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

M Connock, E Frew, B-W Evans, S Bryan, C Cummins, A Fry-Smith, A Li Wan Po and J Sandercock

March 2006
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The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy.  
A systematic review

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Abstract

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

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Objectives: To examine the clinical effectiveness and cost-effectiveness of newer antiepileptic drugs (AEDs) for epilepsy in children: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin.


Review 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.

Results: The quality of the randomised controlled trial (RCT) data was generally poor. 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 benign epilepsy with centrotemporal spikes), 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. Annual drug costs of the newer agents ranges from around £400 to £1200, depending on age and concomitant medications. An AED that 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. The results of the decision-analytic model 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.

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. 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.
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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

<table>
<thead>
<tr>
<th>Glossary</th>
<th>Definition</th>
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<tr>
<td>Computed tomography</td>
<td>A non-invasive imaging technique using X-rays to produce pictures as though they were successive slices through the body.</td>
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<tr>
<td>Cytochrome P monooxygenase</td>
<td>A family of enzyme systems, especially rich in the liver, which modify drugs and a wide variety of other molecules by introducing an oxygen molecule into their structure using molecular oxygen as a source. They are important in sending drugs on their elimination pathway from the body and/or in activating drugs to their therapeutic form.</td>
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<tr>
<td>Electroencephalogram</td>
<td>Uses a system of electrodes placed in various positions over the scalp that detect the electrical activity in underlying regions of the brain. The electrode signals are displayed as wave patterns through time. Abnormal patterns can help in the diagnosis of epilepsy and in some cases aid the localisation of the part of the brain initiating seizure activity. EEG is best performed and interpreted by experienced personnel.</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>A non-invasive imaging method based on the principles of nuclear magnetic resonance. Use of contrast agents improves sensitivity and/or specificity of the imaging. MRI allows detection and localisation of damaged or abnormal brain structures. Functional MRI gives images depending on blood oxygen supply to brain structures which reflect their functional performance.</td>
</tr>
<tr>
<td>Positron emission tomography</td>
<td>An imaging system that highlights active regions of the brain. It uses a glucose-like tracer molecule tagged with a radioactive atom that decays by emitting a positron. The emitted positron immediately collides with an electron, they mutually annihilate and their mass energy is converted into back-to-back γ-rays that travel out of the brain and are detected with gamma cameras. The information gathered by the cameras is integrated to form an image. Active regions of the brain will contain more tracer and produce a stronger signal.</td>
</tr>
<tr>
<td>Single photon emission computed tomography</td>
<td>SPECT imaging involves the rotation of a photon detector array around the body to acquire data from multiple angles.</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>A&amp;E</td>
<td>accident and emergency</td>
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<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AED</td>
<td>antiepileptic drug</td>
</tr>
<tr>
<td>ARIF</td>
<td>Aggressive Research Intelligence Facility</td>
</tr>
<tr>
<td>BECTS</td>
<td>benign (partial) epilepsy with centrotetal (rolandic) spikes</td>
</tr>
<tr>
<td>CAE</td>
<td>childhood absence epilepsy</td>
</tr>
<tr>
<td>CCTR</td>
<td>Controlled Clinical Trials Register (Cochrane)</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DARE</td>
<td>Database of Reviews of Effectiveness</td>
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<tr>
<td>DCE</td>
<td>discrete choice experiment</td>
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<td>EED</td>
<td>Economic Evaluation Database</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EL</td>
<td>executive letter</td>
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<tr>
<td>GABA</td>
<td>(\gamma)-aminobutyric acid</td>
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<td>GPRD</td>
<td>General Practice Research Database</td>
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<td>HEED</td>
<td>Health Economic Evaluation Database</td>
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<td>HRQoL</td>
<td>health-related quality of life</td>
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<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
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<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>ITT</td>
<td>intention-to-treat</td>
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<tr>
<td>JME</td>
<td>juvenile myoclonic epilepsy</td>
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<tr>
<td>MHD</td>
<td>monohydroxy derivative</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NGPSE</td>
<td>National General Practice Study of Epilepsy</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NMDA</td>
<td>(N)-methyl-D-aspartate</td>
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<td>ONS</td>
<td>Office of National Statistics</td>
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<td>PEM</td>
<td>prescription event monitoring</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>QALY</td>
<td>quality-adjusted life-year</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<td>RCT</td>
<td>randomised controlled trial</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<td>SUDEP</td>
<td>sudden unexpected death in epilepsy</td>
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<tr>
<td>TTO</td>
<td>time trade-off</td>
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<td>VNS</td>
<td>vagus nerve stimulation</td>
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All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.
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.
Objectives/purpose of review

Since the 1980s, several new drugs for treatment of epilepsies have been developed and have gradually diffused into clinical practice. In childhood epilepsy they are most often used as add-on therapy to conventional drugs or as a second-line monotherapy; however, some are used as first-line therapy (e.g. lamotrigine for generalised seizures and vigabatrin for infantile spasms) and there is a clear potential for other uses in first-line monotherapy. Tolerability is a primary consideration, in addition to effectiveness, particularly as in cases of refractory epilepsy drug administration is often gradually titrated to the maximally tolerated dosage before changing to an alternative or trying additional drugs.

The following questions will be addressed concerning the use of these drugs:

1. What is the clinical effectiveness, tolerability and cost-effectiveness of newer antiepileptic drugs (AEDs) used in monotherapy when compared with current standard drug treatment for epilepsy in children?
2. What is the clinical effectiveness, tolerability and cost-effectiveness of newer AEDs used as add-on therapy when compared with current standard drug treatment for epilepsy in children?

The population of interest for this review is children with newly diagnosed epilepsy or treatment-resistant epilepsy. Single seizures, status epilepticus, seizures following neurosurgery or head injury, febrile convulsions and trigeminal neuralgia are excluded from the appraisal. As effectiveness and the balance between harm and benefits of drug treatment vary according to epilepsy syndrome and seizure type, the above questions will need to be addressed for both individual syndromes (e.g. Lennox–Gastaut syndrome and West’s syndrome) and for broad groups of seizure types (e.g. generalised, absence or partial).

Children are defined here as neonates (birth to 1 month), infants (1 month to 2 years), children (2 to 12 years) and adolescents (12 to 18 years). Some studies containing information relevant for this review may be trials in adults that include a substantial proportion of people under 18 years old.

The optimal choice of drug for adolescents may differ from that for younger children, as side-effects, particularly cosmetic ones, may reduce the acceptability of the drug. Given the teratogenic potential of some AEDs and also that some enzyme-inducing AEDs reduce the effectiveness of oral contraceptives, special consideration needs to be given to their use in adolescent girls.

Some kinds of epilepsy are associated with brain damage or, rarely, frequent severe seizures may lead to brain damage. Antiepileptic treatment for these children requires careful monitoring as some treatments may cause or exacerbate learning difficulties and adverse effects of treatment may be difficult to ascertain.

Nature of the disease

Epilepsy is a condition in which epileptic seizures recur. The many seizure types can be defined as intermittent, paroxysmal stereotyped disturbances of consciousness, behaviour, emotion, motor function, perception or sensation (which may occur singly or in any combination) that on clinical grounds result from cortical neuronal discharge. Important consequences for children and young people with epilepsy include not only the seizures themselves, but also the social, educational and psychological impact of the condition and treatment. Seizures can be broadly categorised as ‘partial’, which begin locally, or as ‘generalised’ (including absence seizures), which involve abnormal activity in both cortical hemispheres. Partial seizures can be subcategorised as simple (consciousness unimpaired) or complex (consciousness impaired). Seizure type, age at onset, EEG findings and associated features, including whether the epilepsy is symptomatic or cryptogenic, may allow the identification of an epilepsy syndrome (e.g. West’s and Lennox–Gastaut syndromes), but in 30–40% of children it is not possible to identify a syndrome. The choice of drug treatment and the prognosis of childhood epilepsy depend upon the syndrome or, where a syndrome has not been identified, upon
the seizure type. About one-quarter of patients have epilepsy resistant to traditional therapy; in children, refractory seizures are most often generalised.

‘Newer’ drugs for epilepsy

Since 1989, seven new AEDs have become available in the UK for use in the treatment of epilepsy: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin. Licensed indications vary within the age group of 0–18 years and, with the exception of tiagabine and levetiracetam, are licensed to some extent for children aged 12 years and under.

‘Standard’ treatments and comparisons to be made

Current standard treatments include older antiepileptics (e.g. carbamazepine, phenytoin, valproate), surgery and, rarely, ketogenic diet. This review will consider the use of the newer AEDs compared with current best practice in the UK, i.e. treatment which would be recommended if none of the newer agents were available (‘standard’ treatment). Note that for some conditions, standard treatment may not involve the use of AEDs.

Drug doses with AEDs are dependent on the pharmacokinetics and pharmacodynamics of the drugs in individual patients, which in turn depend on factors such as age/size of patient and concomitant drug treatment. A particularly important aspect of randomised controlled trials (RCTs) is therefore that appropriate doses of both intervention and comparator drug have been employed so that a valid assessment can be made of the relative effectiveness and tolerability of the intervention. Appropriate doses of comparators will be taken into account when assessing the quality of studies.
Chapter 2
Background

Description of underlying health problem

Nature of condition

Epilepsy is a condition in which epileptic seizures recur. Epileptic seizures are episodes of sudden disruption of brain function associated with abnormal high firing rates and synchronisation of neurons in defined regions of the brain. Synchronised high firing rate of populations of neurons is in itself a normal brain activity, but the following distinguishing features characterise an epileptic event:

- paroxysmal nature – sudden emergence from and quick return towards previously relatively normal neuronal brain activity
- disruption of normal brain function
- involvement of all or most of the neurons in a defined brain region
- association with high firing rate in many of the neurons in the involved region.

The diagnosis of epilepsy, however, is made on clinical grounds, and the history of the events is critically important, as further investigations may be negative in the presence of epilepsy. Many other conditions of childhood and adolescence can be mistaken for epilepsy, and where a child with apparent epilepsy does not respond to treatment, the diagnosis may need to be reviewed.

An epileptic seizure is a single episode of disturbance. Seizures are enormously diverse and are accompanied by an array of clinical manifestations; they are broadly categorised into partial seizures, involving a small, localised region of the brain in one hemisphere, and generalised, which simultaneously involve both sides of the brain. Partial seizures may evolve secondarily into generalised. Partial seizures accompanied by impaired consciousness are termed complex in distinction from simple seizures in which consciousness is unaffected; during a complex partial seizure the patient may appear as if in a trance and may exhibit automated behaviours such as lip smacking or fidgeting hand movements. It can be difficult to correctly identify seizures, for example, determination of an infant’s state of consciousness is difficult. The precise form of partial seizures is determined by their site of origin and may involve, for example, twitching on one side of the body or experience of sensations such as déjà vu. Generalised seizures may be of the following forms:

- Tonic seizures cause a sudden increase in muscle tone and may result in falling backwards.
- Atonic seizures cause a sudden loss in muscle tone and may result in falling forwards (a form of ‘drop attack’).
- Clonic seizures are marked by alternate contraction and relaxation of muscle(s) occurring in rapid succession.
- Myoclonic seizures have sudden, brief, shock-like contractions of muscles that may involve the whole body or be restricted to one area.
- Absence seizures involve very brief losses of consciousness in which entry and exit from seizure state are rapid. They may involve minor automatisms (previously known as petit mal).
- Atypical absence seizures involve more gradual exit from and entry into loss of consciousness.
- Tonic–clonic seizures characterised by immediate loss of consciousness, then a tonic phase followed by a clonic phase, accompanied by laboured breathing, incontinence, tongue/mouth biting and skin colour changes (previously known as grand mal).

The many seizure types can be defined as ‘intermittent, paroxysmal stereotyped disturbances of consciousness, behaviour, emotion, motor-function, of perception or sensation, which may occur singly or in any combination’. However, as many other conditions can mimic seizures, a careful clinical diagnosis with a full history is needed, and a single seizure is not generally sufficient to make a diagnosis of epilepsy.

Consequences of epilepsy include the risk inherent in seizures, which includes the possibility of accidents in the course of a seizure and the serious metabolic consequences of long-lasting seizures (status epilepticus) which require immediate treatment and often inpatient care, including intensive care. Additionally there are social, psychological and educational consequences.
Classifications of epilepsy and of epileptic seizures proposed by the International League Against Epilepsy (ILAE) in 19814 and 19895 have become widely adopted especially for research studies of epilepsy. Alternative classifications have been proposed.6,7 The 1989 proposal introduced the concept of ‘epileptic syndrome’. An epileptic syndrome is ‘an epileptic disorder characterised by a cluster of signs and symptoms occurring together’; these include items such as seizure type(s), aetiology, anatomy, precipitating factors, age of onset, severity, timing, diurnal and circadian cycling and sometimes prognosis. A recent proposal by an ILAE task force published in 20018 suggested that the status of syndromes should be characterised as ‘accepted’ or ‘in development’. This proposal introduced the concept of ‘diagnostic entity’ based on precise identification of seizure type(s); it was envisaged that diagnostic entity be used to supplement syndromic diagnoses, or to stand alone when syndromic diagnosis could not be established.

Syndromes are broadly separated into those with seizure initiation that is of local origin (partial seizures, focal or localisation-related seizures) irrespective of subsequent generalisation, or those of generalised origin (initiation involving activity in both brain hemispheres). This dichotomy cannot contain all seizures or syndromes because many intermediate abnormalities exist (e.g. multifocal, diffuse hemispheric, bilaterally symmetrical focal). Classification into syndromes is generally viewed as a clinically useful tool rather than a precisely accurate representation of reality. Many of the clues that allow the localisation-related/generalised distinction to be made for adult epilepsy can be unavailable in the case of infants and children. Further subdivisions that define separate syndromes are based on the presumed aetiology of the condition; idiopathic, symptomatic or cryptogenic (probably symptomatic but with no brain lesion identified) disorders are distinguished. Further designation may be based on the degree of impairment caused by the condition or simply whether the condition is benign or severe in outcome.

**Epilepsy in children**

Clinicians communicating with each other about epilepsy in children commonly do so in terms of epileptic syndrome and this may foster a more precise tailoring of therapies.9 The majority of epilepsy syndromes start in infancy or childhood.10 For about 30–40% of young epileptic patients it is not possible to designate a syndrome. In practice, therapy is then based on seizure type(s) and simple description and classification of ictal behaviours. The recent ILAE task force recommendations provide a framework for this.

Epilepsy in young people differs from that in adults in a number of important respects including:3

- Greater multiplicity of epileptic conditions.
- Heterogeneity with respect to syndrome types, causes and prognoses.
- Usual refractory seizure type is generalised rather than partial.
- Condition may change with age, one syndrome may evolve into another.
- Greater potential impact on the social, educational and behavioural spheres of life.

Postnatal brain maturation continues for many years. In the neonate, the balance of excitatory pathways to inhibitory is at its highest and this may lower the ‘seizure threshold’ and explain the high incidence of seizures in infants. Synaptogenesis is still pronounced after birth, as are other developmental changes including myelination of neurons, dendritic arborisation, alterations in dendritic spine morphology, alterations in neurotransmitters and neuronal pruning. A complex developing system can be expected to be more sensitive to derangement than one in steady state. This may represent one reason why the incidence of epilepsy is highest in infancy and gradually declines through childhood and then adolescence.

The prolonged maturation of the brain is coupled to the gradual acquisition of many behavioural attributes.11 Basic motor skills and some essentials of language are achieved early on. Although the trajectory of development slows until adulthood is attained, these faculties continue to be refined to a greater and greater degree throughout childhood and adolescence. Communication develops in childhood as do other cognitive and social skills. In adolescence, abstract concepts, cause–effect associations, deeper interpersonal relationships and social interactions involving cooperation, competitiveness and ideas of right and wrong develop. Epilepsy and epilepsy treatment can impact on many aspects of development.

Attitudes to epilepsy in society vary, but individuals with epilepsy still meet considerable prejudice in their social interactions. Epileptic fits frighten unaccustomed observers and people with
epilepsy may become stigmatised or rejected. There are psychological consequences for the person with epilepsy resulting from fear of seizures, their unpredictable occurrence, their embarrassing nature and physical consequences. Carers of children with epilepsy may become overprotective and unnecessarily restrict the child’s activities, and the child may be bullied at school or may sustain seizure-related injuries.

Therefore, important consequences for children and young people include not only the seizures themselves but also the impacts of the condition and its treatment upon social life (variety of activities, acceptability by others), on relationships (with friends and peers, siblings and parents), on educational progress (cognitive attainment) and upon psychology (behaviour, self-esteem, loss of original hopes). Additional impacts, such as social stigma, and parental and sibling stress, are sustained by the family unit. Specific measuring tools that aim to encapsulate such impacts have been proposed.12

In a prospective population-based cohort of patients with childhood-onset epilepsy, 27% of patients experienced status epilepticus, with more than half of those patients having two or more episodes;13 73% of cases occurred at onset and 90% within 12 months of onset. Younger age at onset (<6 years old) and partial epilepsy were associated with a higher risk of status. A further prospective population-based study reported status in 9%.14 Hence status epilepticus with its attendant risks and need for hospital treatment is relatively common in childhood epilepsy.

