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

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Executive summary

Health Technology Assessment 2006; Vol. 10: No. 7

Health Technology Assessment
NHS R&D HTA Programme

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Executive summary

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

Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. *Health Technol Assess* 2006;**10**(7).

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/50/02. The protocol was agreed in January 2002. The assessment report began editorial review in February 2004 and was accepted for publication in April 2004. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.