	**4.81 (1.14 to 20.3)**	0%	34.6%	**1.78 (1.10 to 2.87)**
VPS vs GBP	No direct evidence				0.0%	**2.76 (1.14 to 6.70)**
VPS vs LEV	1032	2	3.02 (0.43 to 21.1)	0%	22.0%	1.25 (0.81 to 1.93)
VPS vs LCM	No direct evidence				0.0%	0.40 (0.07 to 2.26)
LTG vs OXC	67	1	1.07 (0.27 to 4.26)	NA	27.6%	0.82 (0.28 to 2.42)
LTG vs TPM	528	2	0.99 (0.31 to 3.09)	0%	30.8%	0.96 (0.61 to 1.51)
LTG vs GBP	78	1	0.89 (0.30 to 2.69)	NA	21.5%	1.49 (0.64 to 3.48)
LTG vs LEV	No direct evidence				0.0%	0.67 (0.33 to 1.35)
LTG vs LCM	No direct evidence				0.0%	0.22 (0.04 to 1.29)
OXC vs TPM	75	1	0.92 (0.26 to 3.21)	NA	25.5%	1.17 (0.40 to 3.41)
OXC vs GBP	65	1	0.84 (0.25 to 2.81)	NA	31.6%	1.83 (0.58 to 5.70)
OXC vs LEV	No direct evidence				0.0%	0.82 (0.25 to 2.70)
OXC vs LCM	No direct evidence				0.0%	0.26 (0.04 to 1.99)
TPM vs GBP	86	1	0.91 (0.36 to 2.3)	NA	0.0%	1.55 (0.68 to 3.53)
TPM vs LEV	No direct evidence				0.0%	0.70 (0.36 to 1.35)
TPM vs LCM	No direct evidence				0.0%	0.22 (0.04 to 1.33)

Table 13. Pairwise and network meta-analysis results - Time to treatment failure due to lack of efficacy for individuals with generalised seizures *(Continued)*

GBP vs LEV	No direct evidence	0.0%	0.45 (0.17 to 1.22)
GBP vs LCM	No direct evidence	0.0%	**0.14 (0.02 to 0.98)**
LEV vs LCM	No direct evidence	0.0%	0.32 (0.05 to 1.91)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 14. Pairwise and network meta-analysis results - Time to 12-month remission for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	525	4	1.00 (0.73 to 1.35)	42%	16.9%	1.03 (0.77 to 1.38)
CBZ vs PHT	430	3	1.03 (0.78 to 1.37)	0%	21.9%	1.04 (0.84 to 1.29)
CBZ vs VPS	816	5	1.06 (0.86 to 1.30)	30%	17.7%	1.08 (0.91 to 1.29)
CBZ vs LTG	907	2	1.08 (0.91 to 1.28)	0%	18.4%	1.06 (0.93 to 1.22)
CBZ vs OXC	591	1	0.97 (0.78 to 1.20)	0%	17.8%	0.95 (0.78 to 1.15)
CBZ vs TPM	962	2	**1.20 (1.00 to 1.44)**	0%	21.9%	1.13 (0.94 to 1.36)
CBZ vs GBP	666	1	**1.32 (1.09 to 1.60)**	NA	20.4%	**1.29 (1.06 to 1.57)**
CBZ vs LEV	1567	3	1.09 (0.92 to 1.29)	0%	22.3%	1.08 (0.94 to 1.24)
CBZ vs ZNS	582	1	1.05 (0.85 to 1.30)	NA	18.9%	1.10 (0.94 to 1.29)

Table 14. Pairwise and network meta-analysis results - Time to 12-month remission for individuals with focal seizures *(Continued)*

CBZ vs LCM	806	1	1.00 (0.83 to 1.19)	NA	100.0%	1.00 (0.81 to 1.22)
PHB vs PHT	465	4	0.91 (0.66 to 1.26)	0%	37.7%	1.01 (0.75 to 1.36)
PHB vs VPS	80	2	0.97 (0.54 to 1.73)	0%	8.7%	1.05 (0.76 to 1.44)
PHB vs LTG	No direct evidence				0.0%	1.03 (0.75 to 1.42)
PHB vs OXC	No direct evidence				0.0%	0.92 (0.66 to 1.28)
PHB vs TPM	No direct evidence				0.0%	1.10 (0.78 to 1.54)
PHB vs GBP	No direct evidence				0.0%	1.25 (0.88 to 1.76)
PHB vs LEV	No direct evidence				0.0%	1.05 (0.76 to 1.44)
PHB vs ZNS	No direct evidence				0.0%	1.07 (0.77 to 1.48)
PHB vs LCM	No direct evidence				0.0%	0.97 (0.68 to 1.38)
PHT vs VPS	245	4	0.92 (0.64 to 1.31)	0%	14.2%	1.04 (0.81 to 1.33)
PHT vs LTG					0.0%	1.02 (0.80 to 1.31)
PHT vs OXC	318	2	0.94 (0.65 to 1.36)	0%	11.5%	0.91 (0.71 to 1.17)
PHT vs TPM	No direct evidence				0.0%	1.09 (0.83 to 1.43)
PHT vs GBP	No direct evidence				0.0%	1.24 (0.93 to 1.64)
PHT vs LEV	No direct evidence				0.0%	1.04 (0.80 to 1.34)
PHT vs ZNS	No direct evidence				0.0%	1.06 (0.81 to 1.38)
PHT vs LCM	No direct evidence				0.0%	0.96 (0.71 to 1.29)
VPS vs LTG	267	3	0.90 (0.54 to 1.49)	0%	4.1%	0.98 (0.80 to 1.21)
VPS vs OXC	No direct evidence				0.0%	0.88 (0.68 to 1.12)
VPS vs TPM	128	2	0.62 (0.33 to 1.18)	59%	0.9%	1.05 (0.82 to 1.33)
VPS vs GBP	No direct evidence				0.0%	1.19 (0.92 to 1.53)
VPS vs LEV	190	1	0.91 (0.74 to 1.11)	0%	29.3%	1.00 (0.81 to 1.23)
VPS vs ZNS	No direct evidence				0.0%	1.02 (0.81 to 1.28)
VPS vs LCM	No direct evidence				0.0%	0.92 (0.70 to 1.20)
LTG vs OXC	511	1	0.87 (0.69 to 1.01)	NA	15.6%	0.89 (0.72 to 1.10)
LTG vs TPM	683	2	1.12 (0.92 to 1.36)	0%	19.5%	1.06 (0.88 to 1.29)

Table 14. Pairwise and network meta-analysis results - Time to 12-month remission for individuals with focal seizures *(Continued)*

LTG vs GBP	660	1	**1.21 (1.00 to 1.47)**	NA	19.9%	1.21 (0.99 to 1.48)
LTG vs LEV	902	2	1.02 (0.86 to 1.20)	0%	23.6%	1.01 (0.87 to 1.18)
LTG vs ZNS	658	1	1.07 (0.88 to 1.29)	NA	24.7%	1.04 (0.87 to 1.23)
LTG vs LCM	No direct evidence				0.0%	0.94 (0.73 to 1.20)
OXC vs TPM	498	1	**1.29 (1.02 to 1.63)**	NA	18.9%	1.20 (0.95 to 1.51)
OXC vs GBP	509	1	**1.39 (1.10 to 1.75)**	NA	19.0%	**1.36 (1.07 to 1.72)**
OXC vs LEV	No direct evidence				0.0%	1.14 (0.90 to 1.43)
OXC vs ZNS	No direct evidence				0.0%	1.16 (0.91 to 1.48)
OXC vs LCM	No direct evidence				0.0%	1.05 (0.79 to 1.40)
TPM vs GBP	647	1	1.08 (0.88 to 1.32)	NA	24.8%	1.14 (0.91 to 1.41)
TPM vs LEV	No direct evidence				0.0%	0.95 (0.77 to 1.18)
TPM vs ZNS	No direct evidence				0.0%	0.97 (0.77 to 1.22)
TPM vs LCM	No direct evidence				0.0%	0.88 (0.67 to 1.16)
GBP vs LEV	No direct evidence				0.0%	0.84 (0.67 to 1.05)
GBP vs ZNS	No direct evidence				0.0%	0.86 (0.67 to 1.09)
GBP vs LCM	No direct evidence				0.0%	0.77 (0.58 to 1.03)
LEV vs ZNS	660	1	1.05 (0.87 to 1.27)	NA	28.0%	1.02 (0.86 to 1.21)
LEV vs LCM	No direct evidence				0.0%	0.92 (0.72 to 1.18)
ZNS vs LCM	No direct evidence				0.0%	0.91 (0.70 to 1.17)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 15. Pairwise and network meta-analysis results - Time to 12-month remission for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	158	3	**1.90 (1.00 to 3.62)**	0%	40.5%	1.31 (0.87 to 1.98)
CBZ vs PHT	121	2	0.90 (0.49 to 1.64)	65%	7.2%	0.97 (0.73 to 1.31)
CBZ vs VPS	412	4	0.99 (0.70 to 1.40)	0%	40.4%	0.99 (0.82 to 1.21)
CBZ vs LTG	74	1	0.92 (0.53 to 1.59)	NA	17.8%	1.19 (0.90 to 1.57)
CBZ vs OXC	61	1	1.28 (0.67 to 2.43)	NA	14.2%	1.26 (0.83 to 1.91)
CBZ vs TPM	191	2	0.84 (0.53 to 1.35)	0%	24.5%	1.07 (0.83 to 1.39)
CBZ vs GBP	72	1	0.90 (0.51 to 1.59)	NA	19.1%	1.29 (0.80 to 2.07)
CBZ vs LEV	251	2	0.98 (0.63 to 1.54)	77%	15.3%	0.99 (0.77 to 1.26)
CBZ vs LCM	78	1	1.04 (0.58 to 1.88)	NA	100.0%	1.04 (0.58 to 1.87)
PHB vs PHT	130	3	0.77 (0.36 to 1.65)	6%	9.9%	0.74 (0.48 to 1.15)
PHB vs VPS	98	2	0.87 (0.40 to 1.89)	42%	12.4%	0.76 (0.50 to 1.14)
PHB vs LTG	No direct evidence				0.0%	0.90 (0.57 to 1.44)
PHB vs OXC	No direct evidence				0.0%	0.96 (0.56 to 1.66)
PHB vs TPM	No direct evidence				0.0%	0.82 (0.52 to 1.28)
PHB vs GBP	No direct evidence				0.0%	0.98 (0.54 to 1.80)
PHB vs LEV	No direct evidence				0.0%	0.75 (0.48 to 1.17)
PHB vs LCM	No direct evidence				0.0%	0.79 (0.39 to 1.62)
PHT vs VPS	269	4	1.15 (0.72 to 1.83)	0%	36.1%	1.02 (0.78 to 1.33)
PHT vs LTG	No direct evidence				0.0%	1.22 (0.87 to 1.71)
PHT vs OXC	154	2	1.29 (0.68 to 2.46)	0%	19.2%	1.29 (0.87 to 1.92)
PHT vs TPM	No direct evidence				0.0%	1.10 (0.79 to 1.52)