Adolescents with epilepsy have needs of their own which must be addressed. In this transitional period, adolescents need to develop independence and learn to manage their condition themselves. New factors enter into the choice of and compliance with AED therapy, as cosmetic side-effects, reproductive health issues and new social behaviours including drinking alcohol enter the equation. Seizure control has important social-consequences in terms of driving and occupation.3

Epilepsies relevant to children3 include the following:

1. Lennox–Gastaut syndrome.15,16 Syndrome definitions vary but this condition is recognised as a devastating paediatric epilepsy. The mean age of onset is 26–28 months; it is associated with severe seizures of multiple types, frequent injuries incurred during seizure (especially tonic–clonic and atonic), developmental delay, retarded and regressive mental capacity and behavioural problems that may place a great burden on carers and families. The patho-physiology is unknown but some have postulated a common pathogenic mechanism as infantile spasms. Seizures are often resistant to therapy, and mortality is high at 3% (mean follow-up 8.5 years) to 7% (mean follow-up 9.7 years), with death often related to accidents. Lennox–Gastaut syndrome accounts for 1–4% of childhood epilepsies and for 10% of epilepsy with onset less than 5 years of age.

2. Infantile spasms. Infantile spasms16,17 represent a unique seizure type and, according to the ILAE, also an epileptic syndrome. West’s syndrome is an older syndrome term for patients with infantile spasms, hypsarrhythmic EEG pattern and mental retardation and represents about 1–5% of all childhood epilepsy. Patients with infantile spasms may suffer other seizure types that may precede or accompany spasms. Several disorders mimic infantile spasms and correct diagnosis relies on video-EEG monitoring. Infantile spasms ‘are brief 1–5-s contractions of trunk with extension and elevation of the arms, tonic extension of the legs, with clusters of 3–20 spasms typically occurring several times a day in untreated patients’.16 Most patients present within the first year of life, with peak onset between 4 and 6 months. Most spasms remit spontaneously, with or without treatment; by mid-childhood, however, other seizure types arise in 50–70% and chronic intractable epilepsy occurs in about half with a history of spasms. Some patients with spasms evolve to Lennox–Gastaut syndrome. High case fatality rates have been reported with most deaths occurring before the age of 10 years with the most common cause being infection.

3. Childhood absence epilepsy (CAE). This syndrome is relatively common (>5% of childhood epilepsies, with higher incidence in girls than boys) and is characterised by absence seizures as the initial and predominant seizure type and by particular features of EEG pattern. Age of onset is between 3 and 12 years3 with peak onset at 6–7 years of age. Although CAE is relatively benign, it may be associated with minor cognitive/learning difficulties,18 which rarely may outlast the epilepsy and be a lifelong problem.11 A proportion (~15%) of CAE patients may later exhibit juvenile myoclonic epilepsy (JME), which is probably a lifelong condition but usually is controlled with drug therapy. JME accounts for 5–10% of
childhood epilepsy. A 30% rate of inadvertent pregnancy has been reported in young adult girls who had CAE, indicative of poor social outcome for CAE.

4. Benign (partial) epilepsy with centrotemporal (rolandic) spikes (BECTS)

The most common childhood form of partial epilepsy, BECTS account for 10–15% of childhood epilepsy. Age of onset is between 3 and 13 years with a peak between 7 and 9 years. As seizures usually cease by mid-adolescence, prognosis is excellent.

There are many other epilepsy syndromes of adolescence and childhood; often they are age dependent, some are common and some occur rarely. For 30–40% of children, however, a specific epileptic syndrome will not be identified. Table 1 shows epilepsy diagnoses in prevalence and incidence studies that have used the ILAE classification. The syndromes described above, although important, constitute a minority of childhood epilepsy syndromes. It should be noted that evidence on effectiveness of a treatment in one epilepsy type or syndrome cannot be generalised to all childhood epilepsy types or syndromes.

The treatment of immediate post-traumatic seizures, status epilepticus, febrile convulsions and neonatal seizures is beyond the scope of this report.

### Diagnosis

A recent systematic review considered what elements (e.g. expertise, services and tests) were required to make an accurate first diagnosis and initiate and monitor treatment. The reviewers were unable to identify an agreed gold standard for use in first diagnosis or in diagnostic studies of epilepsy. The evidence base for diagnostic procedures was found to be weak, for example, only three of 42 studies with a diagnostic focus reporting sensitivity and specificity values. A National Clinical Guideline for Diagnosis and Management of epilepsy in adults categorised the literature pertinent to diagnosis at the lowest level, grade C, indicating an absence of directly applicable clinical studies of good quality. Similarly, a recent national statement on good practice for care of people with epilepsy identified literature pertinent to diagnosis as dependent only on expert and user opinion. However, reports focusing on misdiagnoses were judged to depend on well-designed non-experimental studies.

### Table 1 Prevalence and Incidence of ILEA-Classified Epilepsy Syndromes of Childhood

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th></th>
<th>Incidence</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prevalence/1000</td>
<td>n</td>
<td>%</td>
<td>Prevalence/1000</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>Endziniene</td>
<td>Lithuania, 1995</td>
<td></td>
<td></td>
<td></td>
<td>Ericksson</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Localisation-related epilepsies</td>
<td>189</td>
<td>50.0</td>
<td>2.13</td>
<td>134</td>
<td>41.0</td>
<td>21</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15</td>
<td>4.0</td>
<td>0.17</td>
<td>24</td>
<td>8.0</td>
<td>8</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>63</td>
<td>17.7</td>
<td>0.71</td>
<td>35</td>
<td>11.0</td>
<td>4</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>111</td>
<td>29.4</td>
<td>1.25</td>
<td>75</td>
<td>22.0</td>
<td>9</td>
</tr>
<tr>
<td>Generalised epilepsies</td>
<td>113</td>
<td>29.9</td>
<td>1.27</td>
<td>158</td>
<td>48.0</td>
<td>14</td>
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<tr>
<td>Idiopathic</td>
<td>55</td>
<td>14.6</td>
<td>0.62</td>
<td>75</td>
<td>23.0</td>
<td>9</td>
</tr>
<tr>
<td>Cryptogenic/symptomatic</td>
<td>18</td>
<td>4.8</td>
<td>0.20</td>
<td>45</td>
<td>14.0</td>
<td>4</td>
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<tr>
<td>Symptomatic</td>
<td>35</td>
<td>9.3</td>
<td>0.39</td>
<td>38</td>
<td>12.0</td>
<td>1</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>5</td>
<td>1.3</td>
<td>0.06</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Undetermined partial or generalised</td>
<td>60</td>
<td>15.9</td>
<td>0.68</td>
<td>5</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>Presumably symptomatic</td>
<td>16</td>
<td>4.2</td>
<td>0.16</td>
<td>4</td>
<td>0.18</td>
<td>–</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>44</td>
<td>11.6</td>
<td>0.44</td>
<td>11.6</td>
<td>0.50</td>
<td>0.0</td>
</tr>
<tr>
<td>Both partial and generalised</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Unclassified</td>
<td>16</td>
<td>4.2</td>
<td>0.18</td>
<td>71</td>
<td>11.6</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>378</td>
<td></td>
<td></td>
<td>32</td>
<td></td>
<td>36</td>
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### Table 2

<table>
<thead>
<tr>
<th>Epilepsy Syndrome</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West’s infantile spasms</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Lennox–Gastaut</td>
<td></td>
<td>6 2 0 0 4</td>
</tr>
</tbody>
</table>
In their systematic review, Ross and colleagues found evidence to support the following conclusions:

- Diagnostic procedures supported by the literature to rule in a diagnosis of epilepsy, prevent delayed or missed diagnosis and predict remission outcome are a complete history and physical examination, including neuropsychological assessment and a standard EEG.
- Other diagnostic interventions [e.g. computed tomography (CT) and magnetic resonance imaging (MRI)] are more important to rule out secondary causes of seizures or to resolve uncertain diagnoses.

According to the UK Good Practice statement, all patients with a first seizure should be seen by a specialist with an interest (and presumed expertise) in epilepsy within 28 days of referral. Detection and recognition of seizures and seizure types are fundamental for diagnosis and require a detailed description of the supposed epileptic event by a first-hand witness who, for epilepsy in children, is likely to be a parent, guardian or carer. Video recordings of the event are particularly useful, as are recordings of examples of epileptic and non-epileptic seizure that can be shown to parents to discover if any resemble their child’s attacks. Verbal accounts by the patient add useful information regarding states of consciousness, postseizure amnesia and the presence of an aura, but are clearly not available from preverbal children. Some infantile seizures may be extremely subtle and difficult to detect even with skilled observers so that they remain undetected and underappreciated.

Because some seizure types result in falls that may incur physical injury, there may be a tendency for premature diagnosis in an attempt to forestall harm. For this reason, because there are many medical causes of seizure other than epilepsy, and because of the inherent difficulties in distinguishing possible causes and types of seizure that occur in children, misdiagnosis may possibly be frequent. Grunewald and colleagues reported that of 15 cases of juvenile myoclonic epilepsy referred to a specialist epilepsy clinic, only one had been assigned a putative diagnosis of JME and definitive diagnosis had been delayed by a mean of 14.5 years. Recent concerns have been expressed about the frequency of misdiagnosis of children’s epilepsy in the UK and the opinion expressed that its origins may be attributable to a dearth of available specialist paediatric neurologists and paediatricians with interest and expertise in epilepsy and to inadequate recording and interpretation of EEG results. There is a lack of evidence bearing on the nature of training and experience desirable for specialist care-givers.

Further to seizure description and EEG, imaging methods may be employed that can strengthen and or extend diagnosis. Their use depends on diagnosis of the epilepsy, especially with regard to the likelihood that surgery may be beneficial (see below). Procedures include CT scan, positron emission tomography (PET), single photon emission computed tomography (SPECT) and MRI. Guidelines for imaging children with epilepsy have been produced by the British Paediatric Association.

**Aetiology and pathology**

For about three-quarters of childhood epilepsies no cause can be found. It is presumed that many of these have an as yet unidentified genetic basis.

Causes are extremely numerous, in many cases very rare, and include the following:

- tumours and developmental malformations (e.g. tuberous sclerosis) with associated brain pathologies
- chromosomal abnormalities and mitochondrial diseases
- metabolic disorders including monogenetic disturbances such as those involving oxidation of long-chain fatty acids and turnover of phospho- and sphingolipids
- a mutation specifically resulting in epilepsy (e.g. potassium channel mutation in benign familial neonatal convulsions) or in a complex syndrome often involving epilepsy (e.g. tuberous sclerosis)
- infections
- head injury
- hypoxic-ischaemic injury.

Investigations have sought to unravel the mechanisms underlying the development of epileptic seizures, but details of the phenomenon are poorly understood. Basic understanding of the cellular physiology of neurons and their supporting glia cells has revealed the fundamental involvement of voltage-gated ion channels, that regulate neuron excitability and synaptic processes responsible for communication among neurons. Potassium channels (regulating hyperpolarisation of neuronal plasma membrane) and factors controlling the levels of the neurotransmitter γ-aminobutyric acid (GABA) and its interaction...
with post-synaptic receptors have emerged as important factors. In most circumstances GABAergic neurons exert inhibitory influences that can be construed as constraints on potential spread of excitation to large populations of neurons with attendant reduced risk of seizure. In other circumstances, neurons may respond aberrantly to GABA so that it exerts an excitatory effect. Such differences may apply in different syndromes and provide one explanation for the observation that a given therapeutic strategy may reduce seizures for one patient but exacerbate them for another.

It is difficult to investigate individual neurone behaviour simultaneously in large populations such as are known to be involved in an epileptic seizure. However, epileptic neuronal events involve such large populations of cells that the concomitant electrical changes invoked can often be detected with electrodes applied externally to the scalp during an EEG examination. Sometimes localising the origin of seizures requires the use of depth electrodes. Features of ictal (during seizure) EEG records when integrated with all available clinical data can characterise particular types of epilepsy and may aid localisation of the brain region involved. The ictal features of EEG recordings in infants exhibit a wide range of patterns that are not efficiently identified by available automated algorithms so that complete review of the recording is recommended.

New methods of analysis can allow the detection of hidden patterns within EEG recordings that define a so-called pre-ictal state for some seizures in some epilepsies (e.g. focal temporal lobe epilepsy). Such procedures offer the possibility of anticipating seizures and therefore ultimately of avoiding them.

It is possible that recurrent seizures may damage brain tissue. Laboratory studies demonstrate that hyperactivity of neurons can be cytotoxic and result in cell death. Evidence indicates that this is due to accumulation of intracellular calcium as a result of prolonged stimulation of GABA receptors, especially those of the N-methyl-D-aspartate (NMDA) variety. Some epilepsies are associated with progressive neurological deterioration, neuron loss and cognitive deficits and others with sclerosis in particular brain regions. Hermann and colleagues reported that deficits in temporal tissue volume and poorer cognitive status are associated with early onset of temporal lobe epilepsy. The tissue deficit was extended to areas away from the focal origin of seizures and the associations were independent of the duration of disease and its treatment, suggesting that the important factor was the early developmental stage of the brain in early onset. Hence the developing brain could be more susceptible to damage than the mature brain. An alternative notion expressed is that the plasticity of a developing brain might offer compensative capacity for reorganisation and repair in case of damage. However, it is always uncertain whether a common underlying factor causes both seizures and damage, or whether seizures and their treatment cause or exacerbate the damage. The majority of children with epilepsy, however, do not experience progressive cognitive decline. Learning difficulties are relatively common, and may result from underlying lesions, unrecognised seizures, subclinical epileptiform activity, adverse effects of AEDs and emotional and psychological problems.

**Epidemiology**

Estimates of the extent of children’s epilepsy in the UK are problematic. Reliability depends on epidemiological studies with unbiased sample selection, precisely defined, meaningful and accurately applied diagnostic criteria and efficient case ascertainment. The heterogeneous and complex nature of the condition means that correct diagnosis is difficult, especially in the very young. In consequence of a lack of consensus on definitive diagnostic criteria, definitions of epilepsy employed in epidemiological studies appear mainly to be dictated by features of the database available; hence even studies published by the same authors within a few years of each other may employ varying definitions. Studies are best served by specialist diagnosis of cases performed on an individual basis.

Recently two types of study have provided age-related information. Wallace and colleagues exploited the Office of National Statistics (ONS) General Practice Research Database (GPRD) that included 2,052,922 persons highly representative of the UK population. In this study, diagnosis of ascertained cases could not be done on an individual basis, and case definition was determined from a composite of database entry details. Kurtz and colleagues, MacDonald and colleagues and Heaney and colleagues performed prospective studies in which case ascertainment was likely to be high, diagnoses were based on individual case assessment (usually by a specialist) and the ‘unselected’ study population was based on 13–20 general practices or a cohort defined at birth. Case definition and methods of case ascertainment were not the same.
in these studies and this is reflected in differing reported estimates in incidence for given age bands and the variation in observed incidence trends with age (Table 2). Because of these disparities, and to place UK studies in context, Table 2 includes incidence reported in similarly conducted prospective studies for European and Canadian populations resembling that of the UK.

Using the range of incidence values from prospective studies of UK populations and the age structure of England and Wales (ONS Census 2001), we calculate that the annual number of new consultations for children with epilepsy is in the range 4000–14,000 for ages 0–14 years and 5000–15,000 for ages 0–19 years. Approximately 1% of these would occur in an average-sized health authority of 500,000 persons.

Many new consultations follow seizures where epilepsy is suspected (possible or likely) but where definitive diagnosis of epilepsy does not result. Using the data of Kurtz and colleagues, the ratio of possible plus likely cases to validated cases up to the age of 16 years is ~35. A ratio of only about 1:1 (definite epilepsy:possible epilepsy + other seizures) was observed in the National General Practice Study of Epilepsy (NGPSE) among newly diagnosed cases in a cohort of 1195 (all ages) identified from 275 general practices. Taking consultations for these conditions into account would greatly inflate, to an uncertain degree, the estimate of the number of new consultations.

Prevalent cases of epilepsy in children will increase service demand above that provided for incident and suspected cases. The impact of prevalent cases on services is difficult to gauge; it has been estimated that about 20–30% of all epilepsies in children are severe (depending on definition used) and would require close medical monitoring and repeated consultation. Prevalence has been
defined as the proportion of all the individuals of a defined age that are diagnosed as having ‘active epilepsy’. Because the occurrence of seizures is intermittent and seizure frequency is highly variable, difficulties arise in defining ‘active epilepsy’. Various definitions have been used. Kurtz and colleagues\textsuperscript{40} identified children who were continuing AED therapy or who had had a seizure (i.e. further to a previous seizure) during the previous 2 years and reported prevalence gradually rising from 3.9/1000 at age 7 years to 4.9/1000 at age 16 years. This rise in prevalence with test age may reflect a higher rate of accumulation of new cases than rate of remission of established cases or sampling problems with a small cohort. Similar prevalence estimates based on various definitions of active epilepsy have been reported for children in other European populations that can be expected broadly to resemble the UK: Norway 5.1/1000 (6–12 year olds);\textsuperscript{47} Sweden 4.2/1000 (0–16 year olds);\textsuperscript{47} Finland 3.94/1000 (0–15 year olds);\textsuperscript{21} Lithuania 4.25/1000 (0–15 year olds);\textsuperscript{20} Estonia 4.3/1000 (5–9 year olds).\textsuperscript{48} Based on a review of many studies Cowan and colleagues\textsuperscript{49} estimated prevalence to the age of 15 years to be ~5–7/1000.

