Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation


CRD summary

This well-conducted review included a large number of studies with little consistent good-quality evidence on the clinical and cost effectiveness of newer antiepileptic drugs. The authors’ conclusions that evidence did not support newer antiepileptic drugs as monotherapy or adjunctive therapy over older drugs and did not differentiate between the effectiveness of individual newer antiepileptic drugs are likely to be reliable.

Authors’ objectives

To assess the clinical effectiveness, tolerability and cost effectiveness of newer drugs for epilepsy in adults.

Searching

The Cochrane Library, DARE, HTA database, MEDLINE, EMBASE, PsycINFO, NRR, Science Citation Index, Index to Scientific and Technical Proceedings and a range of internet resources, including national guidelines websites, were searched from inception to dates in 2002. The bibliographies of included articles and pharmaceutical industry submissions were reviewed for further studies. No date or language restrictions were applied. Full search strategies were given in an appendix to the report.

Study selection

RCTs (parallel or crossover) designed to assess the equivalence, non-inferiority or superiority of newer antiepileptic drugs in adults (aged 18 years or over) with newly diagnosed or refractory epilepsy were eligible for inclusion; the findings of previous systematic reviews were summarised separately. Non-randomised experimental and observational studies were included for the assessment of safety and tolerability outcomes. Studies of patients with single seizures, status epilepticus, seizures following neurosurgery or head injury and trigeminal neuralgia were excluded.

For studies of mixed populations, data were extracted for relevant populations (where possible). Included studies were required to compare newer antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin) as monotherapy or adjunctive therapy against older antiepileptic drugs (acetazolamide, benzodiazepines, carbamazepine, ethosuximide, barbiturates, phenytoin and valporate), another newer antiepileptic drug or placebo. Dosing regimens and follow-up periods varied widely. Studies were generally short term (less than one year). Analysis focused on the following outcome measures: proportion seizure free; proportion of responders (minimum 50% reduction in seizure frequency); time to withdrawal; time to first seizure; quality of life measures; cognitive function measures; safety (adverse events and mortality); and tolerability (withdrawals). A wide range of other outcomes were reported.

Only English-language articles were included in the analyses; details of studies published in other languages were summarised briefly.

Two reviewers independently screened all titles and abstracts for relevance. Disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality

The methodological quality of included RCTs was assessed using pre-specified reported criteria that addressed: eligibility criteria and methods of randomisation; allocation concealment; blinding; baseline comparability between groups; use of appropriate dosing regimens; assessment of adherence, accounting for participants and completeness of follow-up; use of power calculations, intention-to-treat analyses and handling of missing data. Additional method-specific criteria were applied to crossover trials and equivalence trials.

Cohort and case-control studies were assessed using the criteria published in Centre for Reviews and Dissemination
Quality assessment was conducted by one reviewer and independently checked by a second.

**Data extraction**
Effect-size data were extracted as relative risks or hazard ratios and their 95% confidence intervals (CIs), as appropriate. Data were extracted by one reviewer, who used standardised database forms, and independently checked by a second reviewer.

**Methods of synthesis**
Data from included studies were presented in tables and discussed in a narrative, grouped by monotherapy or adjunctive therapy, comparison type (newer antiepileptic drug versus placebo, older antiepileptic drug or other newer antiepileptic drug), intervention and outcome measure. Summary effect measures were calculated using a fixed-effect model where studies were judged to be clinically and statistically homogeneous; statistical heterogeneity was assessed using the Q statistic and a significance threshold of $p = 0.10$.

**Results of the review**
In addition to the summary of 13 previous systematic reviews, 108 effectiveness studies and 21 economic studies were included in the review.

Full results of the quality assessment of included studies were detailed in the report. In general, the quality assessment for RCTs was hampered by poor reporting of methods of randomisation, allocation concealment and blinding. The quality of non-randomised studies was generally poor.

**Effectiveness of monotherapy**:
Twenty one RCTs assessed the effectiveness of the three newer antiepileptic drugs licensed for monotherapy (12 lamotrigine studies, eight oxcarbazepine studies and one topiramate study). Two studies, one in participants with refractory epilepsy (n=102) and one in participants with newly diagnosed epilepsy (n=67), compared oxcarbazepine with placebo. Both studies reported the proportion of seizure-free participants, but only the larger trial reported a statistically significant result (relative risk 13.0, 95% CI: 2.3 to 76.4); this study also reported data on time to withdrawal, which appeared to favour oxcarbazepine. The second study reported data on time to first seizure, which appeared to favour oxcarbazepine (oxcarbazepine 11.7 days, placebo 3.2 days, $p=0.0457$), but no hazard ratio was reported.

Seventeen studies (n=4,857) compared newer with older antiepileptic drugs. Most of these studies were conducted in participants with newly diagnosed epilepsy. There was limited, poor quality evidence of a significant improvement in cognitive function with lamotrigine (one study) and oxcarbazepine (one study), compared with older antiepileptic drugs (carbamazepine). No consistent statistically significant differences were found for any other outcome. One equivalence study (n=309) compared the effectiveness of two newer antiepileptic drugs (lamotrigine and gabapentin); the clinical relevance of this study was unclear as gabapentin was not licensed for monotherapy. Data from this study were designated commercial in confidence.