Table 15. Pairwise and network meta-analysis results - Time to 12-month remission for individuals with generalised seizures *(Continued)*

PHT vs GBP	No direct evidence				0.0%	1.32 (0.79 to 2.21)
PHT vs LEV	No direct evidence				0.0%	1.01 (0.73 to 1.40)
PHT vs LCM	No direct evidence				0.0%	1.07 (0.55 to 2.06)
VPS vs LTG	555	3	1.27 (0.64 to 2.50)	0%	12.4%	1.19 (0.95 to 1.50)
VPS vs OXC	No direct evidence				0.0%	1.27 (0.85 to 1.90)
VPS vs TPM	585	2	1.86 (0.94 to 3.71)	0%	4.3%	1.08 (0.87 to 1.34)
VPS vs GBP	No direct evidence				0.0%	1.30 (0.82 to 2.07)
VPS vs LEV	1032	2	1.10 (0.59 to 2.04)	55%	53.2%	0.99 (0.82 to 1.20)
VPS vs LCM	No direct evidence				0.0%	1.05 (0.56 to 1.94)
LTG vs OXC	67	1	1.39 (0.75 to 2.59)	NA	17.8%	1.06 (0.69 to 1.63)
LTG vs TPM	525	2	0.87 (0.52 to 1.45)	0%	23.9%	0.90 (0.72 to 1.14)
LTG vs GBP	78	1	0.98 (0.56 to 1.69)	NA	22.7%	1.09 (0.68 to 1.73)
LTG vs LEV	No direct evidence				0.0%	0.83 (0.62 to 1.12)
LTG vs LCM	No direct evidence				0.0%	0.88 (0.46 to 1.68)
OXC vs TPM	74	1	0.62 (0.34 to 1.14)	NA	18.3%	0.85 (0.56 to 1.29)
OXC vs GBP	65	1	0.70 (0.37 to 1.33)	NA	17.7%	1.02 (0.59 to 1.76)
OXC vs LEV	No direct evidence				0.0%	0.78 (0.50 to 1.22)
OXC vs LCM	No direct evidence				0.0%	0.82 (0.40 to 1.69)
TPM vs GBP	85	1	1.13 (0.66 to 1.92)	NA	24.7%	1.20 (0.76 to 1.90)
TPM vs LEV	No direct evidence				0.0%	0.92 (0.70 to 1.22)
TPM vs LCM	No direct evidence				0.0%	0.97 (0.51 to 1.84)
GBP vs LEV	No direct evidence				0.0%	0.76 (0.47 to 1.26)
GBP vs LCM	No direct evidence				0.0%	0.80 (0.38 to 1.71)
LEV vs LCM	No direct evidence				0.0%	1.05 (0.56 to 1.99)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam

LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 16. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	525	4	0.90 (0.70 to 1.15)	45%	17.4%	0.95 (0.75 to 1.20)
CBZ vs PHT	430	3	0.97 (0.75 to 1.26)	0%	18.2%	1.01 (0.84 to 1.21)
CBZ vs VPS	816	5	1.15 (0.97 to 1.37)	47%	12.5%	**1.15 (1.00 to 1.32)**
CBZ vs LTG	1467	7	1.11 (0.96 to 1.27)	20%	11.4%	1.08 (0.97 to 1.20)
CBZ vs OXC	591	2	1.02 (0.84 to 1.24)	0%	17.4%	0.94 (0.80 to 1.10)
CBZ vs TPM	962	2	1.15 (0.98 to 1.34)	0%	24.2%	1.08 (0.94 to 1.24)
CBZ vs GBP	666	1	**1.17 (1.00 to 1.38)**	70%	3.8%	1.13 (0.98 to 1.31)
CBZ vs LEV	1567	3	1.10 (0.97 to 1.25)	0%	31.2%	1.07 (0.97 to 1.18)
CBZ vs ZNS	582	1	1.00 (0.82 to 1.20)	NA	19.3%	1.07 (0.94 to 1.22)
CBZ vs LCM	806	1	0.97 (0.82 to 1.13)	NA	100.0%	0.97 (0.82 to 1.13)
PHB vs PHT	465	4	0.90 (0.68 to 1.20)	0%	37.1%	1.06 (0.83 to 1.35)
PHB vs VPS	80	2	1.00 (0.58 to 1.72)	0%	7.5%	1.21 (0.93 to 1.56)
PHB vs LTG	No direct evidence				0.0%	1.14 (0.88 to 1.46)
PHB vs OXC	No direct evidence				0.0%	0.99 (0.75 to 1.29)
PHB vs TPM	No direct evidence				0.0%	1.13 (0.86 to 1.48)
PHB vs GBP	No direct evidence				0.0%	1.19 (0.91 to 1.57)
PHB vs LEV	No direct evidence				0.0%	1.12 (0.87 to 1.44)
PHB vs ZNS	No direct evidence				0.0%	1.13 (0.87 to 1.47)

Table 16. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with focal seizures *(Continued)*

PHB vs LCM	No direct evidence				0.0%	1.02 (0.77 to 1.35)
PHT vs VPS	245	4	0.91 (0.69 to 1.20)	0%	17.3%	1.14 (0.93 to 1.39)
PHT vs LTG	90	1	1.71 (0.57 to 5.12)	NA	0.9%	1.07 (0.88 to 1.31)
PHT vs OXC	318	2	0.85 (0.63 to 1.16)	0%	12.6%	0.93 (0.76 to 1.14)
PHT vs TPM	No direct evidence				0.0%	1.07 (0.86 to 1.33)
PHT vs GBP	No direct evidence				0.0%	1.13 (0.90 to 1.41)
PHT vs LEV	No direct evidence				0.0%	1.06 (0.87 to 1.30)
PHT vs ZNS	No direct evidence				0.0%	1.07 (0.86 to 1.32)
PHT vs LCM	No direct evidence				0.0%	0.96 (0.75 to 1.22)
VPS vs LTG	266	3	0.83 (0.57 to 1.22)	0%	5.3%	0.94 (0.80 to 1.10)
VPS vs OXC	No direct evidence				0.0%	**0.82 (0.67 to 1.00)**
VPS vs TPM	128	2	0.76 (0.46 to 1.25)	48%	1.7%	0.94 (0.78 to 1.12)
VPS vs GBP	No direct evidence				0.0%	0.99 (0.81 to 1.20)
VPS vs LEV	190	2	0.95 (0.80 to 1.12)	0%	32.9%	0.93 (0.80 to 1.09)
VPS vs ZNS	No direct evidence				0.0%	0.93 (0.78 to 1.12)
VPS vs LCM	No direct evidence				0.0%	0.84 (0.68 to 1.04)
LTG vs OXC	511	1	0.87 (0.71 to 1.07)	NA	15.3%	0.87 (0.73 to 1.03)
LTG vs TPM	683	2	1.01 (0.85 to 1.21)	0%	18.9%	0.99 (0.86 to 1.15)
LTG vs GBP	660	1	1.07 (0.90 to 1.27)	NA	23.8%	1.05 (0.90 to 1.23)
LTG vs LEV	902	2	0.94 (0.81 to 1.10)	0%	22.2%	0.99 (0.88 to 1.11)
LTG vs ZNS	658	1	1.03 (0.87 to 1.23)	NA	24.8%	0.99 (0.87 to 1.14)
LTG vs LCM	No direct evidence				0.0%	0.89 (0.74 to 1.08)
OXC vs TPM	498	1	1.16 (0.95 to 1.43)	NA	19.0%	1.14 (0.95 to 1.38)
OXC vs GBP	509	1	**1.23 (1.00 to 1.51)**	NA	20.4%	**1.21 (1.00 to 1.46)**
OXC vs LEV	No direct evidence				0.0%	1.14 (0.95 to 1.37)
OXC vs ZNS	No direct evidence				0.0%	1.14 (0.94 to 1.39)
OXC vs LCM	No direct evidence				0.0%	1.03 (0.82 to 1.29)
TPM vs GBP	647	1	1.06 (0.88 to 1.26)	NA	26.5%	1.06 (0.89 to 1.25)

Table 16. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with focal seizures *(Continued)*