**Prognosis**

Clinical experience makes it obvious that prognosis of children’s epilepsies varies with seizure type and syndrome. For some syndromes, such as typical rolandic epilepsy, essentially all patients achieve permanent remission.\textsuperscript{11,50,51} It is probable that approximately one-third of all epilepsies that start in childhood will, by puberty, have shown a remission which is usually sustained throughout adult life.\textsuperscript{3} However, accurate estimations of the proportions of patients with persistent disease and with more or less severe disease are hampered by:

- complex and multifaceted definitions of syndromes and seizure types
- lack of consensus on the definition of ‘remission’
- lack of consensus on the definition of ‘refractory’, ‘intractable’ and ‘uncontrolled’ epilepsy
- referral bias inherent in hospital-based series
- differences in length of follow-up
- problems with loss to follow-up.

To determine outcome and identify early prognostic factors Berg and colleagues\textsuperscript{52} prospectively studied a community-based cohort of children (N = 613; >1 month to <16 years old) newly diagnosed with epilepsy. Follow-up was at 2 and 4 years after diagnosis; losses to follow-up were <5%. Of 595 children followed-up at 2 years, 53% were classified as having good outcome [1 year of remission (seizure-free) at time of follow-up], 7.7% as having bad outcome [intractable epilepsy defined as (a) failure of two AEDs for seizure control or (b) failure of one for seizure control and two for intolerable side-effects and at least one seizure per month on average over an 18-month period] and 38.3% had indeterminate outcome (neither good nor bad). At 4 years of follow-up (N = 390), 65% were in 2 years of remission (i.e. seizure free), 10% were intractable (as above) without 2-year remission and 23.5% had indeterminate outcome. Most (83% and 87%, respectively) classified as good and bad outcomes at 2 years remained so at 4 years. However, 55% of those with indeterminate outcome at 2 years were reclassified as good outcome at 4 years. Only 0.5 and 8% with good and intermediate outcome, respectively, at 2 years were reclassified as bad outcome at 4 years. Such results might argue that waiting for remission in refractory children’s epilepsy may be a false hope and that exploration of suitability for surgery should be undertaken relatively early.

The National General Practice Study of Epilepsy\textsuperscript{43} identified a cohort of 792 patients (209, 26% <15 years old) with newly diagnosed epilepsy (564 definite epilepsy, 228 probable). It was reported that 54% of those with definite epilepsy had experienced 1 year of seizure-free remission at 1 year of follow-up and 79% at 2 years of follow-up. At 4 years of follow-up 78% had experienced 2 years of remission. These numbers correspond reasonably to those of Berg and colleagues.\textsuperscript{52}

Berg and colleagues\textsuperscript{52} identified prognostic factors at two years follow-up. Positively associated with bad outcome were age at onset of <1 year and a diagnosis of symptomatic or cryptogenic generalised epilepsy; negatively associated with bad outcome were late age of onset (5–9 years) and partial or generalised idiopathic epilepsy. Symptomatic epilepsy was negatively associated with good outcome.

**Significance in terms of ill-health**

A Europe-based cohort study\textsuperscript{53} in which 25% of participants were <15 years old reported a modestly increased risk of accident [hazard ratio 1.6; 95% confidence interval (CI) 1.3 to 2.1] and of illness (hazard ratio 1.3; 95% CI 1.2 to 1.4) in people with epilepsy (excluding symptomatic epilepsy) compared with age- and sex-matched controls recruited amongst relatives and friends of patients. Age-specific data were not presented.
Recruitment was from hospitals with relatively advanced facilities so that the patients studied probably represent those with more severe epilepsy. Population-based studies would be expected to generate lower estimates of relative risk but have not been performed.

Children with epilepsy carry an increased risk of premature death,
but this depends partly on conditions co-morbid with epilepsy which may carry increased mortality. In a population-based retrospective cohort study of 692 patients diagnosed with epilepsy in childhood, Camfield and colleagues\textsuperscript{55} reported that at 20 years from diagnosis, 6.1\% of the cohort had died. The frequency of death was 5.3 (95\% CI 2.29 to 8.32) times higher than in the reference population in the 1980s and 8.8 (95\% CI 4.16 to 13.43) times higher in the 1990s. This study was done in Nova Scotia, which has a predominantly Scottish, German and Arcadian population and where organisation of medical services favours complete case ascertainment. Children with secondarily generalised epilepsy were at greater risk than those with absence, generalised or partial epilepsy, and patients with neurological disorders at much greater risk (22.2) of death at 20 years postdiagnosis than those without. Of the 26 deaths, 22 were ‘not unexpected’ and resulted from disorders severe enough to cause functional neurological deficit. The remaining deaths were two suicides, one homicide and one case of probable sudden unexpected death in epilepsy (SUDEP) in a 21-year-old. A Dutch prospective hospital-based cohort study was estimated to have recruited 80\% of the population and followed 472 children for 5 years from diagnosis.\textsuperscript{56} There were nine deaths, a mortality rate of 3.8 per 1000 person years. All of the deaths were in children with symptomatic epilepsy and none fulfilled the criteria for SUDEP. The overall mortality risk relative to the general population was 0 (95\% CI 0 to 2.2) in children with non-symptomatic epilepsy and 22.9 (95\% CI 7.9 to 37.9) in children with symptomatic epilepsy. A study that used multiple sources to ascertain possible cases of SUDEP in persons aged under 18 years in Ontario between 1988 and 1998,\textsuperscript{57} however, found 27 cases (mostly patients with generalised tonic clonic seizures), eight of which were in children with idiopathic epilepsy. The rate of SUDEP was estimated as 2 per 10,000 person years.

It can be concluded that:

- Much of the excess mortality following a childhood diagnosis of epilepsy occurs in patients with symptomatic epilepsy/neurological disorder.
- Mortality in childhood in children with idiopathic epilepsy is very little different from that of the general child population.
- SUDEP is rare in childhood, but has been reported.

The study by Cockerell and colleagues\textsuperscript{58} put the burden of epilepsy in the UK at a cost of £1930 million/year. The estimate was based on cost analysis of patients who were part of the National Epilepsy Survey and the NGPSE (begun in 1984) and was published in 1994. About 64\% of the cost was attributed to losses of employment; direct and indirect medical costs accounted for 9\% with most due to ‘active epilepsy’. Other estimates have been published,\textsuperscript{59,60} but subdivisions of estimates to determine the proportion accounted for by children have not been calculated.

Current service provision

Goals of service provision

“In clinical practice the goal of therapy for epilepsy is the best quality of life maintained over the longest time with the fewest seizures (preferably none), fewest side effects, and fewest medications together with a minimisation of hidden or overt long term detrimental after effects.”\textsuperscript{61} These outcomes are unlikely to be routinely recorded in many UK settings and an evidence base upon which judgements could be made about what are the most efficient and appropriate therapies and services to achieve these outcomes is largely absent.

Medical management of epilepsy involves hospital specialists and GPs. According to reporters of the NGPSE,\textsuperscript{62} the most widely followed model of epilepsy management in the UK is one of referral from primary care to hospital clinics followed by investigation, treatment and follow-up at primary, secondary or shared care levels. Systematic reviews\textsuperscript{23,63} have concluded that the current literature can only partially assist in developing management programmes for patients with epilepsy and that the most clinically effective model for outpatient and general practice care for epilepsy patients is unknown.

A systematic review\textsuperscript{63} comparing general neurology outpatient clinics with specialist epilepsy clinics commented on the relative lack of relevant quality studies. More research evidence was available on whether specialist epilepsy nurses
improve outcomes relative to usual care in primary, secondary and tertiary care settings. No significant differences in terms of seizure frequency or severity were found. One RCT that compared quality of life (QoL) outcomes found no difference between specialist epilepsy nurse provision and usual care. Evidence from the paediatric setting is lacking, but paediatric neurology services will often include a clinical nurse specialist.

**Standards of current service provision**

Great concern has been expressed in government reports, local and national audit reports and patient satisfaction questionnaires over the standard of epilepsy services in the UK (e.g. Kitson and Shorvon[64] and Hanna and colleagues[65]). Generally standards of care have been described as inadequate and poor. Problems of service provision identified include:

- patchy access to service provision across the country
- lack of systematic follow-up of patients
- investigations not always used appropriately
- insufficient access to specialised investigations
- patients often seen in hospital by non-specialist
- low numbers of specialists with clinical–pharmacological expertise in epilepsy
- use of inappropriate polypharmacy
- patient non-compliance with medication
- low levels of patient knowledge and instruction.

Government policy on epilepsy care was set out in executive letter EL(95)120,[66] the purpose of which was to encourage improvement in the efficiency and delivery of epilepsy care in the primary and secondary medical services and to ensure continuity of care throughout a patient’s life, to plan services according to the patient’s and their carers’ wishes, and to avoid discrimination against people with epilepsy in the NHS workplace. A short-term assessment of the impact of the policy statement was made by Brown and Lee, 1998[67] and a further assessment by Brown and colleagues[68] in 1999.

More recently, the National Sentinel Audit of epilepsy-related deaths[65] sought to establish whether deficiencies in the standard of clinical management or overall healthcare package could have contributed to deaths of persons with epilepsy in the UK. Three key areas relating to deaths of people with epilepsy were reviewed: investigations into the deaths; care prior to death; and contact with the bereaved family.

The audit was poorly served by the quality of death certification and the true number of epilepsy-related deaths was impossible to determine. Of the 81 children (<18 years old) reported to the audit as having died in the year from September 1999 to August 2000 with epilepsy mentioned on their death certificate, it was possible to use data to assess the care received by only 22. Of these, 17 had never seen a consultant and two others had only seen one in an accident and emergency (A&E) department. For 17, care was considered less than adequate. The opinion was expressed that 50% of these 22 deaths were potentially or possibly avoidable for medical reasons. The report urged caution in the interpretation of the results because analysis was only possible where adequate medical records were available, leading to a small and possibly non-representative sample.

The government has given a commitment to consider in full the recommendations of the National Sentinel Audit and to develop an action plan to address key issues within three months of the publication of the report [Hansard 2002; answer by Jacqui Smith to question by Dr Evan Harris (56669)].

**Current service provision**

Diagnosis of childhood epilepsy, initiation of therapy and initial follow-up are provided by paediatricians and paediatric neurologists. Most follow-up care for people with epilepsy in the UK is undertaken in general practices. Follow-up of children is likely to be shared with the hospital consultant. With the exception of epilepsies developing very soon after birth (i.e. in a hospital setting) and the new cases that present at A&E units, the majority of presentations will be in general practice. Also, GPs are involved in the routine management of chronic epilepsy and are well placed to monitor the effectiveness of therapy.

Because of the difficulties of diagnosis, it is widely recommended[25,65,69] that following the first seizure patients be promptly referred to a specialist clinician with particular interest in epilepsy (e.g. a paediatric neurologist usually based at a tertiary centre, or a paediatrician). At present in the UK there are 61 paediatric neurologists, approximately 1 per million of population,[32,65] hence many children will see a general paediatrician, ideally one with an interest in epilepsy. Recommendations have been made to double the number of paediatric neurologists in the next decade and to increase the number of consultants in neurology from 326 (in 2001) to 496 by 2010. A 1996 audit indicated that only 18% of clinics reached the desired target of less than
1 month’s waiting time from the time of suspected seizure. A study of 119 general practices in the UK published in 1995\textsuperscript{70} indicated that only 6\% of patients with epilepsy attended a specialist epilepsy clinic. There are \(~\)100 epilepsy specialist nursing posts which have been developed in hospital and community settings; the number of posts filled by qualified personnel is uncertain.

Children judged to have a low likelihood of seizure recurrence after a first seizure and those found to have a low seizure rate are likely to be monitored without initiating treatment. At this and other times some children with epilepsy may have special needs with respect to learning or behavioural difficulties, for which there should be concurrent provision.

Adolescents with epilepsy need services appropriate to their needs, providing transitional care that allows adolescents to move securely to independent and informed management of their own condition and to adult services.

Once diagnosis has been established and a treatment strategy selected, the following checklist has been suggested for first review of the patient by the primary care team:

- discuss diagnosis
- review seizure frequency and consider a seizure diary
- discuss risks and benefits of AEDs
- inform the carer/parent/patient’s gaps in knowledge
- discuss impact on patient’s QoL
- provide contact details for patient organisations
- discuss pregnancy and contraception with girls and women as appropriate
- agree a timetable for follow-up.

In practice, it is likely that monitoring is often reactive rather than proactive so that changes in frequency or severity of seizures or intolerance to AEDs or altered status of the patient (e.g. approach of sexual maturity, potential pregnancy) may remain undetected until the patient approaches the GP. Probably about 30\% of children with epilepsy will continue to experience seizures despite treatment; they will be identified by GPs and through hospital follow-up and may require further specialist follow-up and may be considered for changes in therapy and other treatment modalities.

The systematic review by Ross and colleagues\textsuperscript{23} concluded that there was good evidence that some patients do well without treatment, the difficulty being the correct identification of these individuals. For typical benign rolandic epilepsy, which has excellent prognosis (the disorder disappears in 100\% of cases by mid-teenage years), treatment is optional and becoming less popular with parents owing to concern over potential side-effects of AEDs.

**Treatment with AEDs**

Use of an AED is the first treatment option considered. Surveys have shown that in The Netherlands and the USA >80\% of children with epilepsy are treated with AEDs;\textsuperscript{71,72} it is likely that similar practice occurs in the UK. Appendix 2 summarises AED treatment choices suggested in The Royal College of Paediatrics and Child Health’s formulary. Treatments will be guided by diagnosis and age.

The clinician who treats epileptic children with AED therapy confronts several difficulties, including:

1. Multiple diagnoses within which typical and several atypical categories may coexist.
2. Multiple drug choices with
   (a) differing supposed effectiveness for different seizure types and syndromes
   (b) different side-effect profiles
   (c) different interactions with other drugs
   (d) different enzyme-inducing properties and different interactions with endocrine functions
   (e) different dose regimes, with sometimes complex titration programmes with attendant difficulties of gauging advisable dose for children of different ages and different cognitive development
   (f) indeterminate and unpredictable long-term undesirable side-effects.
3. Problems of judging the relative success of the adopted therapy in the face of:
   (a) likely frequent but indeterminate non-compliance\textsuperscript{73}
   (b) inherent unpredictability of seizure frequency through time
   (c) necessity in most cases for the patient’s parent/carer to record frequency and types of seizures
   (d) lack of easily monitored patient-centred validated outcome measures.
4. Difficulties of deciding if and when to stop or change AED therapy.
5. Lack of paediatric-specific published guidelines for treatment validated by high-level evidence (a list of guidelines is provided in Appendix 8 of *Epilepsy care: making it happen*\textsuperscript{74})
6. The necessity/desirability to consider the use of AEDs outside their licensed indications.

The systematic review by Ross and colleagues found some evidence to support the view that access to healthcare professionals with clinical/pharmacological expertise would optimise patient care and minimise mistakes in the choice of dosage, timing and selection of AED. However, they comment that studies define optimum outcome one-dimensionally (seizure frequency) and that studies might be subject to bias since they were led by academic neurologists and suggested expertise lay with academic neurologists.

Because controlled studies of AEDs in children have been small in number and have been conducted to answer regulatory questions, the use of AEDs has been largely guided by as yet unvalidated positive effects observed in case reports, open clinical trials and short-duration controlled trials. For approximately one-third of drugs, serious problems are identified postapproval; examples among AEDs include pancreatitis for valproate, aplastic anaemia for felbamate and visual field defects for vigabatrin. Herranz and colleagues studied 392 children given long-term monotherapy with phenobarbital, primidone, phenytoin, carbamazepine or valproate and found that side-effects occurred in 50%.

For various reasons, adverse events profiles of AEDs may not be the same as for adults. More detailed consideration of these factors is given in Appendices 3 and 4, in Appendix 5 interaction of AEDs with the contraceptive pill is considered and in Appendix 6 AEDs and teratogenicity.

Because of the many potential unwanted effects of AEDs (e.g. aggravation of seizures, appearance of new seizure types, AED-induced encephalopathy, possible AED-associated deterioration in learning, memory and cognitive abilities), clinicians have expressed concern about widespread over-treatment of children. Facets of over-treatment include unnecessarily fast escalation of dosage, use of AED when not required, unnecessary long-term continuation of therapy and inappropriate use of polytherapy. Despite clinical consensus that febrile convulsions do not require prophylactic therapy, the practice is widespread; the 12-year follow-up study of children with febrile convulsions conducted by the NGPSE reported that 11% of 220 children had received medication, and in one-third of these cases this was for simple febrile convulsions.

Assessment of risks associated with taking AEDs is difficult, especially in special populations such as children, as drugs have in the past often been tested only in trials after initial approval of a drug by a regulatory authority, and then only for limited indications and in limited age ranges. Postmarketing surveillance and alert observation by prescribers help to reduce progressively the degree of uncertainty about risk. However, poor reporting, lack of standardisation and difficulties of collation of data mean that risks from side-effects and adverse events are difficult to quantify. Unfortunately only one prescription event monitoring (PEM) study for an AED has been published (for gabapentin). A report of postmarketing experience of topiramate with particular reference to cognition has also been published. An unpublished PEM study failed to detect the visual field defects associated with vigabatrin, yet a case–control study estimated that 52% of vigabatrin patients had definite visual field defects (compared with 0% of control epileptics not taking vigabatrin) and a retrospective study of vigabatrin-treated patients who attended a regional epilepsy clinic found that 43% of 98 tested had visual field abnormality with no alternative cause. In a follow-up study, 16 of 29 children treated with vigabatrin (mean 35.7 months) showed evidence of visual abnormality. With these risks in mind, except for the case of West's syndrome, it is likely vigabatrin would be used as a last-resort AED.

