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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

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 partial 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 withdrawal of allocated treatment, remission and first seizure of 10 AEDs (carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide) currently used as monotherapy in children and adults with partial onset seizures (simple partial, complex partial or secondary generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus).

Search methods

We searched the following databases: Cochrane Epilepsy's Specialised Register, CENTRAL, MEDLINE and SCOPUS, and two clinical trials registers. We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators, and experts in the field. The date of the most recent search was 27 July 2016.

Selection criteria

We included randomised controlled trials of a monotherapy design in adults or children with partial onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types).

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Data collection and analysis

This was an individual participant data (IPD) review and network meta-analysis. Our primary outcome was 'time to withdrawal of allocated treatment', and our secondary outcomes were 'time to achieve 12-month remission', 'time to achieve six-month remission', 'time to first seizure post-randomisation', and 'occurrence of adverse events'. We presented all time-to-event outcomes as Cox proportional hazard ratios (HRs) with 95% confidence intervals (CIs). We performed pairwise meta-analysis of head-to-head comparisons between drugs within trials to obtain 'direct' treatment effect estimates and we performed frequentist network meta-analysis to combine direct evidence with indirect evidence across the treatment network of 10 drugs. We investigated inconsistency between direct estimates and network meta-analysis via node splitting. Due to variability in methods and detail of reporting adverse events, we have not performed an analysis. We have provided a narrative summary of the most commonly reported adverse events.

Main results

IPD was provided for at least one outcome of this review for 12,391 out of a total of 17,961 eligible participants (69% of total data) from 36 out of the 77 eligible trials (47% of total trials). We could not include IPD from the remaining 41 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.

We were able to calculate direct treatment effect estimates for between half and two thirds 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, so confidence intervals of estimates were wide.

Network meta-analysis showed that for the primary outcome 'Time to withdrawal of allocated treatment,' for individuals with partial seizures; levetiracetam performed (statistically) significantly better than both current first-line treatments carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam), and carbamazepine performed significantly better than gabapentin and phenobarbitone (high-quality evidence). For individuals with generalised onset seizures, first-line treatment sodium valproate performed significantly better than carbamazepine, topiramate and phenobarbitone (moderate- to high-quality evidence). Furthermore, for both partial and generalised onset seizures, the earliest licenced treatment, phenobarbitone seems to perform worse than all other treatments (moderate- to high-quality evidence).

Network meta-analysis also showed that for secondary outcomes 'Time to 12-month remission of seizures' and 'Time to six-month remission of seizures,' few notable differences were shown for either partial or generalised seizure types (moderate- to high-quality evidence). For secondary outcome 'Time to first seizure,' for individuals with partial seizures; phenobarbitone performed significantly better than both current first-line treatments carbamazepine and lamotrigine; carbamazepine performed significantly better than sodium valproate, gabapentin and lamotrigine. Phenytoin also performed significantly better than lamotrigine (high-quality evidence). In general, the earliest licenced treatments (phenytoin and phenobarbitone) performed better than the other treatments for both seizure types (moderate- to high-quality evidence).

Generally, direct evidence and network meta-analysis estimates (direct plus indirect evidence) were numerically similar and consistent with confidence intervals of effect sizes overlapping.

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

Authors' conclusions

Overall, the high-quality evidence provided by this review supports current guidance (e.g. NICE) that carbamazepine and lamotrigine are suitable first-line treatments for individuals with partial onset seizures and also demonstrates that levetiracetam may be a suitable alternative. High-quality evidence from this review also supports the use of sodium valproate as the first-line treatment for individuals with generalised tonic-clonic seizures (with or without other generalised seizure types) and also demonstrates that lamotrigine and levetiracetam would be 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.

PLAIN LANGUAGE SUMMARY

Antiepileptic drug monotherapy (single drug treatment) for epilepsy

Background

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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: partial 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 partial 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. In this review, we evaluated the evidence from 77 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 12,391 people from 36 of the 77 trials; for the remaining 5570 people from 41 trials, data were not available to use in this review.

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 10 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

Out of the 45 possible pairwise comparisons of the 10 drugs of interest in the review, data from clinical trials were available for just over half of these comparisons but for many only a single trial had made a comparison of the two drugs and the comparison did not include many people.

Our 'network' analysis showed that the oldest drugs in the network (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 (withdrawing from the treatment) compared to the newer drugs such as lamotrigine and levetiracetam.

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 partial seizures and moderate- to high-quality evidence for individuals with generalised tonic-clonic seizures, as less information is 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 partial onset seizures and also show that levetiracetam would also be a suitable treatment. Results of this review also support the use of sodium valproate as the first-line treatment for individuals with generalised tonic-clonic seizures and also show that lamotrigine and levetiracetam would be suitable alternatives, 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 review authors searched for studies that had been published up to 27 July 2016.

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