TPM vs LEV	No direct evidence				0.0%	0.99 (0.85 to 1.17)
TPM vs ZNS	No direct evidence				0.0%	1.00 (0.83 to 1.19)
TPM vs LCM	No direct evidence				0.0%	0.90 (0.73 to 1.11)
GBP vs LEV	No direct evidence				0.0%	0.94 (0.80 to 1.12)
GBP vs ZNS	No direct evidence				0.0%	0.95 (0.79 to 1.14)
GBP vs LCM	No direct evidence				0.0%	0.85 (0.69 to 1.06)
LEV vs ZNS	660	1	1.06 (0.89 to 1.26)	NA	26.0%	1.00 (0.88 to 1.15)
LEV vs LCM	No direct evidence				0.0%	0.90 (0.75 to 1.09)
ZNS vs LCM	No direct evidence				0.0%	0.90 (0.73 to 1.11)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 17. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	158	3	**1.78 (1.05 to 3.02)**	13%	25.5%	1.35 (0.96 to 1.90)
CBZ vs PHT	121	2	0.69 (0.39 to 1.23)	31%	9.9%	1.05 (0.83 to 1.33)
CBZ vs VPS	412	4	0.90 (0.65 to 1.23)	30%	23.5%	0.98 (0.84 to 1.14)
CBZ vs LTG	319	5	1.26 (0.80 to 2.00)	0%	19.1%	1.14 (0.93 to 1.41)

Table 17. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with generalised seizures *(Continued)*

CBZ vs OXC	61	1	1.28 (0.71 to 2.29)	NA	13.2%	1.29 (0.90 to 1.83)
CBZ vs TPM	191	2	0.89 (0.60 to 1.31)	0%	26.3%	1.05 (0.86 to 1.29)
CBZ vs GBP	72	1	1.03 (0.61 to 1.74)	NA	18.0%	1.28 (0.84 to 1.94)
CBZ vs LEV	251	2	1.00 (0.73 to 1.38)	60%	23.8%	1.01 (0.84 to 1.21)
CBZ vs LCM	78	1	1.41 (0.82 to 2.42)	NA	100.0%	1.36 (0.81 to 2.28)
PHB vs PHT	130	3	0.77 (0.39 to 1.49)	0%	21.2%	0.78 (0.54 to 1.12)
PHB vs VPS	98	2	0.67 (0.32 to 1.38)	8%	14.4%	0.72 (0.51 to 1.02)
PHB vs LTG	No direct evidence				0.0%	0.85 (0.58 to 1.23)
PHB vs OXC	No direct evidence				0.0%	0.95 (0.60 to 1.51)
PHB vs TPM	No direct evidence				0.0%	0.78 (0.54 to 1.13)
PHB vs GBP	No direct evidence				0.0%	0.95 (0.56 to 1.60)
PHB vs LEV	No direct evidence				0.0%	0.75 (0.52 to 1.07)
PHB vs LCM	No direct evidence				0.0%	1.01 (0.54 to 1.87)
PHT vs VPS	394	5	0.97 (0.65 to 1.47)	0%	30.9%	0.93 (0.75 to 1.16)
PHT vs LTG	91	1	0.51 (0.10 to 2.68)	NA	1.9%	1.09 (0.84 to 1.41)
PHT vs OXC	154	2	1.41 (0.83 to 2.40)	0%	19.4%	1.23 (0.88 to 1.71)
PHT vs TPM	No direct evidence				0.0%	1.00 (0.78 to 1.30)
PHT vs GBP	No direct evidence				0.0%	1.22 (0.78 to 1.90)
PHT vs LEV	No direct evidence				0.0%	0.96 (0.75 to 1.23)
PHT vs LCM	No direct evidence				0.0%	1.29 (0.73 to 2.29)
VPS vs LTG	555	3	1.15 (0.66 to 2.00)	0%	14.3%	1.17 (0.98 to 1.38)
VPS vs OXC	No direct evidence				0.0%	1.31 (0.93 to 1.85)
VPS vs TPM	585	2	1.46 (0.83 to 2.56)	55%	6.1%	1.08 (0.91 to 1.27)
VPS vs GBP	No direct evidence				0.0%	1.30 (0.86 to 1.97)
VPS vs LEV	1032	2	1.13 (0.77 to 1.66)	0%	45.4%	1.03 (0.91 to 1.17)
VPS vs LCM	No direct evidence				0.0%	1.39 (0.81 to 2.38)
LTG vs OXC	67	1	1.18 (0.66 to 2.10)	NA	16.0%	1.13 (0.79 to 1.61)
LTG vs TPM	525	2	0.75 (0.46 to 1.23)	0%	20.4%	0.92 (0.77 to 1.10)

Table 17. Pairwise and network meta-analysis results - Time to 6-month remission for individuals with generalised seizures *(Continued)*

LTG vs GBP	78	1	0.94 (0.56 to 1.59)	NA	20.4%	1.12 (0.74 to 1.69)
LTG vs LEV	No direct evidence				0.0%	0.88 (0.72 to 1.09)
LTG vs LCM	No direct evidence				0.0%	1.19 (0.68 to 2.08)
OXC vs TPM	74	1	0.64 (0.37 to 1.11)	NA	17.2%	0.82 (0.57 to 1.17)
OXC vs GBP	65	1	0.80 (0.45 to 1.44)	NA	17.4%	0.99 (0.61 to 1.61)
OXC vs LEV	No direct evidence				0.0%	0.78 (0.55 to 1.13)
OXC vs LCM	No direct evidence				0.0%	1.06 (0.56 to 1.97)
TPM vs GBP	85	1	1.25 (0.76 to 2.06)	NA	23.4%	1.21 (0.81 to 1.82)
TPM vs LEV	No direct evidence			NA	0.0%	0.96 (0.78 to 1.18)
TPM vs LCM	No direct evidence			NA	0.0%	1.29 (0.74 to 2.25)
GBP vs LEV	No direct evidence			NA	0.0%	0.79 (0.52 to 1.21)
GBP vs LCM	No direct evidence			NA	0.0%	1.06 (0.55 to 2.07)
LEV vs LCM	No direct evidence			NA	0.0%	1.35 (0.78 to 2.33)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 18. Pairwise and network meta-analysis results - Time to first seizure for individuals with focal seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]

Table 18. Pairwise and network meta-analysis results - Time to first seizure for individuals with focal seizures *(Continued)*

CBZ vs PHB	581	6	1.27 (0.93 to 1.73)	46%	11.5%	**0.81 (0.65 to 1.00)**
CBZ vs PHT	432	4	1.06 (0.77 to 1.45)	0%	21.8%	1.03 (0.88 to 1.22)
CBZ vs VPS	813	5	1.13 (0.89 to 1.43)	31%	16.9%	**1.28 (1.12 to 1.45)**
CBZ vs LTG	2184	9	0.88 (0.76 to 1.03)	0%	31.4%	**1.23 (1.11 to 1.35)**
CBZ vs OXC	591	2	1.08 (0.83 to 1.41)	69%	0.4%	1.01 (0.85 to 1.20)
CBZ vs TPM	962	2	**1.24 (1.03 to 1.49)**	0%	26.5%	1.08 (0.94 to 1.24)
CBZ vs GBP	666	2	**1.43 (1.20 to 1.70)**	44%	15.4%	**1.40 (1.22 to 1.61)**
CBZ vs LEV	1552	3	0.89 (0.75 to 1.06)	68%	11.9%	**1.21 (1.08 to 1.37)**
CBZ vs ZNS	582	1	1.16 (0.87 to 1.54)	NA	18.6%	**1.33 (1.13 to 1.57)**
CBZ vs LCM	806	1	0.99 (0.79 to 1.25)	NA	100.0%	1.14 (0.93 to 1.39)
PHB vs PHT	463	5	0.78 (0.58 to 1.05)	0%	49.9%	**1.28 (1.02 to 1.6)**
PHB vs VPS	80	2	0.67 (0.33 to 1.36)	0%	7.3%	**1.58 (1.24 to 2.01)**
PHB vs LTG	No direct evidence				0.0%	**1.52 (1.21 to 1.92)**
PHB vs OXC	No direct evidence				0.0%	1.26 (0.97 to 1.63)
PHB vs TPM	No direct evidence				0.0%	**1.34 (1.04 to 1.72)**
PHB vs GBP	No direct evidence				0.0%	**1.74 (1.35 to 2.24)**
PHB vs LEV	No direct evidence				0.0%	**1.51 (1.18 to 1.92)**
PHB vs ZNS	No direct evidence				0.0%	**1.65 (1.26 to 2.16)**
PHB vs LCM	No direct evidence				0.0%	**1.41 (1.05 to 1.90)**
PHT vs VPS	245	4	0.90 (0.58 to 1.39)	0%	13.4%	**1.23 (1.02 to 1.49)**
PHT vs LTG	90	1	1.12 (0.56 to 2.27)	NA	3.8%	1.19 (0.99 to 1.42)
PHT vs OXC	318	2	0.78 (0.50 to 1.22)	0%	10.4%	0.98 (0.80 to 1.20)
PHT vs TPM	111	1	2.00 (0.36 to 11.2)	NA	0.7%	1.04 (0.85 to 1.28)
PHT vs GBP	No direct evidence				0.0%	**1.36 (1.10 to 1.67)**
PHT vs LEV	No direct evidence				0.0%	1.18 (0.96 to 1.43)
PHT vs ZNS	No direct evidence				0.0%	**1.29 (1.03 to 1.62)**
PHT vs LCM	No direct evidence				0.0%	1.10 (0.85 to 1.43)

Table 18. Pairwise and network meta-analysis results - Time to first seizure for individuals with focal seizures *(Continued)*