Hence the use of AEDs in paediatric epilepsy, like many realms of clinical practice in the management of the condition, is poorly supported by the literature. A consequence of this is that paediatricians often prescribe drugs in an 'off-licence' (drug or formulation not licensed) or 'off label' (drug not licensed for child's age range, indication, formulation or dose) manner. Without such prescribing, paediatricians' therapeutic options would be severely limited, but there may be no relevant RCT or pharmacokinetic evidence.

Several attempts have been made to rationalise drug treatment options by integrating data from clinical trials with those derived from other studies and some of these apply specifically to children. Such 'rational' strategies implicitly or explicitly score or categorise drugs across a matrix of characteristics which encompass such features as mechanism of action, pharmacokinetics, ease of use for children of different ages, drug interactions, efficacy (seizure reduction), neurotoxicity, psychiatric interactions, idiosyncratic reactions, chronic adverse effects, teratogenicity and comfort factor (a clinician's personal experience determining confidence in predicted effects).

Background
Valproate, carbamazepine and vigabatrin or steroids are the usual drugs of first choice in the UK for children with generalised and typical absence seizures, for partial seizures with or without secondary generalisation and for infantile spasms, respectively.

Should the first drug deliver intolerable side-effects and/or fail to achieve seizure control, an additional or substitute drug is considered. Substitute monotherapy is a possible choice on the grounds that unwanted side-effects are more likely with two than one drug. Careful withdrawal of the first drug and gradual introduction of the substitute is mandatory. Alternatively withdrawal of the first drug may be delayed so that combined treatment lasts for sufficient time to assess the second drug as a possible line of treatment.

The range of second-line drugs, used as add-on or substitute, is more varied than that of first-line drugs and includes consideration of additional standard and newer AEDs such as lamotrigine, ethosuximide, clonazepam, topiramate, levetiracetam, gabapentin, tiagabine and benzodiazepines, depending on diagnosis and clinical judgement. Some may reduce the frequency of one type of seizure but increase that of another type, hence close monitoring is desirable. Effects of AEDs can influence hormone metabolism and thereby endocrine profiles, menstrual cycles and other aspects of reproductive physiology. This and the potential interactions in drug metabolism during dual or polytherapy have to be taken into consideration when tailoring drug therapy for the individual patient.

Non-AED treatments

When pharmacotherapy has failed, then evaluation for other treatment options should be undertaken. Ideally a logical tailored treatment strategy should be developed in which potential benefits and risks are balanced. Non-drug options most likely to be considered are surgery, vagus nerve stimulation (VNS) and a ketogenic diet. Clinicians must make a decision about when AEDs have failed. This judgement may be influenced as much by the local availability of alternative treatments and lack of reliable information regarding their efficacy as by outcome measures of the current AED treatment that the child is receiving. Some might consider AEDs to have failed when two monotherapy options have been tried but without delivering acceptable outcome in terms of seizure relief and freedom from side-effects; however, with the availability of an increasingly wide choice of AEDs, others may judge it reasonable to attempt multiple changes in monotherapy and then, in the face of continued failure, combination (add-on) therapy. However, the prognosis for seizure control with add-on AED treatment after failure of monotherapy is not good.

Surgery is a radical intervention and a treatment option associated with high initial cost. Some children with refractory partial epilepsy might benefit from surgical treatment. Operative treatment includes hemispherectomy (where a child with very severe epilepsy has a pre-existing hemiplegia associated with a contralateral defect), corpus callosotomy, focal cortical resection of the temporal lobe, focal cortical resection of extratemporal regions of the brain and multiple subpial resections. The aim is to remove or disconnect tissue responsible for seizures while leaving functional parts (the ‘eloquent cortex’) as intact as possible. Hence suitability for surgery depends on the ability to identify the responsible tissue and also on the likely functional impact on the patient. In the past, a surgical option for epilepsy, especially for children, has been adopted with caution because of:

- hesitancy in adapting surgical procedures developed for adults
- uncertainty that the epilepsy might be self-limiting
- worries concerning postoperative neurological deficit
- inherent risk of surgery in small children
- risk associated with invasive work-up procedures (e.g. intracranial electrode recordings)
- lack of strong recommendation in practice guidelines because of an absence of RCT evidence on efficacy
- apparent lack of resources and perceived costs of preoperative procedures to determine whether the patient is a good candidate for surgery.

A systematic review published in 1999 estimated that ~8–25% of children newly diagnosed with epilepsy might go forward for assessment for surgery (modern MRI + EEG). Of those with normal MRI, ~1–5% may have further explorative imaging (SPECT or PET), which may identify a lesion. Functional MRI (monitoring functional areas by detecting changes in cerebral blood flow during performance of tasks) may be used to delineate functional regions. Approximately half of those assessed will be judged suitable for some form of surgery. The review concluded that there was observational evidence that surgery renders
A ketogenic diet is one in which a major proportion of metabolisable calories come from fatty acids derived from triglycerides. Maintenance on a ketogenic diet produces high plasma levels of ketone bodies (acetoacetate, \(\beta\)-hydroxybutyrate and acetone). The source of ketone bodies is hepatic acetate (acytetyl-CoA) derived from oxidation of fatty acids. The metabolic situation induced mimics starvation in which body fat stores are metabolised in order to spare structural protein and limited carbohydrate reserves. High levels of ketone bodies are achieved gradually as the diet is maintained and metabolic adaptation occurs in many tissues in which there is a shift from glucose to ketone bodies as an energy source of prime importance. Work on laboratory animals demonstrates a rise in seizure threshold with raised plasma ketone body levels, and prospective studies have indicated efficacy with some child and infant epilepsies.\(^97,98\) The mechanism(s) of action are uncertain. Potential benefits of the ketogenic diet include its lack of a sedative effect with greater alertness of patients (improvements in attention, comprehension, activity level and endurance). Potential side-effects include cardiac complications, acidosis leading to kidney stones and bone demineralisation. In addition, compliance with this difficult diet is not always good and can result in discontinuation. The profound metabolic changes imposed by the ketogenic diet mean that it should be introduced under close supervision, preferably in a hospital setting. A recent audit survey (51% response rate) in the UK reported that 17% of hospitals used ketogenic diet with one-third initiating the diet at home and two-thirds in hospital.\(^99\) No consistent policy on vitamin supplementation existed.

### Description of technologies

#### Description of new intervention

Since 1989, seven new antiepileptic drugs have been introduced in the UK: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin.

The licensed indications of these drugs vary, with oxcarbazepine, lamotrigine and vigabatrin licensed as mono- and add-on therapy (vigabatrin as monotherapy for West’s syndrome only) and gabapentin, levetiracetam, tiagabine and topiramate for add-on therapy only. The drugs also vary in the age groups for which they are indicated, with thresholds of 2, 6, 12 and 16 years. Levetiracetam is only licensed...
for age 16 years and over and its effectiveness therefore is not considered in this review.

Appendix 1 gives details of the licensed indications for each drug, along with information on dosage, adverse effects and cost. At least nine other new AEDs are in various stages of clinical and preclinical development.  

**Mechanism of action**

Under normal circumstances, neuronal activity depends on a controlled balance between excitatory and inhibitory influences on the electrical activity across the cell membrane. The pathophysiology of epilepsy probably involves a local imbalance among these factors, which leads to a focus of neuronal instability. Two main mechanisms appear to be important in the action of AEDs:

- inhibition of sodium channel function, to limit the spread of neuronal instability, e.g. lamotrigine, oxcarbazepine
- enhancement of the inhibitory actions of GABA, e.g. tiagabine, vigabatrin, topiramate.

Other mechanisms include inhibition of calcium channels and inhibition of glutamate activity, e.g. lamotrigine, topiramate.

The particular mechanisms of action of each of the newer drugs are summarised below.

**Gabapentin** (Neurontin® – Parke-Davis), available as 100-, 300- and 400-mg capsules and 600- and 800-mg tablets. Gabapentin is structurally related to the neurotransmitter GABA but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site have not been elucidated. In addition to being used for the treatment of epilepsy, gabapentin is indicated for the treatment of neuropathic pain.

**Lamotrigine** (Lamictal® – GlaxoSmithKline), available as 25-, 50-, 100- and 200-mg tablets and 2-, 5-, 25- and 100-mg dispersible/chewable tablets. Results from pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage-gated sodium channels. It produces a use- and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate, in addition to inhibiting glutamate-evoked bursts of action potentials.

**Levetiracetam** (Keppra® – UCB Pharma), available as 250-, 500- and 1000-mg tablets. Levetiracetam is a pyrrolidone derivative chemically unrelated to existing antiepileptic therapies. The mechanism of action of levetiracetam is unknown, but does not appear to involve inhibitory or excitatory neurotransmission.

**Oxcarbazepine** (Trileptal® – Novartis), available as 150-, 300- and 600-mg tablets. The pharmacological activity of oxcarbazepine is primarily manifested through its metabolite, the monohydroxy derivative (MHD). Oxcarbazepine is the 10-keto analogue of carbamazepine, which is an established AED. The mechanism of action of oxcarbazepine and the MHD is believed to be based on blockage of voltage-sensitive sodium channels, resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing and reduced propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects.

**Tiagabine** (Gabitril® – Sanofi-Synthelabo), available as 5-, 10- and 15-mg tablets. Tiagabine is a potent and selective inhibitor of both neuronal and glial GABA uptake, which results in an increase in GABA-mediated inhibition in the brain. Tiagabine lacks significant affinity for the neurotransmitter receptor binding sites and/or uptake sites.

**Topiramate** (Topamax® – Janssen-Cilag), available as 25-, 50-, 100- and 200-mg tablets and 15-, 25- and 50-mg sprinkle capsules. Topiramate is classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity: (1) it reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation, indicative of a state-dependent blockade of voltage-sensitive sodium channels; (2) it markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of NMDA at the NMDA receptor subtype; and (3) it weakly antagonises the excitatory activity of the kainate/α-amino-3-hydroxy-5-methyl-4-isoxasole propionic acid (AMPA) subtype of glutamate receptor. Topiramate also inhibits some isoenzymes of carbonic anhydrase, but this pharmacological effect is weaker than that of
acetazolamide (a known carbonic anhydrase inhibitor), and is not believed to be a major component of topiramate’s antiepileptic activity.

Vigabatrin (Sabril® – Aventis), available as 500-mg tablets and 500 mg powder sachets. Treatment with vigabatrin leads to an increase in the concentration of GABA, the major inhibitory neurotransmitter in the brain. Vigabatrin was designed as a selective irreversible inhibitor of GABA-transaminase, the enzyme responsible for the breakdown of GABA.
Chapter 3
Effectiveness

Methods for reviewing effectiveness

Search strategy
Studies employing the new AEDs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin were searched. A scoping search was undertaken to identify existing and ongoing reviews.

Primary studies were identified using the following sources:

1. Bibliographic databases. Since the NHS Centre for Reviews and Dissemination (CRD) was undertaking a technology assessment report of newer drugs for epilepsy in adults, there was collaboration between the two centres, with the work shared as indicated and references exchanged.
   (a) MEDLINE (Ovid), 1966–October 2001 (Birmingham)
   (b) MEDLINE and PreMEDLINE (Silverplatter), 1999–March 2002 (NHS CRD)
   (c) EMBASE (Ovid) 1980–February 2002 (Birmingham)
   (d) Cochrane Library Controlled Clinical Trials Register (CCTR), 2002 Issue 1 (Birmingham).
   (e) Science Citation Index (Web of Science), 1981–February 2002 (Birmingham).
   (f) National Research Register, 2002 Issue 1 (Birmingham).
2. Checking citations of relevant studies.
3. Contact with experts in the field.
4. Invited industry submissions.

No date or language restrictions were placed on the literature searches.

Data for the economic model were identified by further searches of the following sources to identify existing decision-analytic models, costs, cost-effectiveness and QoL:

1. Bibliographic databases:
   (a) MEDLINE (Ovid), 1966–March 2002
   (b) EMBASE (Ovid), 1980–March 2002
   (c) NHS Database of Reviews of Effectiveness (DARE)
   (d) NHS Database of Reviews of Effectiveness (DARE)
   (e) NHS CRD administration database (undertaken by NHS CRD)

2. Internet sites of national health economic units.

Details of search strategies are provided in Appendix 7.

Inclusion and exclusion criteria

Inclusion criteria
• Study design: RCTs of any of the newer AEDs as monotherapy or combined therapy for treatment of epilepsy.
• Study population: persons with epilepsy under 18 years old and mixed age groups with epilepsy if including persons less than 18 years old.

Exclusion criteria
• Trials recruiting only patients with single seizure, status epilepticus, seizures following surgery, febrile convulsions, trigeminal neuralgia or cortical myoclonus.

Data extraction strategy
Two reviewers independently abstracted the data. A third reviewer resolved discrepancies. One reviewer screened foreign language publications using English abstracts if available. Translations were obtained where necessary. Studies with mixed age groups were identified during the inclusion/exclusion process. The data reported in these studies were categorised according to (1) whether the study results report data for the different age groups separately and (2) the number of participants in different age-groups. Data for patients under 18 years old in these trials were extracted where possible.

Data were extracted on the following:
• Study design.
• Study population: seizure types and frequencies, and epileptic syndrome; baseline comparability of intervention and control groups.
• Intervention and comparator, including: drug; doses; mode of administration; and duration of treatment.
• Outcomes measured, including: identification of all outcomes which study protocols state would be measured; the specific measurement tool or data collection method; when, how and by whom the outcome data were collected; drop-outs; cross-overs and losses to follow-up for each outcome.
• Study results: as raw numbers where available, plus any summary measures with standard deviations, p-value and CIs where reported.

Quality assessment strategy
The quality of RCTs was assessed by examining methods of randomisation, concealment of allocation, blinding, losses to follow-up and methods of analysis [intention to treat (ITT)]. Two reviewers independently examined trial quality. Disagreements were resolved by consensus.

Results
Number and types of studies identified
The searches identified 4062 studies. Removal of duplicate references reduced this number to 3585. One reviewer scanned these to eliminate obviously irrelevant studies. Two reviewers scanned the remaining 1307 references; 396 studies were identified that were judged by at least one reviewer possibly to fulfil inclusion criteria. Hard copies of these 396 publications were sought from library and other sources. This yielded 360 hard copies. Seven of these were missed duplicate references, leaving 353. Thirty-six references were not obtainable in hard copy. They are tabulated in Appendix 11. All except six of these were cited as journal supplements or conference proceedings. Four of the 36101–104 were excluded on the basis of closer examination of titles and or abstracts or contact with authors.

Two reviewers examined the 353 unique retrieved hard copies according to inclusion criteria. Agreement between reviewers was moderate to good (kappa score 0.67). Disagreements were resolved by discussion. A total of 101 publications were identified, reporting on a total of 84 trials which met inclusion criteria. Only 20 studies were identified in which data specific to patients under 18 years old was reported. In all but one of these most of the trial participants were <18 years of age. Five of these 20 studies had been published in abstract form only; the other 15 were published as full papers. Trial details are tabulated in Appendix 13.

In the 64 other included studies, the majority of patients were >18 years of age and in 63/64 no outcome data were presented for those <18 years old. On the basis of information in the trial reports, they were judged definitely or likely to contain under 18-year-olds in both intervention and comparator arms of the trial. The reports are listed in Appendix 8 and details regarding study population, intervention and study design in each publication are provided in Appendix 9.

A list of the excluded publications with brief comments on the reasons for exclusion is given in Appendix 10.

Three systematic reviews of AED use in children were found; one105,106 considered drug treatment for infants and children with West’s syndrome, another treatments for acute tonic-clonic convulsions including status epilepticus107 and the third treatment for generalised convulsive status epilepticus.108 In addition, other systematic reviews were identified (listed in Table 3) that analysed the use of the newer AEDs that are the topic of the present review, or other new or standard AEDs, and were based on trials in adults or populations of mixed ages very predominantly adult or on a mixture of adult/mixed age and child trials with the great majority being adult/mixed age trials. The use of these reviews to draw conclusions with regard to children would require very cautious extrapolation in the absence of evidence directly comparing a drug across adult and child populations.

A number of protocols for ongoing systematic reviews were also identified and are listed Table 4.