**Effectiveness of Adjunctive therapy**:
Sixty seven RCTs assessed the effectiveness of newer antiepileptic drugs as adjunctive therapy (10 gabapentin studies, 21 lamotrigine studies, three levetiracetam studies, two oxcarbazepine studies, 14 topiramate studies, 15 vigabatrin studies). For all newer antiepileptic drugs versus placebo (56 studies, mostly in participants with partial seizures) there was some evidence of significant differences in the proportion of responders in favour of newer antiepileptic drugs, but follow up was limited. Pooled effect sizes were calculated for lamotrigine (relative risk 2.3, 95% CI: 1.1 to 4.4; six studies, n=276), tiagabine (relative risk 3.1, 95% CI: 1.9 to 5.0; three studies, n=546) and topiramate, with the last at three different doses and follow-up periods: 175mg/day to 400 mg/day and 20-week follow up (relative risk 2.3, 95% CI: 1.4 to 3.9; two studies, n=160); 400mg/day with undefined follow-up (relative risk 2.9, 95% CI: 1.6 to 5.5; two studies, n=137); and 600mg/day with 12 to 18-week follow up (relative risk 3.5, 95% CI: 2.3 to 5.3; three studies, n=327).
There were no data for levetiracetam, lamotrigine or oxcarbazepine for newer versus older antiepileptic drugs (seven studies). Data for other newer antiepileptic drugs were limited to single studies conducted in participants with partial seizures and having limited follow-up; the available data (for proportion seizure free, proportion of responders, quality of life and cognitive outcomes) showed mainly non-significant differences. Comparisons between newer antiepileptic drugs were largely limited to single studies conducted in participants with partial seizures and having limited follow-up. One study (n=282) of gabapentin versus vigabatrin found a significant difference in the proportion of responders in favour of vigabatrin (relative risk 0.76, 95% CI: 0.60 to 0.95) and one study found significant differences in the quality of life of patients with intellectual disabilities in favour of gabapentin over lamotrigine.

Safety and tolerability:

Eighty RCTs reported adverse events. There was no consistent evidence from these studies on the relative safety and tolerability of newer antiepileptic drugs. Observational data showed some evidence for the occurrence of possible serious, rare and long-term adverse events beyond those reported in RCTs.

Cost information

Cost-effectiveness analyses indicated that monotherapy of newer antiepileptic drugs was similarly effective to and more costly than other antiepileptic drugs for patients with newly diagnosed partial seizures; hence, older antiepileptic drugs were more likely to be cost effective. There was considerable uncertainty in the results.

Newer antiepileptic drugs used as an adjunctive therapy for refractory patients with partial seizures were more effective and more costly than continuing with existing treatment alone. Combination therapy may be cost effective at a willingness to pay threshold of £20,000 per quality-adjusted life-year (QALY). There was considerable uncertainty in the results.

Authors’ conclusions

There was little good-quality evidence to support the use of monotherapy or adjunctive therapy newer antiepileptic drugs in preference to older drugs, or to differentiate between the effectiveness of individual newer antiepileptic drugs. Evidence generally indicated that newer antiepileptic drugs were effective in comparison with placebo, but trials were often short term and in mixed populations of participants with partial and generalised onset seizures. Newer antiepileptic drugs used as monotherapy may be cost effective where other drugs were contra-indicated or where there was a previous failure to respond. Newer antiepileptic drugs as adjunctive therapy may be cost-effective at a willingness to pay threshold of £20,000 per quality-adjusted life-year.

CRD commentary

This was a well conducted review that addressed a series of clearly defined research questions. The search strategy was comprehensive and, although only English-language studies were included in the analyses, all identified studies eligible for inclusion were reported. The review methodology, including the quality assessment of included studies, was rigorous and clearly reported, which minimised the potential for error and/or bias. Study characteristics and results were fully reported and methods of synthesis appropriate to individual data sets were employed. Although the number of included studies was large, the available evidence was generally weak and the authors’ cautious conclusions were appropriate.

Implications of the review for practice and research

Practice: The authors did not state any recommendations for practice.

Research: The authors recommended more trials that directly compared newer versus older and newer versus other newer antiepileptic drugs were needed. These should consider different treatment sequences and both monotherapy and adjunctive therapy, and should include quality of life outcomes. Trials should adopt appropriate study designs that ideally followed the guidance of the International League Against Epilepsy. Effectiveness and cost-effectiveness data were particularly required for patients with generalised onset seizures and in specific populations (such as patients with intellectual disabilities and pregnant women). Studies that assessed cognitive outcomes should use standardised testing protocols and approaches to outcome assessment. Observational data were required to provide information on the use of antiepileptic drugs in practice.
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