VPS vs LTG	257	3	**0.44 (0.26 to 0.74)**	55%	2.1%	0.96 (0.83 to 1.12)
VPS vs OXC	No direct evidence				0.0%	**0.79 (0.65 to 0.98)**
VPS vs TPM	128	2	0.65 (0.37 to 1.15)	52%	2.0%	0.85 (0.71 to 1.01)
VPS vs GBP	No direct evidence				0.0%	1.10 (0.91 to 1.32)
VPS vs LEV	190	2	1.00 (0.76 to 1.30)	0%	28.2%	0.95 (0.81 to 1.13)
VPS vs ZNS	No direct evidence				0.0%	1.05 (0.85 to 1.28)
VPS vs LCM	No direct evidence				0.0%	0.89 (0.70 to 1.14)
LTG vs OXC	511	1	1.07 (0.82 to 1.41)	NA	17.8%	0.82 (0.69 to 0.98)
LTG vs TPM	683	1	**1.27 (1.02 to 1.58)**	NA	18.7%	0.88 (0.76 to 1.01)
LTG vs GBP	660	1	**1.58 (1.27 to 1.96)**	NA	21.3%	1.14 (0.99 to 1.32)
LTG vs LEV	891	2	0.86 (0.69 to 1.07)	0%	25.2%	0.99 (0.87 to 1.13)
LTG vs ZNS	658	1	1.04 (0.80 to 1.35)	NA	23.0%	1.09 (0.92 to 1.28)
LTG vs LCM	No direct evidence				0.0%	0.93 (0.74 to 1.16)
OXC vs TPM	498	1	1.18 (0.91 to 1.53)	NA	21.1%	1.06 (0.88 to 1.29)
OXC vs GBP	509	1	**1.47 (1.14 to 1.90)**	NA	23.5%	**1.38 (1.14 to 1.67)**
OXC vs LEV	No direct evidence				0.0%	1.20 (0.98 to 1.47)
OXC vs ZNS	No direct evidence				0.0%	**1.32 (1.05 to 1.66)**
OXC vs LCM	No direct evidence				0.0%	1.13 (0.87 to 1.46)
TPM vs GBP	647	1	**1.25 (1.02 to 1.53)**	NA	28.2%	**1.30 (1.11 to 1.53)**
TPM vs LEV	No direct evidence				0.0%	1.13 (0.94 to 1.34)
TPM vs ZNS	No direct evidence				0.0%	**1.24 (1.01 to 1.52)**
TPM vs LCM	No direct evidence				0.0%	1.06 (0.83 to 1.35)
GBP vs LEV	No direct evidence				0.0%	0.87 (0.73 to 1.04)
GBP vs ZNS	No direct evidence				0.0%	0.95 (0.77 to 1.17)
GBP vs LCM	No direct evidence				0.0%	0.81 (0.64 to 1.04)
LEV vs ZNS	660	1	1.13 (0.86 to 1.48)	NA	27.6%	1.10 (0.93 to 1.30)

Table 18. Pairwise and network meta-analysis results - Time to first seizure for individuals with focal seizures *(Continued)*

LEV vs LCM	No direct evidence	0.0%	0.94 (0.74 to 1.19)
ZNS vs LCM	No direct evidence	0.0%	0.86 (0.66 to 1.11)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 19. Pairwise and network meta-analysis results - Time to first seizure for individuals with generalised seizures

Comparison[a]	Direct Evidence				Network meta-analysis	
	Number of participants	Number of studies	HR (95% CI)[b]	I^2	Direct evidence[c]	HR (95% CI)[b]
CBZ vs PHB	237	5	1.59 (0.64 to 3.98)	53%	27.9%	1.13 (0.82 to 1.56)
CBZ vs PHT	150	3	0.50 (0.18 to 1.37)	0%	11.7%	0.91 (0.71 to 1.16)
CBZ vs VPS	411	4	0.74 (0.43 to 1.28)	63%	12.9%	0.87 (0.73 to 1.04)
CBZ vs LTG	367	7	0.74 (0.47 to 1.15)	0%	33.7%	1.11 (0.90 to 1.37)
CBZ vs OXC	61	1	0.93 (0.40 to 2.19)	NA	13.0%	1.23 (0.83 to 1.83)
CBZ vs TPM	191	2	0.81 (0.47 to 1.38)	0%	27.1%	1.03 (0.83 to 1.28)
CBZ vs GBP	72	1	0.63 (0.30 to 1.34)	NA	16.9%	1.22 (0.77 to 1.91)
CBZ vs LEV	251	2	0.95 (0.57 to 1.58)	0%	56.7%	0.96 (0.77 to 1.20)
CBZ vs LCM	78	1	1.77 (0.76 to 4.10)	NA	100.0%	1.06 (0.41 to 2.75)
PHB vs PHT	161	4	0.36 (0.11 to 1.13)	0%	22.1%	0.80 (0.57 to 1.14)
PHB vs VPS	98	2	1.11 (0.42 to 2.91)	70%	7.5%	0.77 (0.55 to 1.08)

Table 19. Pairwise and network meta-analysis results - Time to first seizure for individuals with generalised seizures *(Continued)*

PHB vs LTG	No direct evidence				0.0%	0.98 (0.69 to 1.41)
PHB vs OXC	No direct evidence				0.0%	1.09 (0.67 to 1.76)
PHB vs TPM	No direct evidence				0.0%	0.91 (0.63 to 1.31)
PHB vs GBP	No direct evidence				0.0%	1.08 (0.63 to 1.85)
PHB vs LEV	No direct evidence				0.0%	0.85 (0.59 to 1.23)
PHB vs LCM	No direct evidence				0.0%	0.94 (0.34 to 2.57)
PHT vs VPS	394	4	1.38 (0.57 to 3.34)	49%	12.7%	0.96 (0.76 to 1.21)
PHT vs LTG	91	1	0.90 (0.34 to 2.36)	NA	13.1%	1.22 (0.94 to 1.59)
PHT vs OXC	154	2	1.58 (0.68 to 3.67)	0%	19.5%	1.36 (0.93 to 1.98)
PHT vs TPM	208	1	0.18 (0.02 to 1.40)	NA	3.0%	1.14 (0.87 to 1.49)
PHT vs GBP	No direct evidence				0.0%	1.34 (0.83 to 2.17)
PHT vs LEV	No direct evidence				0.0%	1.06 (0.80 to 1.41)
PHT vs LCM	No direct evidence				0.0%	1.17 (0.44 to 3.14)
VPS vs LTG	541	3	**2.2 (1.02 to 4.73)**	0%	18.5%	**1.27 (1.07 to 1.52)**
VPS vs OXC	No direct evidence				0.0%	1.41 (0.95 to 2.09)
VPS vs TPM	585	2	**2.10 (1.06 to 4.17)**	68%	6.9%	1.18 (0.98 to 1.42)
VPS vs GBP	No direct evidence				0.0%	1.39 (0.89 to 2.19)
VPS vs LEV	1032	1	1.51 (0.65 to 3.49)	0%	20.1%	1.10 (0.93 to 1.31)
VPS vs LCM	No direct evidence				0.0%	1.22 (0.46 to 3.21)
LTG vs OXC	67	1	0.94 (0.41 to 2.16)	NA	14.3%	1.11 (0.74 to 1.65)
LTG vs TPM	525	1	0.80 (0.40 to 1.58)	NA	17.7%	0.93 (0.77 to 1.12)
LTG vs GBP	78	1	0.63 (0.30 to 1.33)	NA	18.6%	1.10 (0.70 to 1.71)
LTG vs LEV	No direct evidence				0.0%	0.87 (0.68 to 1.10)
LTG vs LCM	No direct evidence				0.0%	0.96 (0.36 to 2.54)
OXC vs TPM	74	1	0.85 (0.38 to 1.88)	NA	17.6%	0.84 (0.56 to 1.25)
OXC vs GBP	65	1	0.68 (0.29 to 1.57)	NA	18.2%	0.99 (0.58 to 1.68)
OXC vs LEV	No direct evidence				0.0%	0.78 (0.51 to 1.19)
OXC vs LCM	No direct evidence				0.0%	0.87 (0.31 to 2.43)

Table 19. Pairwise and network meta-analysis results - Time to first seizure for individuals with generalised seizures *(Continued)*

TPM vs GBP	85	1	0.80 (0.40 to 1.59)	NA	23.7%	1.18 (0.76 to 1.84)
TPM vs LEV	No direct evidence				0.0%	0.93 (0.73 to 1.19)
TPM vs LCM	No direct evidence				0.0%	1.03 (0.39 to 2.74)
GBP vs LEV	No direct evidence				0.0%	0.79 (0.49 to 1.27)
GBP vs LCM	No direct evidence				0.0%	0.87 (0.30 to 2.51)
LEV vs LCM	No direct evidence				0.0%	1.10 (0.42 to 2.94)

CBZ: carbamazepine
CI: confidence interval
ESL: eslicarbazepine acetate
GBP: gabapentin
HR: hazard ratio
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
NA: not applicable
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide
a. Order of drugs in the table: most commonly used drug first (CBZ), then drugs were ordered approximately by the date they were licenced as a monotherapy treatment (oldest first).
b. HRs and 95% CIs were calculated from fixed-effects analyses. HR < 1 indicates an advantage to the second drug in the comparison; results in highlighted in bold are statistically significant.
c. Proportion of the NMA estimate contributed by direct evidence

Table 20. Summary of adverse event data

Drug	Number of studies for which AE data is available	Number of participants in studies with AE data available (% of total randomised)	Number of participants for which at least one AE is reported (% of total data available)[a,b]
CBZ	46 (IPD for 18 studies)	5748 (94%)	3757 (65%)
PHB	8 (IPD for 2 studies)	640 (78%)	275 (43%)
PHT	15 (IPD for 3 studies)	1057 (76%)	614 (58%)
VPS	21 (IPD for 7 studies)	2250 (86%)	1399 (62%)
LTG	24 (IPD for 15 studies)	3368 (95%)	1733 (51%)
OXC	10 (IPD for 2 studies)	1021 (90%)	634 (62%)
LEV	14 (IPD for 6 studies)	2503 (96%)	1697 (68%)
TPM	6 (IPD for 5 studies)	1209 (95%)	920 (76%)

Table 20. Summary of adverse event data *(Continued)*

GBP	4 (IPD for 2 studies)	948 (100%)	506 (53%)
ZNS	3 (IPD for 2 studies)	685 (100%)	377 (55%)
LCM	1 (IPD provided)	445 (100%)	328 (74%)
ESL	1 (No IPD available)	401 (100%)	306 (76%)
Total	**68 studies (IPD for 26 studies)**	**20,275 (92%)**	**12,546 (62%)**

AE:adverse event
CBZ: carbamazepine
ESL: eslicarbazepine acetate
GBP: gabapentin
IPD: individual participant data
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

[a]Adverse event data were provided as detailed individual participant data for 26 trials and we extracted summary adverse event information from 42 trial publications. No adverse event data were reported in 21 trial publications.