Mixed age studies
The information reported on the age of trial participants varied in these publications. Age range data were reported in 59 of the 64 studies (Table 5). Some only reported an age range for eligible patients that would imply inclusion of <18-year-olds. Others reported the age range of all randomised patients or of the participants in each study arm. Five provided no information on the age range of eligible or randomised patients but did supply median or mean ages, or mean and standard deviation, sometimes for all randomised patients or sometimes by study arm. These were considered likely to have <18-year-olds on the basis that their mean/median ages were similar
TABLE 3 Systematic reviews

Newer AEDs

<table>
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<tr>
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<td>Add-on</td>
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<td>Jette, 2000</td>
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<td>Add-on</td>
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<tr>
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<tr>
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Other AEDs

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<td>Marson, 2001</td>
<td>Carbamazepine and valproate</td>
<td>Mono</td>
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<td>Carbamazepine and valproate</td>
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<td>Ramsay, 1997</td>
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<td>Tudur Smith, 2001</td>
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<td>25</td>
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<td>Carbamazepine and phenytoin</td>
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TABLE 4 Systematic reviews in preparation

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<td>Kalviainen, 2001</td>
</tr>
<tr>
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<td>Posner, 2001</td>
</tr>
<tr>
<td>5</td>
<td>Preston, 2002</td>
</tr>
<tr>
<td>6</td>
<td>Tudur Smith, 2001</td>
</tr>
</tbody>
</table>

with those quoted for studies that definitely included <18-year-olds.

A few (N = 4) small studies provided individual patient ages; two of these had no patients ≤16 years of age and the other two only one each. In 22 studies (3 reported in duplicate) the age range of the randomised patients in each study arm was provided. In only 18 of these trials were there patient(s) in both study arms of ≤16 years of age. A further 16 studies (one reported in duplicate) provided the age range of all randomised patients but not by study arm. In five of these there were no patients ≤16 years of age, and in three the low end of the age range was 16 years. Out of the 59 studies (in 68 reports) providing information on age range the low end of the age range was 17 years in nine, 16 years in 17, 15 years in eight, 14 years in three, 13 years in four, 12 years in 10, 11 years in one, 10 years in three and in three studies the lower end of the age range was <10 years. The mean, median and mode of the upper end of the age ranges were 64, 65 and 70 years, respectively. In one study the lower end of the range was specified as <16 years. It is clear that in the great majority of these 'mixed age' studies the proportion of patients who were children or adolescents was small, yielding little useful information about younger patients at the level of the clinical trial.

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**TABLE 5** Mixed age studies giving age range of patients

<table>
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<tr>
<th>No.</th>
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<th>N</th>
<th>Mean age*</th>
<th>Median age*</th>
<th>Age range*</th>
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<td>15–75</td>
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<td>13–68</td>
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<td>3</td>
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<td>Binnie, 1989b</td>
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<td>Cramer, 2000c</td>
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<td>–</td>
<td>16–70</td>
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<tr>
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<td>Brodie, 1997f</td>
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<td>–</td>
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<td>–</td>
<td>17–58</td>
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<td>Canger, 1997h</td>
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<tr>
<td>52</td>
<td>Vigabatrin</td>
<td>Tartara, 1986yy</td>
<td>23</td>
<td>30.5</td>
<td>30</td>
<td>17–50</td>
</tr>
<tr>
<td>53</td>
<td>Vigabatrin</td>
<td>Rimmer, 1987zz</td>
<td>6</td>
<td>18</td>
<td>–</td>
<td>10–25</td>
</tr>
<tr>
<td>54</td>
<td>Vigabatrin</td>
<td>Tassinari, 1987aa</td>
<td>31</td>
<td>28.9</td>
<td>–</td>
<td>10–58</td>
</tr>
<tr>
<td>55</td>
<td>Vigabatrin</td>
<td>Reynolds, 1999bb</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>16–65</td>
</tr>
<tr>
<td>56</td>
<td>Vigabatrin</td>
<td>Gillham, 1993cc</td>
<td>48</td>
<td>32.5</td>
<td>–</td>
<td>17–53</td>
</tr>
<tr>
<td>57</td>
<td>Lamotrigine</td>
<td>Carment, 1999dd</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>2–7</td>
</tr>
<tr>
<td>58</td>
<td>Lamotrigine</td>
<td>Montours, 1999ee</td>
<td>29</td>
<td>–</td>
<td>25, 26</td>
<td>12–7</td>
</tr>
</tbody>
</table>

*a If necessary the mean age has been averaged for all arms of trial. When reported, the median age is given for each arm of the trial.

b 13 patients <16 years old.

c Data presented for 13 placebo and eight topiramate patients >16 years old.

d 119 patients >16 years old.
Partial seizures (with or without secondary generalisation)

Eight randomised controlled trials were identified; two of these were conducted in a newly diagnosed population and six in populations which were refractory or inadequately controlled on existing AED treatment.

Newly diagnosed partial seizures

Two trials were identified conducted in a newly diagnosed population (Tables 6–9). Nieto-Barrera, 2001 compared lamotrigine and carbamazepine in a mixed age population. Zamponi, 1999 compared vigabatrin and carbamazepine in children. Both trials were ‘open label’, that is, treatment was not blinded. Blinding may be difficult or impossible when active controls have characteristic and easily identifiable side-effects; also, choice of formulation and differences in dose and titration periods may make blinding more difficult, but not necessarily impossible.

Quality assessment

Neither trial gives an adequate description of the method of randomisation or concealment of allocation.

There are particular concerns about the randomisation in Zamponi, 1999. This trial report states only that patients were ‘treated in a random fashion’, but it is not clear that an appropriate method of randomisation was used. This concern is based on two points. First, there is a large difference in the numbers randomised to each arm for a single centre study (32 versus 38), although this imbalance could arise from the use of simple randomisation. Second, there is a very large difference in the ages of the patients on the two arms, with a mean age of 9 years 5 months on carbamazepine versus 7 years 4 months on vigabatrin. The impression of two separate cohorts rather than a randomised comparison is strengthened by the reporting of this trial, which
TABLE 7 Quality assessment (newly diagnosed partial seizures)

<table>
<thead>
<tr>
<th></th>
<th>Nieto-Barrera, 2001</th>
<th>Zamponi, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>No (except stratified by age and country)</td>
<td>No</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Open label study</td>
<td>Open study</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>Yes (data not reported for children separately)</td>
<td>Can’t tell; large imbalance in numbers randomised for a small single centre study, large age difference, patient characteristics poorly reported</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>No</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes (but see comment)</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Information incomplete</td>
<td>Yes (but see comment)</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>NA</td>
<td>NA (open study)</td>
</tr>
<tr>
<td>Comments</td>
<td>Mixed age trial, ages 2–83 years. Patients aged 13–64 years regarded as a single group but results for age group 2–12 years are reported separately; these results will be used for this review. Numbers withdrawing stated for some but not all reasons; Kaplan–Meier curve for all-cause withdrawal provides estimate of percentage withdrawing</td>
<td>Very poor quality of reporting; Reasons for withdrawal were stated but cannot be certain that these were complete data</td>
</tr>
</tbody>
</table>

The standard of reporting was better for Nieto-Barrera, 2001 but details of randomisation and allocation concealment are not given in the trial report. Most baseline characteristics are only reported for the whole (mixed age) group with some, including baseline seizure frequency, reported separately for age groups <2 years, 2–12 years, 13–64 years and >64 years. Baseline seizure frequency does appear to be somewhat higher in the carbamazepine-treated group aged 2–12 years; mean 10 per month versus 6.8 per month; this difference could arise by chance with appropriate randomisation but does nothing to ease concerns about the integrity of randomisation where this is in doubt. A major weakness of this trial is that ITT analysis was not used, with the primary effectiveness measures excluding patients who did not have follow-up to 22 and 18 weeks, respectively.

**Results**

Both trials suggest that carbamazepine may be slightly more effective but with more side-effects. Nieto-Barrera, 2001 reports better treatment retention during the 6-month follow-up period of the trial, with more patients withdrawing early owing to adverse effects on carbamazepine, but this effect appears to be due in large part to much worse treatment retention for carbamazepine in the elderly population (>64 years old).
### TABLE 8 Results (newly diagnosed partial seizures)

<table>
<thead>
<tr>
<th></th>
<th>Nieto-Barrera, 2001</th>
<th>Zamponi, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Number randomised</td>
<td>75</td>
<td>153</td>
</tr>
<tr>
<td>Number analysed</td>
<td>64</td>
<td>134</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Mean 16.9 mg/day, Median 16.0, 5.2–36.5 mg/day</td>
<td>Mean 3.4 mg/day, Median 2.7, 0.05–10.5 mg/day</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
<td>Total withdrawals: 11 (15), Adverse events: 5 (7)</td>
<td>Total withdrawals: 21 (13), Adverse events: 8 (5)</td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>1. Seizure free in last 16 weeks and follow-up to week 22: CBZ: 48/64 (75%), LTG: 89/134 (66%)</td>
<td>p = 0.205</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Global effectiveness (time to withdrawal from study): Survival analysis not reported [proportions CBZ: 11 (15%), LTG: 21 (13%)]</td>
<td>Not reported</td>
</tr>
<tr>
<td>'Ad hoc' outcomes</td>
<td>Proportion withdrawn for adverse events: CBZ: 5/75 (7%), LTG: 8/158&lt;sup&gt;a&lt;/sup&gt; (5%)</td>
<td>p = 0.761</td>
</tr>
</tbody>
</table>

CBZ, carbamazepine; LTG, lamotrigine; ns, not significant.

<sup>a</sup> Not clear if this is a typographical error.
### TABLE 9 Adverse events (newly diagnosed partial seizures)

<table>
<thead>
<tr>
<th>Criteria for reporting</th>
<th>Nieto-Barrera, 2001</th>
<th>Zamponi, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>47 (63)</td>
<td>80 (51)</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (–)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (16)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7 (9)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>8 (11)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (8)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>30 (40%)</td>
<td>35 (22%)</td>
</tr>
</tbody>
</table>

112 events in 47/75 patients

|                        |                     | Carbamazepine | Vigabatrin |
|------------------------|---------------------|---------------|
|                        |                     |               |
| Any AE                 |                     |               |
| Infection              |                     |               |
| Headache               |                     |               |
| Asthenia               |                     |               |
| Somnolence             |                     |               |
| Pharyngitis            |                     |               |
| Rash                   |                     |               |
| Dizziness              |                     |               |
| Serious AE             |                     |               |
| Drug-related           |                     |               |

106 events in 80/158 patients

AE, adverse event.
There are no significant differences reported for any outcome (for children) in either trial. Interpretation of these results for either trial is difficult given the methodological shortcomings outlined.

Preferably diagnosed partial seizures

Eight RCTs were identified (Tables 10–13). All were placebo-controlled trials investigating the addition of a new drug to existing therapy. Two trials used gabapentin, two used vigabatrin, with one trial for each of lamotrigine, oxcarbazepine, tiagabine and topiramate.

Quality assessment

Four of the trials, by Shapiro, 2000199 Litzinger, 1998200 Valentine, 1998201 and Van Orman, 1998,202 were reported in abstract form only, hence there is very limited information available.

Duchowny, 1998203 Glauser, 2000204 and Elterman, 1999205 all gave adequate descriptions of the method of randomisation and allocation concealment; Appleton, 1999206 did not give details beyond describing the trial as randomised. Patient characteristics in the four trials were balanced, although there was some difference in baseline seizure rates in Duchowny, 1999:203 this imbalance could have arisen by chance and does not in itself cast doubt on the randomisation.

These four trials were described as double-blind, although Duchowny, 1999203 is the only one to give any indication of how blinding was achieved (matching tablets). Of some concern is that all four of these trials described dose titration schedules for the active treatment group only; clearly with appropriate blinding a similar titration schedule would be followed for the placebo group also. Although this may seem a trivial omission, reporting of dose titration for the placebo group and reporting of the maintenance placebo doses achieved are important if only to indicate that adequate blinding was maintained throughout the trial.

Duchowny, 1999203 is the only one of these three trials where AED plasma levels were explicitly not monitored; it reports that one investigator did measure plasma levels and entered these on patient notes, thus breaking the blinding. None of the other three trials, where plasma levels were monitored as part of the trial requirements, mention any attempts to keep the results blinded from the investigators, raising some concern about adequate blinding in these trials.

Appleton, 1999206 claims that ITT analysis was used but then define ITT as ‘all patients who received study medication’, which is not the ITT population; it is not clear from the paper how many patients were randomised (as opposed to how many were included in the ITT population). Duchowny, 1999203 and Elterman, 1999205 both report ITT analysis; Glauser, 2000204 may have used ITT but it is not clear whether three patients excluded from the analysis were excluded because their data were missing or were deliberately excluded because they withdrew from treatment.

Results

Duchowny, 1999203 Glauser, 2000204 Elterman, 1999205 Valentine, 1998201 and Van Orman, 1998202 all report some differences in reduction of seizure rate compared with placebo. The first three of these report median percentage reduction in seizure rate and all report similar results, with around 10% reduction with placebo and around 35% reduction on active treatment. Shapiro, 2000199 found a small trend in favour of gabapentin (using the unusual end-point of response ratio), but this trial was too small to demonstrate any benefit, or indeed to rule out a benefit. Appleton, 1999206 used an inappropriate definition of the ITT population and furthermore the report was dominated by results from a ‘modified ITT’ population; the results reported for the (inappropriately defined) ‘ITT’ population in this trial did not reveal any significant differences between gabapentin and placebo.

As would be expected, more patients withdrew owing to adverse events on active treatment compared with placebo, with the exception of Elterman, 1999205 who reported no withdrawals due to adverse events on topiramate in this small trial.

Partial and generalised seizures

(mixed population)

One RCT, by Guerreiro, 1997207 was identified which included a mixed population of newly diagnosed patients with partial seizures (with or without secondary generalisation) or with generalised tonic–clonic seizures. The trial compared oxcarbazepine with phenytoin as first-line treatment (Tables 14–16).

Quality assessment

The trial was of fairly high quality. It is one of the few trials of those identified which described measures taken to conceal the results of drug plasma level monitoring from investigators; results were provided to investigators labelled only as zero, low, within range or high.
TABLE 10 Summary of trials and trial design (previously diagnosed partial seizures)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (1)</th>
<th>Shapiro, 2000</th>
<th>Duchowny, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Gabapentin</td>
<td>Gabapentin</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>600–1800 mg/day depending on weight (?mode)</td>
<td>40 mg/kg/day (oral syrup)</td>
<td>1–15 mg/kg/day, maximum 750 mg/day (oral; chewable/dispersible caplets or tablets)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Partial seizures</td>
<td>Partial seizures</td>
<td>Partial seizures</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Parallel</td>
<td>Parallel</td>
<td>Parallel</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Add-on</td>
<td>Add-on</td>
<td>Add-on</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>1993–1996</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centres and location</td>
<td>54 centres in Europe, South Africa, USA</td>
<td>Not reported</td>
<td>40 centres in USA, France</td>
</tr>
<tr>
<td>Baseline</td>
<td>6 weeks</td>
<td>2 days</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Titration period</td>
<td>3 days</td>
<td>No titration</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>81 days</td>
<td>3 days</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>None</td>
<td>None</td>
<td>None (tapering phase not part of RCT results)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Medically uncontrolled partial seizures; age 12 years or younger</td>
<td>Partial seizures not controlled by at least 1 AED; age 1–36 months</td>
<td>Partial seizures incompletely controlled by existing therapy; age 2–16 years (USA) or 2–12 years (France)</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/ continuation on study</td>
<td>Postbaseline; patients experiencing at least 1 seizure every 2 weeks and 4 seizures in total during baseline</td>
<td>–</td>
<td>Postbaseline; actual criteria for randomisation not stated but at screening patients were expected to have at least 4 seizures during each consecutive 4-week period of the baseline phase</td>
</tr>
<tr>
<td>Comments on design</td>
<td>Dose titration refers explicitly to gabapentin only; unclear how/if placebo was titrated in same way</td>
<td>Monitoring of seizure rate by continuous video-EEG recording over 72 h</td>
<td>continued</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Oxcarbazepine</td>
<td>Tiagabine</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>30–46 mg/kg/day (oral, tablets) (assumed /day)</td>
<td>0.7 mg/kg/day</td>
<td>125–400 mg/day (oral)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Partial seizures</td>
<td>Refractory partial seizures</td>
<td>Partial seizures</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Parallel</td>
<td>Parallel</td>
<td>Parallel</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Add-on</td>
<td>Add-on</td>
<td>Add-on</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>Not reported [May 1995 to September 1997 (independent submission)]</td>
<td>Not reported [abstract only]</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centres and location</td>
<td>47 centres in Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, USA</td>
<td>Not reported [abstract only]</td>
<td>17 centres in USA, Costa Rica</td>
</tr>
<tr>
<td>Baseline</td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Titration period</td>
<td>2 weeks</td>
<td>Not reported [abstract only]</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>14 weeks</td>
<td>12 weeks</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

continued
Most end-points were assessed only on those patients who did not withdraw during the titration period and so, with the exception of the time to treatment withdrawal outcome the results are not based on the principle of ITT. Another concern is the choice of phenytoin as the comparator for this trial when (as the authors acknowledge) it would not normally be considered as a first-choice treatment for these patients. Ideally, a trial with an active control would use the most effective comparator treatment available.

