The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review

M Connock,¹ E Frew,² B-W Evans,³ S Bryan,² C Cummins,⁴ A Fry-Smith,¹ A Li Wan Po⁵ and J Sandercock¹*

¹ Department of Public Health and Epidemiology, University of Birmingham, UK
² Health Economics Facility, Health Services Management Centre, University of Birmingham, UK
³ Department of Medicine Management, Keele University, UK
⁴ Institute of Child Health, Birmingham, UK
⁵ Centre for Evidence-Based Pharmacotherapy, Aston University, Birmingham, UK

*Corresponding author

Executive summary

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Description of proposed service

Since 1989, seven ‘newer’ antiepileptic drugs (AEDs) have become available: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin. These AEDs have different licensed indications and modes of action; levetiracetam is licensed for use only in patients over the age of 16 years and is therefore not considered in this review. The aim of AED treatment is to reduce epilepsy seizure frequency and enhance patients’ quality of life with as few side-effects and as few co-medications as possible while minimising long-term detrimental effects. This systematic review examines the clinical effectiveness and cost-effectiveness of these newer AEDs for epilepsy in children.

Epidemiology and background

A large proportion of epilepsy begins in childhood. In an average health authority there will be of the order of 40–140 new consultations per annum for epilepsy in children 0–15 years old and around 50–150 for children between 0 and 19 years old. Many more consultations will occur for seizures not diagnosed as epilepsy. The prevalence of epilepsy in children (up to 15 years old) is about 5–7/1000. Many types of epilepsy occur in children, with diagnosis depending on the type of seizure (simple partial, complex partial, partial becoming generalised, generalised) and aetiology (symptomatic, idiopathic, cryptogenic); several epileptic syndromes have been described, including Lennox–Gastaut, infantile spasms (or West’s syndrome), childhood absence epilepsy and benign epilepsy with centrotemporal spikes (BECTS). There are many possible causes of epilepsy but often this cannot be determined. Diagnosis is difficult and misdiagnosis may be frequent. Although some childhood epilepsies are relatively benign, some have a detrimental impact on psychological, social and intellectual development, and in severe cases the effect on the individual, carer(s) and family can be devastating.

Methods

For the systematic review of clinical and cost-effectiveness, studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken. A decision-analytic model was constructed to estimate the cost-effectiveness of the newer agents in children with partial seizures, the only condition where there were sufficient trial data to inform a model.

Number and quality of studies and direction of evidence

The quality of the randomised controlled trial (RCT) data was generally poor, with many giving cause for concern over the integrity of randomisation, quality of blinding and/or analytical methods employed. Most of the trials were conducted for licensing purposes and are therefore of limited use in informing clinical practice; although it is clear that these agents may be useful additions to the list of AEDs available, there are very few data upon which to base a rational prescribing strategy.

Twenty trials were identified which reported outcome data for children with epilepsy; 15 have been published in full and five in abstract form only. Trials were identified in children with partial seizures (with or without secondary generalisation), generalised seizures (including Lennox–Gastaut syndrome), Lennox–Gastaut syndrome, infantile spasms, absence epilepsy and BECTS. Fifteen of the 20 trials identified used placebo as comparator, with five trials using active comparator treatments.

Summary of benefits

For each of the epilepsy subtypes considered in RCTs identified for this review (partial epilepsy with or without secondary generalisation, Lennox–Gastaut syndrome, infantile spasms, absence epilepsy and BECTS), there is some evidence from placebo-controlled trials that the newer agents tested are of some value in the treatment of these conditions. Where active controls have been used, the limited evidence available does not indicate a difference in effectiveness between newer and older drugs.
The data are not sufficient to inform a prescribing strategy for any of the newer agents in any of these conditions. In particular, there is no clinical evidence to suggest that the newer agents should be considered as a first-choice treatment in any form of epilepsy in children.

**Costs**

Annual drug costs of the newer agents range from around £400 to £1200, depending on age and concomitant medications. An AED which is ineffective or has intolerable side-effects will only be used for a short period of time, and many patients achieving seizure freedom will successfully withdraw from drug treatment without relapsing.

**Cost per quality-adjusted life-year (QALY)**

A decision-analytic model was constructed to estimate the cost-effectiveness of the newer agents in children with partial seizures, the only condition where there were sufficient trial data to inform a model. The model was based on a complex patient pathway that attempted to reflect the variety of treatment decisions made and outcomes experienced by patients treated for epilepsy in childhood. There were few reliable data available either for the drug-specific parameters (from the RCTs identified for the clinical effectiveness review) or for many of the more general parameters (from epidemiological and other literature).

The results suggest that the uncertainty in the model is greater than the differences between the drug strategies, with results varying from dominance (the use of newer drugs reduces the utility of treatment) to clearly cost-effective (cost per QALY well within an acceptable range). The results do not suggest that the use of the newer agents in any of the scenarios considered is clearly cost-effective but, similarly, do not indicate that they are clearly not cost-effective.

**Other issues**

It is important to note that there is a substantial difference between the population of newly or recently diagnosed patients, many of whom will have extremely good outcomes regardless of which AEDs are chosen for initial treatment, and the smaller population with intractable epilepsy, who experience little or no benefit after trying a number of different treatments. There is reasonably clear evidence from placebo-controlled trials of the newer agents that they may have some beneficial impact on the disease, and it may be considered desirable that as many treatment options as possible remain available for this group of patients. The cost of using the newer agents in this context for these patients is likely to be small, owing to the relatively small proportion of patients reaching this stage and the likelihood that the duration of treatment would be short unless the drugs were perceived to be of benefit.

**Conclusions**

The prognosis for children diagnosed with epilepsy is generally good, with a large proportion responding well to the first treatment given. A substantial proportion, however, will not respond well to treatment, and for these patients the clinical goal is to find an optimal balance between the benefits and side-effects of any treatment given.

For the newly, or recently, diagnosed population, the key question for the newer drugs is how soon they should be tried. The cost-effectiveness of using these agents early, in place of one of the older agents, will depend on the effectiveness and tolerability of these agents compared with the older agents; the evidence from the available trial data so far suggests that the newer agents are no more effective but may be somewhat better tolerated than the older agents, and so the cost-effectiveness for early use will depend on the trade-off between effectiveness and tolerability, both in terms of overall (long-term) treatment retention and overall utility associated with effects on seizure rate and side-effects. There are insufficient data available to estimate accurately the nature of this trade-off either in terms of long-term treatment retention or utility.

**Need for further research**

Better information is required from RCTs before any rational evidence-based prescribing strategy could be developed. Ideally, RCTs should be conducted from a ‘public health’ perspective, making relevant comparisons and incorporating outcomes of interest to clinicians and patients, with sufficiently long-term follow-up to determine reliably the clinical utility of different treatments, particularly with respect to treatment retention and the balance between effectiveness and...
tolerability. RCTs should mirror clinical practice with respect to diagnosis, focusing on defined syndromes or, where no syndrome is identified, on groups defined by specific seizure type(s) and aetiology.

Epilepsy in children is a complex disease, with a variety of distinct syndromes and many alternative treatment options and outcomes. Diagnosis-specific decision-analytic models are required; further research may be required to inform parameter values adequately with respect to epidemiology and clinical practice.

**Publication**

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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