[b]Most trial publications reported summaries only of the “most common” adverse events; the totals and frequencies are likely to be an underestimation of the true number of events and number of individuals experiencing events. Furthermore, detailed information was provided in the more recent trial publications and individual participant data requests of more recent trials, often involving newer antiepileptic drugs, such as LTG, LEV and TPM, which may indicate that these newer drugs are associated with more adverse events than older drugs such as PHB and PHT, for which less detailed information was available. It was also unclear whether all events reported were 'treatment-emergent' or 'treatment-related.'

Table 21. Adverse events - frequency of most commonly reported events

Event (general description)[a-d]	CBZ	PHB	PHT	VPS	LTG	OXC	TPM	GBP	LEV	ZNS	LCM	ESL	Total
Drowsiness or fatigue	1449	1	1271	449	573	236	628	326	549	96	61	41	5680
Headache or migraine	953	0	843	275	574	137	315	171	620	73	78	27	4066
Dizziness or faintness	751	0	617	174	363	140	269	160	416	44	88	38	3060
Gastrointestinal disturbances	762	20	703	259	403	33	236	142	305	77	64	0	3004
Rash or skin disorder	809	17	718	51	450	77	163	113	139	55	36	6	2634
Mood or behavioural change	294	45	320	158	186	27	415	121	272	80	18	3	1939
Nausea or vomiting	494	1	414	181	247	53	132	92	166	41	38	26	1885
Cognitive disorder	342	41	362	112	219	44	439	127	98	52	21	0	1857
Fever or viral infection	441	0	379	68	176	24	84	58	339	37	66	0	1672
Pain	405	1	346	65	255	6	154	48	252	31	70	0	1633
Laboratory results abnormal	651	0	367	106	117	8	47	19	91	32	119	35	1592
Weight gain	288	0	259	389	171	23	71	258	88	3	5	8	1563
Anxiety/depression	231	0	203	71	188	32	309	82	259	55	37	0	1467
Respiratory disorder	316	0	233	53	124	4	190	23	131	17	68	0	1159
Anorexia or weight loss	134	0	126	32	123	6	394	58	76	87	4	0	1040
Tremor or twitch	185	1	172	274	228	19	56	23	57	8	9	0	1032
Paraesthesia or tingling	66	0	56	22	36	2	708	34	29	9	11	0	973
Sleep disorder or nightmares	125	1	109	54	219	16	147	31	121	27	17	0	867
Visual disturbance	222	0	199	54	97	33	86	59	35	16	10	0	811
Increased/worsened seizures	174	0	151	31	164	6	58	48	142	6	22	1	803

Table 21. Adverse events - frequency of most commonly reported events *(Continued)*

Renal/urinary disorder	204	0	152	30	79	2	92	57	94	29	28	0	767
Ataxia	177	37	209	38	59	18	61	40	35	9	5	0	688
Accidental injury	149	0	100	28	110	5	95	36	58	8	62	0	651
Infection	149	0	121	19	90	4	56	27	63	5	26	0	560
Dental problems	102	0	93	28	71	5	61	24	74	10	15	0	483
Menstrual problems	114	0	110	28	31	1	22	18	39	4	5	0	372
Hair loss	48	0	47	137	23	15	39	8	20	6	2	0	345
Impotence or loss of libido	91	24	114	14	17	0	27	32	11	4	2	0	336
Aphasia	64	7	66	11	30	4	106	22	17	4	3	0	334
Asthenia	67	1	60	31	44	1	31	33	44	13	5	0	330

CBZ: carbamazepine
ESL: eslicarbazepine acetate
GBP: gabapentin
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PHB: phenobarbitone
PHT: phenytoin
TPM: topiramate
VPS: sodium valproate
ZNS: zonisamide

[a]Verbatim or reported terms extracted from publications or provided in individual participant data were grouped under the definitions by one review author (SJN) and any uncertainties in definition were discussed with the senior clinical author (AGM).

[b]Adverse event data were provided as detailed individual participant data for 26 trials and we extracted summary adverse event information from 42 trial publications. No adverse event data were reported in 21 trial publications.

[c] For each event, the number of events was extracted where reported; if only the number of participants experiencing the event was reported, it was assumed that each participant experienced the event once. Therefore, the frequency of some events may be underestimated.

[d] Most trial publications reported summaries only of the “most common” adverse events; the totals and frequencies are likely to be an underestimation of the true number of events and number of individuals experiencing events. Furthermore, detailed information was provided in the more recent trial publications and individual participant data requests of more recent trials, often involving newer antiepileptic drugs, such as LTG, LEV and TPM. which may indicate that these newer drugs are associated with more adverse events than older drugs such as PHB and PHT, for which less detailed information was available. It was also unclear whether all events reported were 'treatment-emergent' or 'treatment-related.'

APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web) search strategy

1. MeSH DESCRIPTOR Carbamazepine Explode All AND CENTRAL:TARGET

2. (Carbamazepin* OR Carbamazepen* OR Carbamezepin* OR CBZ OR SPD417 OR "Apo-Carbamazepine" OR Atretol OR Biston OR Calepsin OR Carbagen OR Carbatrol OR Carbazepin* OR Carbelan OR Epitol OR Equetro OR Finlepsin OR Karbamazepin OR Lexin OR Neurotop OR "Novo-Carbamaz" OR "Nu-Carbamazepine" OR Sirtal OR Stazepin* OR "Taro-Carbamazepine" OR Tegretal OR Tegretol OR Telesmin OR Teril OR Timonil):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2 AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Phenytoin Explode All AND CENTRAL:TARGET

5. (Aleviatin OR Antisacer OR Auranile OR Causoin OR Citrullamon OR Citrulliamon OR Comital OR Comitoina OR Convul OR Danten OR Dantinal OR Dantoin* OR Denyl OR "Di-Hydan" OR "Di-Lan" OR "Di-Phetine" OR Didan OR Difenilhidantoin* OR Difenin OR Difetoin OR Difhydan OR Dihycon OR Dihydantoin OR Dilabid OR Dilantin* OR Dillantin OR Dintoin* OR Diphantoin OR Diphedal OR Diphedan OR Diphenat OR Diphenin* OR Diphentoin OR Diphentyn OR Diphenylan OR Diphenylhydantoin* OR Diphenylhydatanoin OR Ditoinate OR Ekko OR Elepsindon OR Enkelfel OR Epamin OR Epanutin OR Epasmir OR Epdantoin* OR Epelin OR Epifenyl OR Epihydan OR Epilan OR Epilantin OR Epinat OR Epised OR Eptal OR Eptoin OR Fenantoin OR Fenidantoin OR Fenitoin* OR Fentoin OR Fenylepsin OR Fenytoin* OR "Gerot-epilan-D" OR Hidan OR Hidant* OR Hindatal OR Hydant* OR Ictalis OR Idantoi* OR Iphenylhydantoin OR Kessodanten OR Labopal OR Lehydan OR Lepitoin OR Lepsin OR Mesantoin OR Minetoin OR "Neos-Hidantoina" OR Neosidantoina OR Novantoina OR Novophenytoin OR "Om-hidantoina" OR "Om-Hydantoine" OR Oxylan OR Phanantin* OR Phenatine OR Phenatoine OR Phenhydan* OR Phenitoin OR Phentoin OR Phentytoin OR Phenytek OR Phenytex OR Phenytoin* OR PHT OR Ritmenal OR Saceril OR Sanepil OR Silantin OR Sinergina OR Sodanthon OR Sodanto* OR Solantin OR Solantoin OR Solantyl OR Sylantoic OR Tacosal OR Thilophenyl OR TOIN OR Zentronal OR Zentropil):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

6. #4 OR #5 AND CENTRAL:TARGET

7. MeSH DESCRIPTOR Valproic Acid Explode All AND CENTRAL:TARGET

8. (Avugane OR Baceca OR Convulex OR Delepsine OR Depacon OR Depakene OR Depakine OR Depakote OR Deproic OR DPA OR Encorate OR Epiject OR Epilex OR Epilim OR Episenta OR Epival OR Ergenyl OR Mylproin OR Orfiril OR Orlept OR Selenica OR Stavzor OR Valcote OR Valparin OR Valpro* OR VPA):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