Results
No differences were found between the two treatments in terms of proportion achieving seizure freedom, or in seizure frequency during the maintenance period. Similar numbers of patients discontinued treatment due to poor therapeutic effect in the two arms but substantially more patients discontinued phenytoin owing to adverse events. The proportion discontinuing oxcarbazepine in this trial is substantially lower than reported by Glauser, 2000.204 (in previously diagnosed partial epilepsy); the

---

**TABLE 10** Summary of trials and trial design (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically uncontrolled partial seizures; age 3–17 years</td>
<td>Not reported [abstract only]</td>
<td>Not reported [abstract only]</td>
<td>None</td>
</tr>
<tr>
<td>Postbaseline; patients experiencing at least 1 seizure every 4 weeks and at least 8 seizures in total during 8-week baseline period</td>
<td>Not reported [abstract only]</td>
<td>Postbaseline; patients experiencing at least 6 partial seizures (at least 1 every 4-week interval) during baseline</td>
<td></td>
</tr>
<tr>
<td>Dose titration refers explicitly to oxcarbazepine only; unclear how/if placebo was titrated in same way</td>
<td>Abstract with few details of design</td>
<td>Dose titration refers explicitly to topiramate only; not clear how/if placebo was titrated in same way</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported [abstract only]</td>
<td>Not reported [abstract only]</td>
<td>None</td>
</tr>
<tr>
<td>Not reported [abstract only]</td>
<td>Medically uncontrolled partial seizures, with or without secondarily generalised seizures; age between 1 and 16 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing and additional eligibility for randomisation/ continuation on study</th>
<th>Newer drug(s) investigated</th>
<th>Target maintenance dose (mode)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled complex partial seizures with or without secondary generalisation</td>
<td>Vigabatrin</td>
<td>1.5–4 g/day (oral)</td>
</tr>
<tr>
<td>Parallel</td>
<td>Parallel</td>
<td>20, 60, 100 mg/kg/day (mod)</td>
</tr>
<tr>
<td>Add-on</td>
<td>Add-on</td>
<td>Placebo</td>
</tr>
<tr>
<td>Multicentre (n = ?)</td>
<td>Multicentre (n = ?)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Titration period</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Not stated</td>
<td>6 weeks</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Not stated</td>
<td>10 weeks</td>
<td>Not stated</td>
</tr>
<tr>
<td>Not stated</td>
<td>8 weeks</td>
<td>Not stated</td>
</tr>
<tr>
<td>Not stated</td>
<td></td>
<td>Not stated</td>
</tr>
<tr>
<td>Randomised only 75% of target of 120 patients</td>
<td>Dose–response study</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE II Quality assessment (previously diagnosed partial seizures)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (1)</th>
<th>Shapiro, 2000</th>
<th>Duchowny, 1999</th>
<th>Glauser, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>No</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Can't tell</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Can't tell</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Described as ‘double-blind’</td>
<td>Described as ‘double blind’; EEG assessor blinded.</td>
<td>Described as ‘double-blind’</td>
<td>Described as ‘double-blind’</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>No description</td>
<td>– described?</td>
<td>‘lamotrigine and matching placebo’</td>
<td>Yes</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>Yes</td>
<td>Yes</td>
<td>Baseline seizure rates for simple and complex partial seizures appear substantially higher in placebo group</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Can't tell (no description of blinding, and dose titration refers to gabapentin group only)</td>
<td>– [abstract only]</td>
<td>Can't tell; dose titration refers explicitly to lamotrigine only, not clear how/if placebo doses titrated in same way</td>
<td>Can’t tell; dose titration refers to oxcarbazepine group only</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>Claimed, but not used. ‘ITT population defined as all randomised patients who received study medication’</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Not clear (see comment)</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Yes</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>No</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>Yes; including study drug</td>
<td>– [abstract only]</td>
<td>No (but see comments)</td>
<td>Yes; including study drug</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>No</td>
<td>– [abstract only]</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

continued
TABLE 11 Quality assessment (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (1)</th>
<th>Shapiro, 2000</th>
<th>Duchowny, 1999</th>
<th>Glauser, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>–</td>
<td>Abstract with few details</td>
<td>One investigator measured plasma lamotrigine levels in 3 patients and entered concentrations in charts, violating the blinding; these patients were allowed to complete the study. The study site was closed after all study medication properly discontinued</td>
<td>No follow-up available on 3 patients who discontinued treatment prematurely, but not clear if these data were ‘missing’, excluded or never sought (31 patients discontinued in total)</td>
</tr>
<tr>
<td>Appletor, 1999 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Litzinger, 1998</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>No description</td>
<td>No description</td>
</tr>
<tr>
<td>Elterman, 1999</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Valentine, 1998</td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Van Orman, 1998</td>
<td>– [abstract only]</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>No description</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Can’t tell; no description of blinding and dose titration refers to topiramate group only</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Claimed</td>
<td>Claimed</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Yes; including study drug</td>
<td>No</td>
<td>No</td>
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<tr>
<td></td>
<td>– [abstract only]</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>Abstract with few details</td>
<td>127 patients entered baseline; 88 were randomised</td>
<td>Abstract with few details</td>
</tr>
<tr>
<td></td>
<td>– [abstract only]</td>
<td>–</td>
<td>Abstract with few details</td>
<td>Abstract with few details</td>
</tr>
<tr>
<td></td>
<td>Appleton, 1999 (1)</td>
<td>Shapiro, 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Gabapentin</td>
<td>Placebo</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Number randomised</td>
<td>Not stated</td>
<td>Not stated</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Number analysed</td>
<td>128</td>
<td>119</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Withdrawals including</td>
<td>Total withdrawals</td>
<td>21 (17.6)</td>
<td>–</td>
<td>Not reported</td>
</tr>
<tr>
<td>reasons where specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of efficacy</td>
<td>11 (9.2)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
<td>6 (5.0)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Change in AED</td>
<td>0 (–)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4 (3.1)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Results</td>
<td>Response ratio</td>
<td>Placebo –0.079</td>
<td>Placebo –0.048</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.1246</td>
<td>Gabapentin –0.146</td>
<td>Gabapentin +0.018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(see comment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>&gt;50% reduction</td>
<td>Placebo 18%,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = ns</td>
<td>Gabapentin 21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Ad hoc' outcomes</td>
<td>No data reported</td>
<td></td>
<td>No data reported</td>
<td></td>
</tr>
<tr>
<td>Comments (including</td>
<td>All results adjusted whether unadjusted for centre</td>
<td>Abstract only; very limited information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>results reported)</td>
<td>No ITT results available. Report defined ITT as 'all patients treated' and even then, only reported most outcomes for 'modified ITT' population.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Response ratio also reported for 'ITT' population using rank-transformed data due to 'evidence of non-normality'; non-normality would be expected with this statistic and ANOVA is not an ideal means of analysis. Result for 'modified ITT' population reported without transformation and with no comment on normality</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; ITT, intention to treat.
TABLE 12 Results (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Duchowny, 1999</th>
<th>Glauser, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Number randomised</td>
<td>101</td>
<td>98</td>
</tr>
<tr>
<td>Number analysed</td>
<td>101</td>
<td>98</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Not reported</td>
<td>EIAEDs + no VPA (n = 53), mean 11.6, SD 3.6, median 12.9 mg/kg/day; no EIAEDs + VPA (n = 22), mean 2.7, SD 0.4, median 2.7 mg/kg/day; EIAEDs + VPA (n = 18), mean 3.9, SD 0.9, median 4.2 mg/kg/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Withdrawals including reasons where specified</th>
<th></th>
<th>Total withdrawals</th>
<th>18 (17.8)</th>
<th>14 (14.2)</th>
<th>Total withdrawals</th>
<th>10 (7.8)</th>
<th>21 (15.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor response</td>
<td>8 (7.9)</td>
<td>6 (6.1)</td>
<td></td>
<td></td>
<td>Lack of efficacy</td>
<td>4 (3.1)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>6 (5.9)</td>
<td>5 (5.1)</td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>4 (3.1)</td>
<td>14 (10.1)</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>2 (1.9)</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
<td>Non-compliance</td>
<td>0 (–)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (1.9)</td>
<td>2 (2.0)</td>
<td></td>
<td></td>
<td>Withdraw consent</td>
<td>1 (0.8)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (1.9)</td>
<td>2 (2.0)</td>
<td></td>
<td></td>
<td>Lost to follow-up</td>
<td>1 (0.8)</td>
<td>0 (–)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>CI; p-value</th>
<th>Results</th>
<th>CI; p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome(s)</td>
<td>Median % change in frequency of all partial seizures during:</td>
<td>% change in frequency of all partial seizures per 28 days during DB double-blind treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. entire 18-week follow-up</td>
<td>Placebo –6.7%</td>
<td>p = 0.008</td>
<td>Placebo –9%</td>
</tr>
<tr>
<td>2. 12 week maintenance period</td>
<td>Lamotrigine –36.1%</td>
<td>p = 0.008</td>
<td>Oxcarbazepine –35% (median % change)</td>
</tr>
</tbody>
</table>

EIAED, enzyme-inducing AED; VPA, valproate.

continued
**TABLE 12**  Results (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th>Duchowny, 1999</th>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Glauser, 2000</th>
<th>Placebo</th>
<th>Oxcarbazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. % change in frequency of secondarily generalised seizures</td>
<td>Not based on whole population</td>
<td></td>
<td>1. ≥ 50% reduction in all partial seizure frequency</td>
<td>Placebo 22%</td>
<td>Oxcarbazepine 41%</td>
</tr>
<tr>
<td>2. Proportion of patients with ≤ 25%, 26–49% and ≥ 50% reduction in all partial seizures</td>
<td>Results available graphically only</td>
<td></td>
<td>2. % change in frequency of:</td>
<td>45% oxcarbazepine 16%</td>
<td>Not reported</td>
</tr>
<tr>
<td>3. Number of days when each patients was seizure free (all partial seizures)</td>
<td>Placebo +3.2%</td>
<td>Lamotrigine +28.0% (median change)</td>
<td>42% vs 10%</td>
<td>78% vs 33%</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>‘Ad hoc’ outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizure-free patients</td>
<td>Placebo 1/128 vs oxcarbazepine 5/136</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Comments (including % change in seizure frequency adjusted for centre effects)</strong></td>
<td>% change in seizure frequency adjusted for centre effects</td>
<td>Percentage changes reported are median (weekly) % changes</td>
<td>50% responder rates reported for 135 (not ITT population of 136) oxcarbazepine patients (no explanation for missing patient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analysis of responder rate adjusted for centre, sex, age and weight</strong></td>
<td></td>
<td></td>
<td>Changes reported for each seizure type apply only to patients with that type of seizure at baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sample size slightly less than target given in power calculation (267 vs 274)
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tiagabine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number randomised</strong></td>
<td>45</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td><strong>Number analysed</strong></td>
<td>45</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td><strong>Maintenance dose achieved</strong></td>
<td></td>
<td>5.9 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawals including reasons where specified</strong></td>
<td>2 (4.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>1 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Patient choice</strong></td>
<td>1 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### Primary outcomes

<table>
<thead>
<tr>
<th>Results</th>
<th>CI;</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change in frequency of all partial seizures (average monthly rate)</td>
<td>-10.5%</td>
<td>0.034</td>
</tr>
<tr>
<td>% change in secondarily generalised seizures in all partial seizures</td>
<td>-33.1%</td>
<td>Median % reduction</td>
</tr>
<tr>
<td>% with ≥50% reduction in all partial seizures</td>
<td>-31.6%</td>
<td>Not reported</td>
</tr>
<tr>
<td>% with ≥75% reduction in all partial seizures</td>
<td>-16.0%</td>
<td>Not reported</td>
</tr>
<tr>
<td>% with 100% reduction in all partial seizures</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

### Secondary outcomes

<table>
<thead>
<tr>
<th>Results</th>
<th>CI;</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change in secondarily generalised seizures</td>
<td>+10.6%</td>
<td>ns</td>
</tr>
<tr>
<td>% with ≥50% reduction in all partial seizures</td>
<td>-31.6%</td>
<td>Not reported</td>
</tr>
<tr>
<td>% with ≥75% reduction in all partial seizures</td>
<td>9 (20.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>% with 100% reduction in all partial seizures</td>
<td>7 (17.0)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

### 'Ad hoc' outcomes

<table>
<thead>
<tr>
<th>Results</th>
<th>CI;</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental global evaluation (Results not reproduced here)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Comments

Data reported on a subset of patients from a larger randomised trial: results adjusted for centre only.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Vigabatrin</td>
<td>Placebo</td>
<td>Vigabatrin: 20, 60, 100 mg</td>
</tr>
<tr>
<td>Number randomised</td>
<td>Total 88, not stated by arm</td>
<td>Not stated</td>
<td>Total 126, not stated by arm</td>
<td></td>
</tr>
<tr>
<td>Number analysed</td>
<td>88, not stated by arm</td>
<td>Not stated</td>
<td>126 not stated by arm</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Not stated</td>
<td>1.5–4 g/day</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>achieved</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Withdrawals</td>
<td>Not reported</td>
<td>–</td>
<td>Not stated</td>
<td>–</td>
</tr>
<tr>
<td>including reasons</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>where specified</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>≥50% reduction in seizure frequency</td>
<td>Placebo 26.7%</td>
<td>Not stated</td>
<td>Reduction in patient mean monthly seizure frequency</td>
</tr>
<tr>
<td></td>
<td>Vigabatrin 55.8%</td>
<td></td>
<td></td>
<td>p = 0.0142 (100-mg group vs placebo) greater reduction for active arm</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Ad hoc’ outcomes</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments (including</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>whether unadjusted</td>
<td></td>
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<tr>
<td>results reported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td>Placebo</td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td>4 (3.1)</td>
<td>13 (10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (7.0)</td>
<td>10 (8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6 (4.7)</td>
<td>8 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>3 (2.3)</td>
<td>8 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (6.3)</td>
<td>6 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (1.6)</td>
<td>4 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td>Placebo</td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td>4 (3.1)</td>
<td>13 (10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (7.0)</td>
<td>10 (8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6 (4.7)</td>
<td>8 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>3 (2.3)</td>
<td>8 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (6.3)</td>
<td>6 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (1.6)</td>
<td>4 (3.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Criteria for Events in ≥ 2% of patients**
- Events: Viral infection, Nausea/vomiting, Pharyngitis, Hostility, Headache, Fatigue.
- Severe AEs: 3 patients (3 events).

**Considered related to study drug (% events or patients):**
- 34%

**Severe AEs (% of patients):**
- 14 patients (23 events)

**Number of patients (events):**
- 3 patients (3 events)
### TABLE 13  Adverse events (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th>Criteria for reporting</th>
<th>Events in &gt;10% of patients in either group</th>
<th>Duchowny, 1999</th>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Glauser, 2000</th>
<th>Placebo</th>
<th>Oxcarbazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Events Vomiting</td>
<td>19 (18.8)</td>
<td>22 (22.4)</td>
<td></td>
<td>Viral infection</td>
<td>21 (16.2)</td>
<td>19 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>18 (17.8)</td>
<td>24 (24.4)</td>
<td></td>
<td>Fever</td>
<td>20 (15.5)</td>
<td>21 (15.2)</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>22 (21.7)</td>
<td>21 (21.4)</td>
<td></td>
<td>Nausea/vomiting</td>
<td>26 (20.1)</td>
<td>80 (57.9)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>5 (4.9)</td>
<td>21 (21.4)</td>
<td></td>
<td>Somnolence</td>
<td>18 (13.9)</td>
<td>48 (34.7)</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>18 (17.8)</td>
<td>16 (16.3)</td>
<td></td>
<td>Pharyngitis</td>
<td>15 (11.6)</td>
<td>12 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>15 (14.8)</td>
<td>18 (18.3)</td>
<td></td>
<td>Upper RTI</td>
<td>15 (11.6)</td>
<td>10 (7.2)</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>17 (16.8)</td>
<td>14 (14.2)</td>
<td></td>
<td>Headache</td>
<td>23 (17.8)</td>
<td>44 (31.8)</td>
</tr>
<tr>
<td></td>
<td>Accidental injury</td>
<td>15 (14.8)</td>
<td>14 (14.2)</td>
<td></td>
<td>Rhinitis</td>
<td>11 (8.5)</td>
<td>16 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>13 (12.8)</td>
<td>13 (13.2)</td>
<td></td>
<td>Fatigue</td>
<td>11 (8.5)</td>
<td>18 (13.0)</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>12 (11.8)</td>
<td>14 (14.2)</td>
<td></td>
<td>Dizziness</td>
<td>10 (7.7)</td>
<td>40 (28.9)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>7 (6.9)</td>
<td>13 (13.2)</td>
<td></td>
<td>Anorexia</td>
<td>13 (10.0)</td>
<td>9 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>2 (1.9)</td>
<td>12 (12.2)</td>
<td></td>
<td>Ataxia</td>
<td>6 (4.6)</td>
<td>19 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>2 (1.9)</td>
<td>11 (11.2)</td>
<td></td>
<td>Abnormal gait</td>
<td>4 (3.1)</td>
<td>14 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
<td>11 (10.8)</td>
<td>9 (9.1)</td>
<td></td>
<td>Nystagmus</td>
<td>2 (1.5)</td>
<td>14 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>10 (9.9)</td>
<td>11 (11.2)</td>
<td></td>
<td>Diplopia</td>
<td>1 (0.7)</td>
<td>23 (16.6)</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>2 (1.9)</td>
<td>10 (10.2)</td>
<td></td>
<td>Abnormal vision</td>
<td>2 (1.5)</td>
<td>19 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>6 (5.9)</td>
<td>11 (11.2)</td>
<td></td>
<td>Abdominal pain</td>
<td>13 (10.0)</td>
<td>12 (8.6)</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>reporting at least one AE</td>
<td>96 (95.0)</td>
<td>92 (93.8)</td>
<td></td>
<td>Proportion of patients reporting ≥ 1 adverse event</td>
<td>106 (82)</td>
<td>126 (91)</td>
</tr>
</tbody>
</table>

continued
TABLE 13  Adverse events (previously diagnosed partial seizures) (cont’d)

<table>
<thead>
<tr>
<th>Criteria for Events in ≥ 10% of patients reporting in topiramate group</th>
<th>Litzinger, 1998</th>
<th>Elterman, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Placebo</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Coughing</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Somnolence</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mood problems</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nervousness</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Viral infection</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Otitis media</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Purpura</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fever</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Injury</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria for Treatment-related adverse events reporting</th>
<th>Valentine, 1998</th>
<th>Van Orman, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Placebo</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>All events</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Somnolence</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Increased seizure frequency</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

RIT, respiratory tract infection.
### TABLE 14  Summary of trial and trial design (population with partial and generalised seizure types)

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Guerreiro, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>450–2400 mg/day (oral)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Newly diagnosed partial seizures with or without secondary generalisation, and generalised tonic-clonic seizures</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Parallel</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>1991 to 1995</td>
</tr>
<tr>
<td>Centres and location</td>
<td>Multicentre; Brazil and Argentina.</td>
</tr>
<tr>
<td>Baseline</td>
<td>Retrospective baseline</td>
</tr>
<tr>
<td>Titration period</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>No withdrawal phase (optional non-RCT continuation to open study)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Newly diagnosed epilepsy with partial seizures, with or without secondary generalisation; age 5–18 years.</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/continuation on study</td>
<td>NA (retrospective baseline)</td>
</tr>
<tr>
<td>Comments on design</td>
<td>No clear justification given for the use of phenytoin as comparator when it is not generally a first choice treatment.</td>
</tr>
</tbody>
</table>

### TABLE 15  Quality assessment (population with partial and generalised seizure types)

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Guerreiro, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Described as ‘double-blind’</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>‘Tablets with identical appearance’</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>No (except for time to withdrawal outcome)</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>Yes (results reported only as zero, low, within range or high)</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
</tr>
</tbody>
</table>
long (8-week) titration period used in Guerreiro, 1997 may have contributed to the low rate of discontinuation. Overall, time to treatment withdrawal was longer in the oxcarbazepine arm; it is not clear why this difference is reported statistically by means of the odds ratio when the hazard ratio and log-rank statistic are the appropriate form of analysis for this kind of data (the log-rank $p$-value is reported for time to discontinuation due to adverse events).

