The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy: a systematic review

CRD summary
The review identified very few studies that compared the effectiveness of newer antiepileptic drugs to standard drug treatments in children; most studies were placebo-controlled trials conducted to establish effectiveness for licensing purposes. The authors concluded appropriately that there was insufficient information to develop an evidence-based prescribing strategy for newer antiepileptic drugs in children with epilepsy of any type.

Authors' objectives
To assess the clinical and cost effectiveness of newer antiepileptic drugs used in monotherapy or as add-on therapy in comparison with current standard drug treatment for epilepsy in children.

Searching
MEDLINE, PreMEDLINE, EMBASE, Cochrane Controlled Trials Register, Science Citation Index and National Research Register were searched to dates between October 2001 and February 2002; no date or language restrictions were applied. Search strategies were documented in full in an appendix to the report. Additional data were sought through checking of the bibliographies of included studies, contact with experts in the field and invited industry submissions.

Study selection
Randomised controlled trials (RCTs) of any of the newer antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin) as monotherapy or combined therapy for epilepsy in children under 18 years were eligible for inclusion. Studies of mixed populations where data could be separated for a subgroup of participants under 18 years with epilepsy were also eligible. Trials that recruited only patients with single seizure, status epilepticus, post-surgical seizure, febrile convulsions, trigeminal neuralgia or cortical myoclonus were excluded.

Included trials were conducted in children with partial seizures (with or without secondary generalisation), generalised seizures (including Lennox-Gastaut syndrome), Lennox-Gastaut syndrome, infantile spasms, absence epilepsy and benign epilepsy with centrotemporal spikes (BECTS). Several trials were conducted in populations refractory to treatment. Doses and formulations of treatment varied and were documented in the body and appendices of the report. Most included studies were placebo controlled; only five out of 20 used an active comparator. A wide variety of outcome measures were used across the included studies, for example responder rate (proportion of patients with a specified reduction), percentage reduction in seizure frequency/severity, number of seizure free days, time to treatment failure, EEG (electroencephalography) findings and adverse events.

The authors stated neither how studies were selected for the review nor how many reviewers were involved in the selection process.

Assessment of study quality
The methodological quality of included studies was assessed against the following criteria: methods of randomisation; concealment of allocation; blinding; losses to follow-up; and whether or not analysis was by intention to treat (ITT).

Two reviewers independently assessed trial quality. Disagreements were resolved by consensus.

Data extraction
The results of individual studies were extracted as raw data, where possible. Any summary measures reported were extracted with standard deviations, p values, 95% confidence intervals (CIs).
Two reviewers independently extracted data. Disagreements were resolved by a third reviewer.

One reviewer screened non-English language publications. Translations were obtained where necessary.

Methods of synthesis
Results were presented in tables and a narrative synthesis, grouped by seizure type (partial, partial and generalised (mixed population), generalised, Lennox-Gastaut syndrome, infantile spasms, absence epilepsy and BECTs).

Results of the review
Fifteen of the 20 studies (total number of participants was unclear) included were placebo controlled trials. Studies mostly used the new antiepileptic drug as an add-on to existing therapy. In some instances, a responder enriched design was used, where all patients were started on the new drug and responders were randomised to withdraw or continue. The quality of trials was generally poor. Many gave concerns over the randomization process and quality of blinding and/or analytical methods used.

Only five included studies used an active comparator and, of these, only one very small trial (n=22) showed a significant effect, which was for vigabatrin over hydrocortisone in the treatment of infantile spasms due to tuberous sclerosis.

Relevant ongoing trials were also listed.

Overall, for all epilepsy subtypes considered, there was some evidence from placebo-controlled trials that each of the newer antiepileptic drugs assessed was of some value in the treatment of these conditions. Where active controls were used, newer antiepileptic drugs appeared to be no more effective than existing treatments, but were generally better tolerated. Interpretation of the available data was limited by the considerable variation in comparators (where active comparators were used) and drug doses, formulations and titration schedules. There was no evidence to suggest that newer antiepileptic drugs should be considered as a first-line treatment in any form of epilepsy in children.

Cost information
The annual costs of the newer antiepileptic drugs ranged from around £400 to £1,200. The results of decision-analytic modelling suggested that uncertainties in the model were greater than any differences between the drug strategies; there was no clear evidence that newer antiepileptic drugs were or were not cost-effective.

Authors’ conclusions
Current evidence suggested that newer antiepileptic drugs were no more effective, but may be better tolerated, than existing drugs. The cost-effectiveness of newer antiepileptic drugs was dependent on the trade-off between effectiveness and tolerability, both in terms of long-term treatment retention and overall utility associated with effects of seizure rates and occurrence of adverse events. There was insufficient data to assess the nature of this trade-off accurately.

CRD commentary
The review addressed a clearly stated research question and defined appropriate inclusion criteria in relation to intervention, population and study design. Comparators were not defined. The objectives of the review clearly specified determination of effectiveness of newer antiepileptic drugs in comparison with standard drug treatment, but most of the data in the review was derived from placebo controlled trials. Extensive unrestricted searches were conducted and ongoing studies listed, so the review was likely to be a reasonable reflection of the available evidence. The review process incorporated methods likely to minimise error and bias. The methodological quality of included studies was assessed and reported, as were extensive details of the included studies. An appropriate narrative synthesis was undertaken, although the presentation of the results of included studies could have been clearer. However, the authors' conclusions are appropriate given the very limited data of relevance to clinical practice that was available.

Implications of the review for practice and research
Practice: Data were not sufficient to inform a prescribing strategy for any of the newer antiepileptic drugs in any form
of epilepsy in children.

**Research:** Better RCT evidence was required to inform prescribing strategy. Trials should make clinically relevant comparisons and incorporate outcomes of interest to patients and clinicians, with sufficient follow-up to adequately assess the long-term balance between effectiveness and tolerability. RCTs should reflect clinical practice in relation to diagnostic classifications. Diagnosis-specific decision-analytic models were required.

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