9. #7 OR #8 AND CENTRAL:TARGET

10. MeSH DESCRIPTOR Phenobarbital Explode All AND CENTRAL:TARGET

11. (Adonal OR Aephenal OR Agrypnal OR Amylofene OR Aphenylbarbit OR Aphenyletten OR Barbenyl OR Barbinal OR Barbiphen* OR Barbipil OR Barbita OR Barbivis OR Barbonal OR Barbophen OR Bardorm OR Bartol OR Bialminal OR "Blu-Phen" OR Cabronal OR Calmetten OR Calminal OR Cardenal OR Chinoin OR Codibarbita OR Coronaletta OR Cratecil OR Damoral OR Dezibarbitur OR Dormina OR Dormiral OR Dormital OR Doscalun OR Duneryl OR Ensobarb OR Ensodorm OR Epanal OR Epidorm OR Epilol OR Episedal OR Epsylone OR Eskabarb OR Etilfen OR Euneryl OR Fenbital OR Fenemal OR Fenobarbital OR Fenosed OR Fenylettae OR Gardenal OR Gardepanyl OR Glysoletten OR Haplopan OR Haplos OR Helional OR Hennoletten OR Henotal OR Hypnaletten OR Hypnette OR "Hypno-Tablinetten" OR Hypnogen OR Hypnolone OR Hypnoltol OR Hysteps OR Lefebar OR Leonal OR Lephebar OR Lepinal OR Lepinaletten OR Linasen OR Liquital OR Lixophen OR Lubergal OR Lubrokal OR Lumen OR Lumesettes OR Lumesyn OR Luminal OR Lumofridetten OR Luphenil OR Luramin OR Molinal OR Neurobarb OR Nirvonal OR Noptil OR "Nova-Pheno" OR Nunol OR Parkotal OR PB OR Pharmetten OR "Phen-Bar" OR Phenaemal OR Phenemal* OR Phenobal OR Phenobarbit* OR Phenobarbyl OR Phenoluric OR Phenolurio OR Phenomet OR Phenonyl OR Phenoturic OR Phenylethylbarbit* OR Phenylethylmalonylurea OR Phenyletten OR Phenyral OR Phob OR Polcominal OR Prominal OR Promptonal OR "Seda-Tablinen" OR Sedabar OR Sedicat OR Sedizorin OR Sedlyn OR Sedofen OR Sedonal OR Sedonettes OR Sevenal OR Sinoratox OR Solfoton OR "Solu-Barb" OR Sombutol OR Somnolens OR Somnoletten OR Somnosan OR Somonal OR Spasepilin OR Starifen OR Starilettae OR Stental OR Talpheno OR Teolaxin OR Teoloxin OR Thenobarbital OR Theoloxin OR Triabarb OR Tridezibarbitur OR Triphenatol OR Versomnal OR Zadoletten OR Zadonal):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

12. #10 OR #11 AND CENTRAL:TARGET

13. MeSH DESCRIPTOR Oxcarbazepine Explode All AND CENTRAL:TARGET

14. (Oxcarbazepin* OR Actinium OR Barzepin OR Carbox OR Deprectal OR "GP 47680" OR Lonazet OR OCBZ OR Oxalepsy OR OXC OR Oxcarbamazepine OR Oxetol OR Oxpin OR Oxrate OR Oxtellar OR Oxypine OR Pharozepine OR Prolepsi OR Timox OR Trexapin OR Trileptal OR Trileptin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

15. #13 OR #14 AND CENTRAL:TARGET

16. MeSH DESCRIPTOR Lamotrigine Explode All AND CENTRAL:TARGET

17. (Lamotrigin* OR Elmendos OR Epilepax OR "GW 273293" OR Lamictal OR Lamictin OR Lamitor OR Lamitrin OR Lamogine OR Lamotrine OR LTG):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

18. #16 OR #17 AND CENTRAL:TARGET

19. MeSH DESCRIPTOR Gabapentin Explode All AND CENTRAL:TARGET

20. (Gabapentin* OR Aclonium OR Fanatrex OR Gabapetin OR Gabarone OR GBP OR Gralise OR Neogab OR Neurontin OR "Novo-Gabapentin" OR Nupentin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

21. #19 OR #20 AND CENTRAL:TARGET

22. MeSH DESCRIPTOR Topiramate Explode All AND CENTRAL:TARGET

23. (Topiramat* OR Qudexy OR Tipiramate OR Topamax OR "Topiramic acid" OR TPM):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

24. #22 OR #23 AND CENTRAL:TARGET

25. MeSH DESCRIPTOR Levetiracetam Explode All AND CENTRAL:TARGET

26. (Levetiracetam* OR Keppra OR LEV OR Levitiracetam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

27. #25 OR #26 AND CENTRAL:TARGET

28. MeSH DESCRIPTOR Zonisamide Explode All AND CENTRAL:TARGET

29. (Zonisamid* OR Exceglan OR Excegram OR Excegran OR ZNS OR Zonegran):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

30. #28 OR #29 AND CENTRAL:TARGET

31. #3 OR #6 OR #9 OR #12 OR #15 OR #18 OR #21 OR #24 OR #27 OR #30 AND CENTRAL:TARGET

32. ((adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*)):TI AND CENTRAL:TARGET

33. #31 NOT #32 AND CENTRAL:TARGET

34. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

35. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

36. (epilep* OR seizure* OR convuls*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

37. #34 OR #35 OR #36 AND CENTRAL:TARGET

38. eclampsia:TI AND CENTRAL:TARGET

39. #37 NOT #38 AND CENTRAL:TARGET

40. #33 AND #39 AND CENTRAL:TARGET

41. >12/09/2019:CRSCREATED AND CENTRAL:TARGET

#40 AND #41 AND CENTRAL:TARGET

Appendix 2. MEDLINE search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2021).

1. exp Carbamazepine/

2. (Carbamazepin* or Carbamazepen* or Carbamezepin* or CBZ or SPD417 or "Apo-Carbamazepine" or Atretol or Biston or Calepsin or Carbagen or Carbatrol or Carbazepin* or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotop or "Novo-

Carbamaz" or "Nu-Carbamazepine" or Sirtal or Stazepin* or "Taro-Carbamazepine" or Tegretal or Tegretol or Telesmin or Teril or Timonil).tw.

3. 1 or 2

4. exp Phenytoin/

5. (Aleviatin or Antisacer or Auranile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoin* or Denyl or "Di-Hydan" or "Di-Lan" or "Di-Phetine" or Didan or Difenilhidantoin* or Difenin or Difetoin or Difhydan or Dihycon or Dihydantoin or Dilabid or Dilantin* or Dillantin or Dintoin* or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin* or Diphentoin or Diphentyn or Diphenylan or Diphenylhydantoin* or Diphenylhydatanoin or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin* or Epelin or Epifenyl or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fenitoin* or Fentoin or Fenylepsin or Fenytoin* or "Gerot-epilan-D" or Hidan or Hidant* or Hindatal or Hydant* or Ictalis or Idantoi* or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or "Neos-Hidantoina" or Neosidantoina or Novantoina or Novophenytoin or "Om-hidantoina" or "Om-Hydantoine" or Oxylan or Phanantin* or Phenatine or Phenatoine or Phenhydan* or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytex or Phenytoin* or PHT or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodanto* or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentronal or Zentropil).tw.

6. 4 or 5

7. exp Valproic Acid/

8. (Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or DPA or Encorate or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valcote or Valparin or Valpro* or VPA).tw.

9. 7 or 8

10. exp Phenobarbital/

11. (Adonal or Aephenal or Agrypnal or Amylofene or Aphenylbarbit or Aphenyletten or Barbenyl or Barbinal or Barbiphen* or Barbipil or Barbita or Barbivis or Barbonal or Barbophen or Bardorm or Bartol or Bialminal or "Blu-Phen" or Cabronal or Calmetten or Calminal or Cardenal or Chinoin or Codibarbita or Coronaletta or Cratecil or Damoral or Dezibarbitur or Dormina or Dormiral or Dormital or Doscalun or Duneryl or Ensobarb or Ensodorm or Epanal or Epidorm or Epilol or Episedal or Epsylone or Eskabarb or Etilfen or Euneryl or Fenbital or Fenemal or Fenobarbital or Fenosed or Fenylettae or Gardenal or Gardepanyl or Glysoletten or Haplopan or Haplos or Helional or Hennoletten or Henotal or Hypnaletten or Hypnette or "Hypno-Tablinetten" or Hypnogen or Hypnolone or Hypnoltol or Hysteps or Lefebar or Leonal or Lephebar or Lepinal or Lepinaletten or Linasen or Liquital or Lixophen or Lubergal or Lubrokal or Lumen or Lumesettes or Lumesyn or Luminal or Lumofridetten or Luphenil or Luramin or Molinal or Neurobarb or Nirvonal or Noptil or "Nova-Pheno" or Nunol or Parkotal or PB or Pharmetten or "Phen-Bar" or Phenaemal or Phenemal* or Phenobal or Phenobarbit* or Phenobarbyl or Phenoluric or Phenolurio or Phenomet or Phenonyl or Phenoturic or Phenylethylbarbit* or Phenylethylmalonylurea or Phenyletten or Phenyral or Phob or Polcominal or Prominal or Promptonal or "Seda-Tablinen" or Sedabar or Sedicat or Sedizorin or Sedlyn or Sedofen or Sedonal or Sedonettes or Sevenal or Sinoratox or Solfoton or "Solu-Barb" or Sombutol or Somnolens or Somnoletten or Somnosan or Somonal or Spasepilin or Starifen or Starilettae or Stental or Talpheno or Teolaxin or Teoloxin or Thenobarbital or Theoloxin or Triabarb or Tridezibarbitur or Triphenatol or Versomnal or Zadoletten or Zadonal).tw.