Subjective overall evaluations from clinicians and patients were also reported. No differences were reported in the overall evaluations, but both clinicians and patients reported better tolerability of oxcarbazepine. The difference in tolerability is clear in the results of this trial despite the use of a relatively low dose of phenytoin; it is not clear what effect the use of a higher dose of phenytoin might have had on the results for effectiveness and tolerability.

**TABLE 16 Results (population with partial and generalised seizure types)**

<table>
<thead>
<tr>
<th>Guerreiro, 1997</th>
<th>Phenytoin</th>
<th>Oxcarbazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomised</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>Number analysed</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Mean 5.8 mg/kg/day (at start of maintenance period)</td>
<td>Mean 18.8 mg/kg/day (at start of maintenance period)</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Adverse events</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Poor efficacy</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Concomitant illness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Discontinued at baseline</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Results</td>
<td>CI; $p$-value</td>
<td></td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>Proportion of seizure-free patients (of those who reached maintenance period and had at least one seizure assessment during the maintenance period)</td>
<td>46/77 phenytoin 49/81 oxcarbazepine</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>1. Seizure frequency during maintenance</td>
<td>PHT: mean 0.04 OXC: mean 0.07</td>
</tr>
<tr>
<td></td>
<td>2. Overall evaluation (4-point ordinal scale)</td>
<td>No data reported; not clear if ITT analysis</td>
</tr>
<tr>
<td></td>
<td>3. Premature discontinuation due to poor therapeutic effect</td>
<td>3 PHT, 4 OXC</td>
</tr>
<tr>
<td></td>
<td>4. Premature discontinuation due to adverse events</td>
<td>14 PHT, 2 OXC (Log-rank $p = 0.002$)</td>
</tr>
<tr>
<td></td>
<td>5. Overall evaluation of tolerability (4-point ordinal scale)</td>
<td>Not reproduced here</td>
</tr>
<tr>
<td></td>
<td>6. Clinical utility (time to premature discontinuation for any reason)</td>
<td>34/96 PHT, 24/97 OXC OR (PHT vs OXC) 1.99</td>
</tr>
<tr>
<td>‘Ad hoc’ outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments (including whether unadjusted results reported)</td>
<td>Not clear why logistic regression used to analyse treatment retention; survival analysis would be more appropriate. Note that OR obtained in this way will be numerically greater than HR obtained by the appropriate analysis</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazards ratio; OR, odds ratio; OXC, oxcarbazepine; PHT, phenytoin.

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**Generalised seizures**

One trial, by Eriksson, 1998, identified patients with generalised seizures (rather than a specific syndrome associated with generalised seizures). The trial compared lamotrigine against placebo as add-on treatment (Tables 18–20). The trial used a complex design. Initially, all patients were treated with lamotrigine for a variable period of time. Those gaining some benefit from lamotrigine were then randomised to continue lamotrigine or withdraw to placebo. After a 12-week follow-up on the randomised treatment, patients were crossed over, so that lamotrigine was reintroduced for those originally randomised to placebo, and lamotrigine was withdrawn for those originally randomised to lamotrigine.

**Quality assessment**

This trial is poorly reported. A number of methodological details are not available from the trial report, especially with regard to the methods used to conceal allocation and maintain blinding, although the report does state that the results of drug plasma levels were known only to a single study coordinator (it is not stated whether or not this coordinator was involved in patient care). The report states that there was a 3-week ‘wash-out’ period between each 12-week follow-up period, but it is not clear what happened in these 3 weeks; a wash-out period is usually a drug-free period in cross-over trials, but in this case it seems more likely that the period was used gradually to withdraw/reintroduce lamotrigine.

The trial was analysed using each patient as their own control rather than the conventional methods of analysis for a cross-over trial, although some information is given about order effects and treatment × period interaction.

**Results**

Seventeen were randomised, with two patients later withdrawn at parental request. In order to be randomised, patients had to experience some benefit after lamotrigine was introduced: seven had >50% reduction in seizure frequency, nine had a <50% reduction in seizure frequency and one had an increase (of 39%), but nevertheless were perceived to benefit from lamotrigine in terms of reduction in seizure severity or in behaviour or motor skills.

No patients experienced more seizures on placebo than on lamotrigine, and 9/15 experienced >50% reduction on lamotrigine compared with placebo phase.

No adverse events were reported for lamotrigine after randomisation; in the placebo arm, 10 patients experienced fatigue and four experienced ‘more intense’ seizures. The interpretation of the adverse event data is complicated by the fact that this is a withdrawal trial with all patients receiving (and tolerating) a stable dose of lamotrigine at randomisation.

---

**TABLE 17** Adverse events (population with partial and generalised seizure types)

<table>
<thead>
<tr>
<th>Criteria for reporting</th>
<th>Guerreiro, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Phenyoitin</td>
</tr>
<tr>
<td>&gt;5% of patients in either group</td>
<td>(29.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>(22.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>(14.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>(25.5)</td>
</tr>
<tr>
<td>Gum hyperplasia</td>
<td>(10.6)</td>
</tr>
<tr>
<td>Apathy</td>
<td>(13.8)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>(11.7)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>(7.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>(6.4)</td>
</tr>
<tr>
<td>Abnormal thinking</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>(4.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>(8.5)</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Increase in γ-glutamyl transferase</td>
<td>(5.3)</td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>84/94 (89.4%)</td>
</tr>
</tbody>
</table>
### TABLE 18 Summary of trials and trial design (generalised seizures)

<table>
<thead>
<tr>
<th>Eriksson, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
</tr>
<tr>
<td>Type of trial design</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
</tr>
<tr>
<td>Control(s)</td>
</tr>
<tr>
<td>Study start and end dates</td>
</tr>
<tr>
<td>Centres and location</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Titration period</td>
</tr>
<tr>
<td>Maintenance</td>
</tr>
<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/ continuation on study</td>
</tr>
<tr>
<td>Comments on design</td>
</tr>
</tbody>
</table>

### TABLE 19 Quality assessment (generalised seizures)

<table>
<thead>
<tr>
<th>Eriksson, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
</tr>
<tr>
<td>Was the method really random?</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
</tr>
<tr>
<td>Was ITT used?</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>
Two trials were identified in patients with Lennox–Gastaut syndrome (Tables 22–25). Both were placebo-controlled trials of add-on therapy, one using lamotrigine, by Motte, 1997209 and the other topiramate, by Sachdeo, 1999.210 Sachdeo, 1999 included patients up to 30 years of age; although no data are reported separately for the children included in this trial, a substantial proportion of patients were under 18 years old and Lennox–Gastaut syndrome occurs exclusively in childhood, hence this trial is included in this review.

**Quality assessment**

Motte, 1997 is poorly reported, with no details given regarding the method of randomisation, treatment concealment or blinding. There is some imbalance in sex between the arms and a large difference in the numbers randomised to each arm (90 versus 79). The dose titration information refers exclusively to lamotrigine; although it may appear trivial to detail dose titration for placebo, this detail helps to confirm confidence in the blinding procedures. Sachdeo, 1997 does explicitly refer to titration in both arms of the trial, which overall is much better reported. Of concern for
both trials is that drug plasma levels were monitored but no mention is made of any arrangements to conceal the results from investigators; if these results were revealed to investigators during the trial, this would somewhat compromise blinding.

**Results**

Both trials found substantial reductions in seizure frequency compared with placebo; the magnitude of the treatment effects is similar in both trials. Motte, 1997 reports more placebo patients withdrawing for adverse events on placebo than on lamotrigine. Sachdeo reports no patients withdrawing owing to adverse events; however, the dose of topiramate used in this trial is relatively low and, furthermore, clinicians were allowed to withdraw the drug during follow-up and then rechallenge, which may also have contributed to the lack of withdrawals due to adverse events. No patients in either trial withdrew owing to poor efficacy on the active treatment arm.

The results of these trials suggest that lamotrigine and topiramate are more effective than no treatment in this group of patients. Both trials are small, and there are some methodological issues which need to be addressed.

**Infantile spasms (West’s syndrome)**

Three trials were identified in infantile spasms (West’s syndrome), all using vigabatrin (Tables 26–29). Appleton, 1999 (2) was a placebo-controlled trial of vigabatrin as monotherapy in newly diagnosed and previously untreated patients. Vigevano, 1997 and

---

**TABLE 22 Summary of trials and trial design (Lennox–Gastaut syndrome)**

<table>
<thead>
<tr>
<th></th>
<th>Motte, 1997</th>
<th>Sachdeo, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Lamotrigine</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>50–300 mg/day (oral)</td>
<td>6 mg/kg/day (oral assumed)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Lennox–Gastaut syndrome</td>
<td>Lennox–Gastaut</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Parallel</td>
<td>Parallel</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Add-on</td>
<td>Add-on</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>1994–1995</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centres and location</td>
<td>43 centres in USA, Europe</td>
<td>12 centres in USA</td>
</tr>
<tr>
<td>Baseline</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Titration period</td>
<td>6 weeks</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>More than one type of predominantly generalised seizure including tonic–clonic seizures and drop attacks for at least 1 year; age &lt;11 years at onset of epilepsy; intellectual impairment or a clinical impression of intellectual deterioration</td>
<td>Drop attacks (tonic–atonic) + history of or active atypical absence seizures; age 1–30 years; medically uncontrolled</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/continuation on study</td>
<td>Postbaseline; no additional eligibility criteria</td>
<td>Postbaseline; patients who ‘qualified for entry’ were randomised, but no specific criteria for this are mentioned</td>
</tr>
<tr>
<td>Comments on design</td>
<td>Dose titration refers explicitly to lamotrigine only; not clear how/if placebo doses titrated in same way</td>
<td>Trial includes patients up to the age of 30 years; results are not reported separately for children but this trial is included as a substantial proportion of patients are under 18 years old and Lennox–Gastaut is a syndrome which occurs only in childhood, hence these data would otherwise be excluded from both reviews being prepared for NICE</td>
</tr>
</tbody>
</table>

NICE, National Institute for Health and Clinical Excellence.
Chiron, 1997 used adrenocorticotrophic hormone (ACTH) and hydrocortisone, respectively, as control treatments in 'response-mediated' open cross-over designs. Chiron, 1997 recruited patients with infantile spasms which were caused by tuberous sclerosis.

**Quality assessment**
The Appleton trial, 1999 (2) is well reported. The trial had a short follow-up period of just 5 days. The short follow-up was to allow a placebo-controlled trial in a newly diagnosed population without requiring active treatment to be withheld for a protracted period of time; it is not clear why an active control was considered inappropriate.

The trials by Vigevano, 1997 and Chiron, 1997 are reasonably well reported, although neither gives details of randomisation procedures and they were not blinded (blinding may be difficult or impossible when active controls have characteristic and easily identifiable side-effects). It is not clear whether Chiron, 1997 included all randomised patients in the report. Vigevano, 1997 did not define any outcomes in the methods section. All three trials had very small sample sizes (40, 42 and 22 patients).

**Results**
The results of Appleton, 1999 (2) suggest that vigabatrin may be effective in these patients compared with no treatment.

Vigevano, 1997 and Chiron, 1997 both use a 'response-mediated' cross-over design, in which patients who do not respond well to the allocated treatment are crossed over to the alternative treatment during the trial, with responders continuing with the original allocated treatment. This sort of design is ideal for comparing treatment strategies, but not particularly effective in comparing individual drugs. Neither trial is analysed appropriately for the design, so the results we used are taken from the first period of each trial

---

### TABLE 23 Quality assessment (Lennox–Gastaut syndrome)

<table>
<thead>
<tr>
<th></th>
<th>Motte, 1997</th>
<th>Sachdeo, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Can’t tell</td>
<td>Yes</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Can’t tell</td>
<td>Yes</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Described as ‘double-blind’</td>
<td>Investigators, patients, study monitors and observers</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>No description</td>
<td>‘Blinded medication’; no further details</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>No; some imbalance in sex, and also a relatively large difference in the numbers randomised to the two groups (90 vs 79)</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Can’t tell (no description of binding and dose titration refers to gabapentin group only)</td>
<td>Yes</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>Not clear (see comment)</td>
<td>Yes</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>Yes, including lamotrigine</td>
<td>Yes</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Comments</td>
<td>Two patients are excluded for 'lack of completeness'; the report does not state to which arm(s) these patients were allocated</td>
<td>Titration refers explicitly to both arms of trial (i.e. including placebo).</td>
</tr>
<tr>
<td>TABLE 24 Results (Lennox–Gastaut syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motte, 1997</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Lamotrigine</strong></td>
<td></td>
</tr>
<tr>
<td>Number randomised</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>Number analysed</td>
<td>89</td>
<td>78</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Not reported</td>
<td>≤ 25 kg + VPA 13.0 (4.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 25 kg no VPA 3.7 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25 kg + VPA 8.4 (3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25 kg no VPA 3.7 (1.5)</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>14 (15.5)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>7 (7.7)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Worse seizure control</td>
<td>2 (2.2)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>3 (3.3)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>1 (1.1)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>1 (1.1)</td>
<td>0 (–)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>CI; p-value</strong></td>
<td></td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>% change in frequency of major motor seizures (drop attacks and tonic–clonic seizures)</td>
<td>Placebo ~9%</td>
</tr>
<tr>
<td><strong>Sachdeo, 1999</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Topiramate</strong></td>
<td></td>
</tr>
<tr>
<td>Number randomised</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Number analysed</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>92% achieved target dose</td>
<td>Median 5.8 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71% achieved target dose (6 mg/kg/day)</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient choice</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>CI; p-value</strong></td>
<td></td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>% reduction in average monthly seizure rate</td>
<td>Placebo ~8.8%</td>
</tr>
<tr>
<td></td>
<td>Drop attacks:</td>
<td>Placebo +5.1%</td>
</tr>
<tr>
<td></td>
<td>Composite: % reduction in average monthly drop attack rate and PGE</td>
<td>Data not reproduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th>Motte, 1997</th>
<th>Results</th>
<th>CI</th>
<th>Sachdeo, 1999</th>
<th>Results</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. % change in frequency of drop attacks</td>
<td>Placebo –9%</td>
<td>Lamotrigine –34%</td>
<td><em>p</em> = 0.01</td>
<td>Placebo median 5.2%</td>
<td>Topiramate median 25.8%</td>
</tr>
<tr>
<td>2. % change in frequency of tonic–clonic seizures</td>
<td>Placebo +10%</td>
<td>Lamotrigine –36%</td>
<td><em>p</em> = 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. % change in frequency of atypical absences</td>
<td>Placebo –38%</td>
<td>Lamotrigine –13%</td>
<td><em>p</em> = 0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Responder rate, defined as ≥50% reduction in major motor seizures</td>
<td>Placebo 16%</td>
<td>Lamotrigine 33%</td>
<td><em>p</em> = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Ad hoc' outcomes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Comments (including whether unadjusted results reported)</td>
<td>Results adjusted for country effects</td>
<td></td>
<td>Results adjusted for investigator</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PGE, parental global evaluation.
<table>
<thead>
<tr>
<th>Events</th>
<th>Motte, 1997</th>
<th>Sachdeo, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (7.7)</td>
<td>10 (12.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>12 (13.3)</td>
<td>10 (12.6)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6 (6.6)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 (4.4)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9 (10.0)</td>
<td>11 (13.9)</td>
</tr>
<tr>
<td>Cold/viral illness</td>
<td>0 (--)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (6.6)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7 (7.7)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4 (4.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (6.6)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.2)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6 (6.6)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (6.6)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Injury/accident</td>
<td>6 (6.6)</td>
<td>7 (8.8)</td>
</tr>
</tbody>
</table>

