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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 Specialized 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 licenced 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.