12. 10 or 11

13. exp Oxcarbazepine/

14. (Oxcarbazepin* or Actinium or Barzepin or Carbox or Deprectal or "GP 47680" or Lonazet or OCBZ or Oxalepsy or OXC or Oxcarbamazepine or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepine or Prolepsi or Timox or Trexapin or Trileptal or Trileptin).tw.

15. 13 or 14

16. exp Lamotrigine/

17. (Lamotrigin* or Elmendos or Epilepax or "GW 273293" or Lamictal or Lamictin or Lamitor or Lamitrin or Lamogine or Lamotrine or LTG).tw.

18. 16 or 17

19. exp Gabapentin/

20. (Gabapentin* or Aclonium or Fanatrex or Gabapetin or Gabarone or GBP or Gralise or Neogab or Neurontin or "Novo-Gabapentin" or Nupentin).tw.

21. 19 or 20

22. exp Topiramate/

23. (Topiramat* or Qudexy or Tipiramate or Topamax or "Topiramic acid" or TPM).tw.

24. 22 or 23

25. exp Levetiracetam/

26. (Levetiracetam* or Keppra or LEV or Levitiracetam).tw.

27. 25 or 26

28. exp Zonisamide/

29. (Zonisamid* or Exceglan or Excegram or Excegran or ZNS or Zonegran).tw.

30. 28 or 29

31. 3 or 6 or 9 or 12 or 15 or 18 or 21 or 24 or 27 or 30

32. ((adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$) not (monotherap$ or alone or singl$)).ti.

33. 31 not 32

34. exp Epilepsy/

35. exp Seizures/

36. (epilep$ or seizure$ or convuls$).tw.

37. 34 or 35 or 36

38. exp Pre-Eclampsia/ or exp Eclampsia/

39. 37 not 38

40. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

41. clinical trials as topic.sh.

42. trial.ti.

43. 40 or 41 or 42

44. exp animals/ not humans.sh.

45. 43 not 44

46. 33 and 39 and 45

47. limit 46 to ed=20190911-20210412

48. 46 not (1$ or 2$).ed.

49. 48 and (2019$ or 2020$ or 2021$).dt.

50. 47 or 49

51. remove duplicates from 50

Appendix 3. SCOPUS search strategy

(((TITLE (carbamazepine OR carbamezepine OR cbz OR spd417 OR apo-carbamazepine OR atretol OR biston OR calepsin OR carbagen OR carbamazepen OR carbatrol OR carbazepine OR carbelan OR epitol OR equetro OR finlepsin OR karbamazepin OR lexin OR neurotop OR

novo-carbamaz OR nu-carbamazepine OR sirtal OR stazepin OR stazepine OR taro-carbamazepine OR tegretal OR tegretol OR telesmin OR teril OR timonil OR phenytoin OR dihydantoin OR diphenylhydantoin OR diphenylhydantoine OR diphenylhydatanoin OR fenitoina OR phenytoine OR phenytoinum OR aleviatin OR antisacer OR auranile OR causoin OR citrullamon OR citrulliamon OR comital OR comitoina OR convul OR danten OR dantinal OR dantoinal OR dantoine OR denyl OR di-hydan OR di-lan OR di-phetine OR didan OR difenilhidantoina OR difenin OR difetoin OR difhydan OR dihycon OR dilabid OR dilantin OR dilantine OR dillantin OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifenyl OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantin OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR lepitoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phentytoin OR phenytek OR phenytex OR ritmenal OR saceril OR sanepil OR silantin OR sinergina OR sodanthon OR sodantoin OR sodanton OR solantin OR solantoin OR solantyl OR sylantoic OR tacosal OR thilophenyl OR toin OR zentronal OR zentropil OR pht OR "Valproic Acid" OR avugane OR baceca OR convulex OR delepsine OR depacon OR depakene OR depakine OR depakote OR deproic OR epiject OR epilex OR epilim OR episenta OR epival OR ergenyl OR mylproin OR orfiril OR orlept OR selenica OR stavzor OR valcote OR valparin OR valpro OR valproate OR valproic OR vpa OR phenobarbital OR fenobarbital OR phenobarbitol OR phenobarbitone OR "Phenobarbituric Acid" OR phenylethylbarbiturate OR "Phenylethylbarbituric Acid" OR phenylethylmalonylurea OR adonal OR aephenal OR agrypnal OR amylofene OR aphenylbarbit OR aphenyletten OR barbenyl OR barbinal OR barbiphen OR barbiphenyl OR barbipil OR barbita OR barbivis OR barbonal OR barbophen OR bardorm OR bartol OR bialminal OR blu-phen OR cabronal OR calmetten OR calminal OR cardenal OR chinoin OR codibarbita OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dormital OR doscalun OR duneryl OR ensobarb OR ensodorm OR epanal OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenosed OR fenylettae OR gardenal OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR henotal OR hypnaletten OR hypnette OR hypno-tablinetten OR hypnogen OR hypnolone OR hypnoltol OR hysteps OR lefebar OR leonal OR lephebar OR lepinal OR lepinaletten OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumen OR lumesettes OR lumesyn OR luminal OR lumofridetten OR luphenil OR luramin OR molinal OR neurobarb OR nirvonal OR noptil OR nova-pheno OR nunol OR parkotal OR pharmetten OR phen-bar OR phenaemal OR phenemal OR phenemalum OR phenobal OR phenobarbyl OR phenoluric OR phenolurio OR phenomet OR phenonyl OR phenoturic OR phenyletten OR phenyral OR phob OR polcominal OR prominal OR promptonal OR seda-tablinen OR sedabar OR sedicat OR sedizorin OR sedlyn OR sedofen OR sedonal OR sedonettes OR sevenal OR sinoratox OR solfoton OR solu-barb OR sombutol OR somnolens OR somnoletten OR somnosan OR somonal OR spasepilin OR starifen OR starilettae OR stental OR talpheno OR teolaxin OR teoloxin OR thenobarbital OR theoloxin OR triabarb OR tridezibarbitur OR triphenatol OR versomnal OR zadoletten OR zadonal OR pb OR oxcarbazepine OR "GP 47680" OR ocbz OR oxcarbamazepine OR actinium OR barzepin OR carbox OR deprectal OR lonazet OR oxalepsy OR oxetol OR oxpin OR oxrate OR oxtellar OR oxypine OR pharozepine OR prolepsi OR timox OR trexapin OR trileptal OR trileptin OR oxc OR lamotrigine OR "GW 273293" OR lamotrigina OR lamotriginum OR lamictal OR lamotrine OR lamitrin OR lamictin OR lamogine OR lamitor OR ltg OR gabapentin OR gabapentine OR gabapentino OR gabapentinum OR gabapetin OR aclonium OR fanatrex OR gabarone OR neogab OR gralise OR neurontin OR novo-gabapentin OR nupentin OR gbp OR topiramate OR tipiramate OR topiramatum OR "Topiramic acid" OR topamax OR tpm OR levetiracetam OR levetiracetamum OR levitiracetam OR keppra OR lev OR zonisamide OR zonisamida OR zonisamidum OR zonegran OR exceglan OR excegram OR excegran OR zns)) OR (ABS(carbamazepine OR carbamezepine OR cbz OR spd417 OR apo-carbamazepine OR atretol OR biston OR calepsin OR carbagen OR carbamazepen OR carbatrol OR carbazepine OR carbelan OR epitol OR equetro OR finlepsin OR karbamazepin OR lexin OR neurotol OR novo-carbamaz OR nu-carbamazepine OR sirtal OR stazepin OR stazepine OR taro-carbamazepine OR tegretal OR tegretol OR telesmin OR teril OR timonil OR phenytoin OR dihydantoin OR diphenylhydantoin OR diphenylhydantoine OR diphenylhydatanoin OR fenitoina OR phenytoine OR phenytoinum OR aleviatin OR antisacer OR auranile OR causoin OR citrullamon OR citrulliamon OR comital OR comitoina OR convul OR danten OR dantinal OR dantoinal OR dantoine OR denyl OR di-hydan OR di-lan OR di-phetine OR didan OR difenilhidantoina OR difenin OR difetoin OR difhydan OR dihycon OR dilabid OR dilantin OR dilantine OR dillantin OR dintoin OR dintoina OR diphantoin OR diphedal OR diphedan OR diphenat OR diphenin OR diphenine OR dipheninum OR diphentoin OR diphentyn OR diphenylan OR ditoinate OR ekko OR elepsindon OR enkelfel OR epamin OR epanutin OR epasmir OR epdantoin OR epdantoine OR epelin OR epifenyl OR epihydan OR epilan OR epilantin OR epinat OR epised OR eptal OR eptoin OR fenantoin OR fenidantoin OR fentoin OR fenylepsin OR fenytoin OR fenytoine OR gerot-epilan-d OR hidan OR hidantal OR hidantilo OR hidantina OR hidantomin OR hindatal OR hydantal OR hydantin OR hydantoin OR hydantoinal OR hydantol OR ictalis OR idantoil OR idantoin OR iphenylhydantoin OR kessodanten OR labopal OR lehydan OR lepitoin OR lepsin OR mesantoin OR minetoin OR neos-hidantoina OR neosidantoina OR novantoina OR novophenytoin OR om-hidantoina OR om-hydantoine OR oxylan OR phanantin OR phanatine OR phenatine OR phenatoine OR phenhydan OR phenhydanin OR phenitoin OR phentoin OR phentytoin OR phenytek OR phenytex OR ritmenal OR saceril OR sanepil OR silantin OR sinergina OR sodanthon OR sodantoin OR sodanton OR solantin OR solantoin OR solantyl OR sylantoic OR tacosal OR thilophenyl OR toin OR zentronal OR zentropil OR pht OR "Valproic Acid" OR avugane OR baceca OR convulex OR delepsine OR depacon OR depakene OR depakine OR depakote OR deproic OR epiject OR epilex OR epilim OR episenta OR epival OR ergenyl OR mylproin OR orfiril OR orlept OR selenica OR stavzor OR valcote OR valparin OR valpro OR valproate OR valproic OR vpa OR phenobarbital OR fenobarbital OR phenobarbitol OR phenobarbitone OR "Phenobarbituric Acid" OR phenylethylbarbiturate OR "Phenylethylbarbituric Acid" OR phenylethylmalonylurea OR adonal OR aephenal OR agrypnal OR amylofene OR aphenylbarbit OR aphenyletten OR barbenyl OR barbinal OR barbiphen OR barbiphenyl OR barbipil OR barbita OR barbivis OR barbonal OR barbophen OR bardorm OR bartol OR bialminal OR blu-phen OR cabronal OR calmetten OR calminal OR cardenal OR chinoin OR codibarbita OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dormital OR doscalun OR duneryl OR ensobarb OR ensodorm OR epanal OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR

euneryl OR fenbital OR fenemal OR fenosed OR fenylettae OR gardenal OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR henotal OR hypnaletten OR hypnette OR hypno-tablinetten OR hypnogen OR hypnolone OR hypnoltol OR hysteps OR lefebar OR leonal OR lephebar OR lepinal OR lepinaletten OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumen OR lumesettes OR lumesyn OR luminal OR lumofridetten OR luphenil OR luramin OR molinal OR neurobarb OR nirvonal OR noptil OR nova-pheno OR nunol OR parkotal OR pharmetten OR phen-bar OR phenaemal OR phenemal OR phenemalum OR phenobal OR phenobarbyl OR phenoluric OR phenolurio OR phenomet OR phenonyl OR phenoturic OR phenyletten OR phenyral OR phob OR polcominal OR prominal OR promptonal OR seda-tablinen OR sedabar OR sedicat OR sedizorin OR sedlyn OR sedofen OR sedonal OR sedonettes OR sevenal OR sinoratox OR solfoton OR solu-barb OR sombutol OR somnolens OR somnoletten OR somnosan OR somonal OR spasepilin OR starifen OR starilettae OR stental OR talpheno OR teolaxin OR teoloxin OR thenobarbital OR theoloxin OR triabarb OR tridezibarbitur OR triphenatol OR versomnal OR zadoletten OR zadonal OR pb OR oxcarbazepine OR "GP 47680" OR ocbz OR oxcarbamazepine OR actinium OR barzepin OR carbox OR deprectal OR lonazet OR oxalepsy OR oxetol OR oxpin OR oxrate OR oxtellar OR oxypine OR pharozepine OR prolepsi OR timox OR trexapin OR trileptal OR trileptin OR oxc OR lamotrigine OR "GW 273293" OR lamotrigina OR lamotriginum OR lamictal OR lamotrine OR lamitrin OR lamictin OR lamogine OR lamitor OR ltg OR gabapentin OR gabapentine OR gabapentino OR gabapentinum OR gabapetin OR aclonium OR fanatrex OR gabarone OR neogab OR gralise OR neurontin OR novo-gabapentin OR nupentin OR gbp OR topiramate OR tipiramate OR topiramatum OR "Topiramic acid" OR topamax OR tpm OR levetiracetam OR levetiracetamum OR levitiracetam OR keppra OR lev OR zonisamide OR zonisamida OR zonisamidum OR zonegran OR exceglan OR excegram OR excegran OR zns))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") OR (TITLE-ABS-KEY(syndrome) W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR TITLE(seizure OR convuls*) OR (TITLE-ABS-KEY(lafora*) W/4 (disease OR epilep*) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia)) AND NOT INDEX(medl)) AND (TITLE(randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") OR ABS(randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study) AND NOT INDEX(medl))) AND NOT (TITLE((adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*) AND NOT (monotherap* OR alone OR singl*)))

WHAT'S NEW

Date	Event	Description
7 April 2022	Amended	Typos (generated due to a technical glitch) corrected.

HISTORY

Protocol first published: Issue 12, 2014
Review first published: Issue 6, 2017

Date	Event	Description
12 April 2021	New search has been performed	Searches were updated 12 April 2021; 9 new studies have been included.
12 April 2021	New citation required but conclusions have not changed	Conclusions remain the same; however, the review has been expanded to include two new antiepileptic drugs (eslicarbazepine acetate and lacosamide).
14 December 2017	Amended	Abstract revised
14 December 2017	New citation required but conclusions have not changed	Conclusions remain the same

CONTRIBUTIONS OF AUTHORS

SJN wrote the protocol under the supervision of AGM and CT. MS and JW commented on drafts of the protocol and the original review.

SJN and AGM screened all studies for inclusion in the review. SJN and SC (JW for the original review) extracted aggregate data and performed independent risk of bias assessments on all included trials.

SJN, CTS and AGM requested all individual participant data.

SJN and CTS (MS for the original review) prepared individual participant data for analysis, SJN conducted analyses of the review and interpreted results under the supervision of CTS (statistical interpretation) and AGM (clinical interpretation).

SJN wrote the text of the review with the input of CTS and AGM.

DECLARATIONS OF INTEREST

SJN: none known
CTS: none known
SC: none known
AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool.
Professor Marson is funded in part by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).
Professor Marson is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.
Professor Marson is the Co-ordinating Editor of the Cochrane Epilepsy Group; however, he was not involved in the editorial process of this review update.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute of Health Research, UK

  This review update is funded by the National Institute for Health Research (NIHR) [Award reference number: NIHR 129904]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review structure

The title was changed in December 2014 to specify that the review uses individual participant data.

Additional headings were added to the Data extraction and management and Data synthesis and text was re-ordered for easier reading.

Synthesis

We intended to test the proportional hazards assumption of the Cox regression model for each outcome of each trial by testing the statistical significance of a time-varying covariate in the model for each trial and perform sensitivity analyses via interval censored (piecewise) Cox models. However, on reflection, we are unsure of the relevance and importance of the violation of this assumption for a single trial within the whole network. Therefore, instead, we tested the statistical significance of time-varying covariates for all covariates in the primary model (stratified by trial) and if the proportional hazards assumption appeared to be violated, we performed an alternative, more flexible sensitivity analysis fitting a parametric accelerated failure time model to the IPD dataset in preparation for network meta-analysis and compared these results to the results of the primary analysis.

We stated in the protocol that we would "investigate inconsistency via the Bucher Method (Bucher 1997), which applies a z-test to the difference between the direct treatment effect estimate and the indirect estimate for each loop of evidence. Given the simplicity of this test, the influence of the precision of the treatment effect estimate on the result of this test, and the complexity introduced by multi-arm trials and therefore association between treatment effects estimated from arms of the same trial, we used a conservative significance threshold of 10% ($P < 0.1$) to judge the presence of heterogeneity". Given the complexity of the network model fitted (with treatment by epilepsy type interaction) and the number of multi-arm trials included in analysis, we felt that a more formal and less conservative method was needed, therefore, we performed node splitting (Dias 2010) to formally estimate differences between direct and indirect evidence for each comparison, and we fitted a 'design-by-treatment' inconsistency model, a method which evaluates both loop and design inconsistencies, particularly within multi-arm trials (Higgins 2012).

Details of how adverse events would be presented in the review have been added (a narrative report rather than formal analysis).

Sensitivity analysis

Protocol-defined sensitivity analyses were vague in detail as it was unknown exactly what kind of sensitivity analyses might be required. Specific details of required sensitivity analyses are now given.

We stated in the protocol that we intended to perform sensitivity analyses by "excluding any trial judged to be at high risk of bias for any methodological aspect". We performed several sensitivity analyses relating to inconsistencies between data provided to us and published results (mainly described in Other potential sources of bias) and the only other sources of bias (according to the Cochrane risk of bias tool) in the trials providing IPD was the open-label design. Given the long-term and pragmatic nature of these trials, we did not necessarily consider that an open-label design induced bias (as further discussed in Overall completeness and applicability of evidence), therefore, we did not feel such a sensitivity analysis was appropriate.

Changes for the 2021 update

We expanded the list of eligible interventions to include two additional AEDs, lacosamide and eslicarbazepine acetate, licensed for use as monotherapy since the time of the original review protocol (Nolan 2014).

In the 2021 update, we redefined 'time to withdrawal of allocated treatment' as 'time to treatment failure', due to feedback received from the Cochrane Editorial Unit regarding potential confusion regarding 'withdrawal' as a positive or negative outcome of antiepileptic monotherapy. The definitions of reasons for treatment failure/withdrawal for some individuals were reclassified as events or censored observations in line with the definitions of a treatment-related treatment failure used across the series of Cochrane IPD reviews investigating pairwise monotherapy comparisons.

We added analyses of 'time to treatment failure' (due to lack of efficacy and due to adverse events) following feedback on published antiepileptic drug monotherapy reviews that these sub-outcomes would be useful for clinical practice.

We replaced the term 'partial' with 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

We added further clarification to our approach for the Assessment of reporting biases.

We updated the approach for judging certainty of the evidence from GRADE 2008 recommendations to latest CiNeMA recommendations (Nikolakopoulou 2020).

NOTES

Sarah J Nolan (author of the protocol) is now Sarah J Nevitt.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anticonvulsants [therapeutic use]; *Epilepsies, Partial [drug therapy]; *Epilepsy [drug therapy]; Network Meta-Analysis; Phenytoin [therapeutic use]

MeSH check words

Adult; Child; Humans