>10% greater incidence in top arm (i.e. treatment-emergent events)

- Somnolence  (22) (42)
- Anorexia    (20) (40)
- Nervousness (10) (21)
- Behavioural (10) (21)
- Fatigue     (4) (19)
- Dizziness   (0) (10)
- Weight loss (0) (10)
- Severe adverse events (10) (23)
TABLE 26 Summary of trials and trial design (infantile spasms/West’s syndrome)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (2)</th>
<th>Vigevano, 1997</th>
<th>Chiron, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Vigabatrin</td>
<td>Vigabatrin</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>50–150 mg/kg/day (not stated)</td>
<td>Lowest effective tolerated dose, 110–150 mg/kg/day (?mode)</td>
<td>150 mg/kg/day (?mode)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Infantile spasms</td>
<td>Newly diagnosed infantile spasms</td>
<td>Infantile spasms due to tuberous sclerosis</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Parallel</td>
<td>‘Response-mediated’ open cross-over study</td>
<td>‘Response-mediated’ open cross-over</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Placebo</td>
<td>ACTH</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>Not reported</td>
<td>1992–1995</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centres and location</td>
<td>40 centres; Europe, Canada, France</td>
<td>Italy</td>
<td>Multicentre, France</td>
</tr>
<tr>
<td>Baseline</td>
<td>2 or 3 days</td>
<td>None</td>
<td>Not clear</td>
</tr>
<tr>
<td>Titration period</td>
<td>5 days</td>
<td>9 days</td>
<td>No titration</td>
</tr>
<tr>
<td>Maintenance</td>
<td>None</td>
<td>20 days, then continuation (responders) or cross-over (non-responders) for a further 20 days</td>
<td>1 month, then cross-over of non-responders and continuation of responders and cross-overs for a further 1 month</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Newly diagnosed and previously untreated infantile spasms; age 1–20 months</td>
<td>Newly diagnosed and previously untreated infantile spasms (diagnosed within 3 weeks of entry)</td>
<td>Infantile spasms due to tuberous sclerosis</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/continuation on study</td>
<td>Postbaseline; no additional criteria</td>
<td>NA (newly diagnosed population)</td>
<td>NA</td>
</tr>
<tr>
<td>Comments on design</td>
<td>Baseline period varied for patients with and without clusters of spasms</td>
<td>Trial design compares strategies rather than treatments</td>
<td>Patients ‘recently’ diagnosed; prior AED treatment was not an exclusion criterion</td>
</tr>
</tbody>
</table>

only, making each, in effect, a simple parallel trial with a shorter follow-up period.

Vigevano, 1997 suggest that ACTH is somewhat more effective in eliminating spasms but may be less well tolerated than vigabatrin. Chiron, 1997 reports that all patients (11/11) on vigabatrin were spasm-free in the first period compared with 5/11 on hydrocortisone, with hydrocortisone also less well tolerated. The authors suggest that time to response was shorter but no data are presented which clearly demonstrate this. There are some discrepancies in the data reported in tables and text of this trial report, and some suggestion that cross-over criteria were not applied consistently; for example, it is not clear why two patients who responded to hydrocortisone during the first period were crossed over to vigabatrin. This trial is not sufficiently reliable to confirm the belief that vigabatrin may be particularly effective in infantile spasms due to tuberous sclerosis.

All of these trials are very small and there are some methodological difficulties, particularly with the two cross-over trials, which are methodologically weak and poorly reported.

Absence epilepsy

One trial was identified in absence epilepsy, comparing lamotrigine monotherapy against placebo in newly diagnosed typical absence seizures, by Frank, 1999 (Tables 30–33). A ‘withdrawal’ or ‘responder-enriched’ design was used; all patients were initially treated with lamotrigine with those achieving complete seizure...
freedom being randomised to ‘continue’ or ‘withdraw’ active treatment.

**Quality assessment**
The trial report is of reasonable quality, but gives no details of the method of randomisation or concealment of allocation; some imbalances in sex and weight, although consistent with chance in such a small trial, do not increase confidence in the methods used. Drug plasma levels were monitored but no mention is made of any efforts to conceal the results from investigators; failure to do so would somewhat compromise blinding.

**Results**
Substantially more patients remained seizure free whilst continuing with lamotrigine compared with the group withdrawn to placebo (64% versus 21%). Several adverse events are reported for patients receiving lamotrigine but no information about frequency is given.

This is a small trial with some concerns about methodological quality. It suggests that patients who have achieved complete seizure freedom on lamotrigine are more likely to remain seizure free if it is not withdrawn, although a substantial proportion of patients did remain seizure free on the placebo arm.

**BECTS**
One trial was identified in BECTS, comparing gabapentin monotherapy against placebo in newly diagnosed patients. The trial was reported in

---

**TABLE 27 Quality assessment (infantile spasms/West’s syndrome)**

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (2)</th>
<th>Vigevano, 1997</th>
<th>Chiron, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Described as ‘double-blind’</td>
<td>Open-label study</td>
<td>Open-label study</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
<td>Not in any detail</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>Yes</td>
<td>Some imbalance in sex ratios</td>
<td>No; differences compatible with change in such a small trial (see comment)</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Yes (if blinding adequate)</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell; possibly not (see comment)</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
<td>–</td>
<td>Report refers to 22 ‘evaluable patients’; it is not clear that all randomised patients were included. The limited information on the method of randomisation and some imbalances in patient characteristics, especially with respect to duration of infantile spasms prior to the trial, give further cause for concern</td>
</tr>
</tbody>
</table>
### TABLE 28 Results (infantile spasms/West’s syndrome)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (2)</th>
<th>Vigevano, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Number randomised</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Number analysed</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Mean 148 mg/kg</td>
<td>Mean 133 mg/kg</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
<td>None stated</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Irritability/agitation 0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Irritability/raised blood pressure 1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary outcome(s)</th>
<th>Results</th>
<th>CI; p-value</th>
<th>Results</th>
<th>CI; p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. % change spasm frequency:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h assessment</td>
<td>Placebo –25.9% 95% CI –56 to 65%</td>
<td></td>
<td>Vigabatrin –77.9% 95% CI 55 to 89%, p = 0.02</td>
<td></td>
</tr>
<tr>
<td>2-h assessment</td>
<td>Placebo –54.6% 95% CI 4 to 78%</td>
<td></td>
<td>Vigabatrin –71.9% 95% CI 42 to 86%, p = 0.342</td>
<td></td>
</tr>
<tr>
<td>2. Seizure (spasm)-free patients</td>
<td>Placebo 2 (10%)</td>
<td></td>
<td>Vigabatrin 7 (35%) p = 0.063</td>
<td></td>
</tr>
</tbody>
</table>

continued
TABLE 28 Results (infantile spasms/West's syndrome) (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (2)</th>
<th>Vigevano, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
<td><strong>Vigabatrin</strong></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Investigator ‘global assessment’</td>
<td>Placebo: 3 (15%) marked/moderate improvement</td>
<td>4 (20%) patients deteriorated</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2. Repeated EEG recordings</td>
<td>Hypsarrhythmia resolved in 1/2 seizure-free placebo patients vs 5/7 on vigabatrin</td>
<td>–</td>
</tr>
<tr>
<td><strong>‘Ad hoc’ outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70% improvement</td>
<td>Placebo 3/20 (15%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>24-h assessment</td>
<td>Vigabatrin 8/20 (40%)</td>
<td></td>
</tr>
<tr>
<td>2-h assessment</td>
<td>Placebo 11/20 (55%)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Vigabatrin 13/17 (76%)</td>
<td></td>
</tr>
<tr>
<td>No change or worse</td>
<td>Placebo 9/20 (45%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>24-h</td>
<td>Vigabatrin 4/20 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

Comments (including whether unadjusted results reported)

All means and CIs adjusted for geographical region and baseline spasm rate

Three patients appear to be missing from vigabatrin group for the 2-h results

continued
### TABLE 28 Results (infantile spasms/West’s syndrome) (cont’d)

<table>
<thead>
<tr>
<th>Chiron, 1997</th>
<th>Hydrocortisone</th>
<th>Vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number randomised</strong></td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Number analysed</strong></td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Maintenance dose achieved</strong></td>
<td>15 mg/kg/day, except 2 patients 10/11 (and 7/7 after cross-over) 150 mg/kg/day; 1 patients 100 mg/kg/day</td>
<td>10/11</td>
</tr>
<tr>
<td><strong>Withdrawals including reasons where specified</strong></td>
<td>Total withdrawals: 2 (18.2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lack of efficacy: 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Adverse events: 2 (18.2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Change in AED: 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other: 0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>CI; p-value</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Primary outcome(s)** | Proportion spasm free at 1 month | 5/11 hydrocortisone 11/11 vigabatrin  
*p* < 0.01 |
| **Secondary outcomes** | Development quotient | Not ITT, only 8 hydrocortisone and 9 vigabatrin patients evaluated  
Not reported |
| **‘Ad hoc’ outcomes** | Time to response (days on drug prior to becoming spasm free) | Mean time to response:  
Vigabatrin: 4 days (range 0.5–14 days)  
Hydrocortisone: 12.8 days (range 3–30 days)  
*p* = 0.058 |
| **Comments (including whether unadjusted results reported)** | Cross-over criteria were defined as ‘non-responders at 1 month’, with no further criteria given. Criteria do not seem to have been applied consistently, or there are some errors in the text. For example:  
two patients responded to hydrocortisone at day 30, both had side-effects, one was crossed over and one was not; one patient responded to hydrocortisone at day 19, listed as having no side effects but was crossed over to vigabatrin.  
The tabulated data imply that 7 patients crossed over from hydrocortisone to vigabatrin (including the two mentioned above who had responded to hydrocortisone), but the text implies that there were only 6 non-responders who should have crossed over (text states that 5/11 responded). |
<table>
<thead>
<tr>
<th></th>
<th>Appleton, 1999 (2)</th>
<th>Vigevano, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Criteria for reporting</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Not reported</td>
<td>8</td>
</tr>
<tr>
<td>Behaviour change</td>
<td>Not reported</td>
<td>1</td>
</tr>
<tr>
<td>(irritability)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number reporting</td>
<td>6 (30%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>≥ 1 AE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Chiron, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Criteria for reporting</td>
<td>Events reported to or</td>
</tr>
<tr>
<td>observed by investigator; data relate to both study periods</td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>(n events)</td>
</tr>
<tr>
<td>Adverse events (all)</td>
<td>17</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>–</td>
</tr>
<tr>
<td>Hyperexcitability/kinesia</td>
<td>5 (1 severe)</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>3 (1 severe)</td>
</tr>
<tr>
<td>Weight</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (1 severe)</td>
</tr>
<tr>
<td>Axial hypertonia</td>
<td>1</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>
abstract form only, so only limited information is available, summarised in Tables 34–37.

**Mixed population**

One trial was identified in a mixed population, by Chiron, 1996\(^{216}\) recruiting patients who had been treated with vigabatrin on a variety of different clinical trials and had been receiving the drug for various lengths of time with limited benefit (Tables 38–41). The trial used a 'withdrawal' design, randomising patients to continue with vigabatrin or withdraw to placebo.

**Quality assessment**

This trial is poorly reported, with no details of randomisation, concealment of allocation or method of blinding reported. There are substantial imbalances in patient characteristics, which, although consistent with chance in such a small trial, add to concerns about these methodological aspects of the trial. Only the primary outcome could be analysed by ITT owing

---

**TABLE 30** Summary of trials and trial design (absence epilepsy)

<table>
<thead>
<tr>
<th></th>
<th>Frank, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
<td>Maximum 1000 mg/day (oral)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
<td>Typical absence seizures (newly diagnosed)</td>
</tr>
<tr>
<td>Type of trial design</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Control(s)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Study start and end dates</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centres and location</td>
<td>Multi-centre, USA</td>
</tr>
<tr>
<td>Baseline</td>
<td>NA</td>
</tr>
<tr>
<td>Titration period</td>
<td>Minimum 4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>NA</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Newly diagnosed typical absence seizures; age 2–16 years</td>
</tr>
<tr>
<td>Timing and additional eligibility for phase randomisation/continuation on study</td>
<td>Patients achieving seizure freedom during titration were randomised to continue lamotrigine or switch to placebo</td>
</tr>
<tr>
<td>Comments on design</td>
<td>–</td>
</tr>
</tbody>
</table>

**TABLE 31** Quality assessment (absence epilepsy)

<table>
<thead>
<tr>
<th></th>
<th>Frank, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
<td>No</td>
</tr>
<tr>
<td>Was the method really random?</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
<td>Described as ‘double-blind’</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
<td>No description, other than that study medication matched for size, shape, colour, taste</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
<td>Yes (some imbalance in age and weight, consistent with chance and the small sample size)</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
<td>Yes (if blinding adequate)</td>
</tr>
<tr>
<td>Was ITT used?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
<td>Yes, including lamotrigine</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
<td>No</td>
</tr>
</tbody>
</table>

Comments

One patient withdrew consent at start of randomised phase.

Although randomised groups described as ‘reasonably balanced demographically’ there were differences in mean age and weight [8.8 years (SD 3.1) placebo vs 6.9 years (SD 2.3) lamotrigine; weight 40.0 kg (SD 16) placebo vs 30.2 kg (SD 9.9) lamotrigine]
to patients being ‘dropped’ if they experienced a worsening of seizure frequency or severity on withdrawal of vigabatrin.

Results
Fewer patients were withdrawn owing to a worsening of seizure frequency or severity on the vigabatrin arm compared to placebo (7% versus 54%).

The results suggest that patients experiencing a modest benefit with vigabatrin may continue to receive benefit while they remain on the drug. There are a number of methodological concerns, and this is a very small trial. Of interest is that four of the 28 patients selected because vigabatrin was of some benefit had actually experienced increases of 120–200% in seizure rate compared with the period before starting the drug; the benefits were perceived to be in behavioural and functional outcomes.

Summary of RCT evidence
The quality of the 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; 18 of these were conducted exclusively in children. 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.

### TABLE 32 Results (absence epilepsy)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomised</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Number analysed</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
<td>Not reported</td>
<td>Median 5.0 mg/kg/day (range 2–15 mg/kg/day)</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
<td>0</td>
<td>1 (6.6)</td>
</tr>
</tbody>
</table>

| Primary outcome(s) | 21% placebo vs 64% lamotrigine | p = 0.03 |
| Secondary outcomes | –                                 | –         |
| ‘Ad hoc’ outcomes  | –                                 | –         |
| Comments (including whether unadjusted results reported) | Maintenance dose achieved – this is the median dose taken by patients who became seizure free during the open phase |

### TABLE 33 Adverse events (absence epilepsy)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for reporting</td>
<td>Events reported by ≥ 5% of patients</td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>Nervous system complaints (e.g. asthenia, headache, dizziness, hyperkinesia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Events related to infections, ailments common to childhood, or flu syndromes</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Frequencies not reported</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 34 Summary of trials and trial design (BECTS)

<table>
<thead>
<tr>
<th>Bourgeois, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer drug(s) investigated</td>
</tr>
<tr>
<td>Target maintenance dose (mode)</td>
</tr>
<tr>
<td>Seizure or syndrome</td>
</tr>
<tr>
<td>Type of trial design</td>
</tr>
<tr>
<td>Add-on or monotherapy?</td>
</tr>
<tr>
<td>Control(s)</td>
</tr>
<tr>
<td>Study start and end dates</td>
</tr>
<tr>
<td>Centres and location</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Titration period</td>
</tr>
<tr>
<td>Maintenance</td>
</tr>
<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>Timing and additional eligibility for randomisation/continuation on study</td>
</tr>
<tr>
<td>Comments on design</td>
</tr>
</tbody>
</table>

### TABLE 35 Quality assessment (BECTS)

<table>
<thead>
<tr>
<th>Bourgeois, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
</tr>
<tr>
<td>Was the method really random?</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
</tr>
<tr>
<td>Was ITT used?</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>

### TABLE 36 Results (BECTS)

<table>
<thead>
<tr>
<th>Bourgeois, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Number randomised</td>
</tr>
<tr>
<td>Number analysed</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Primary outcome(s)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>‘Ad hoc’ outcomes</td>
</tr>
<tr>
<td>Comments (including whether unadjusted results reported)</td>
</tr>
</tbody>
</table>

58
### TABLE 37 Adverse events (BECTS)

<table>
<thead>
<tr>
<th>Bourgeois, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
</tr>
<tr>
<td><strong>Criteria for reporting</strong></td>
</tr>
<tr>
<td><strong>Events</strong></td>
</tr>
</tbody>
</table>

### TABLE 38 Summary of trial and trial design (mixed population)

<table>
<thead>
<tr>
<th>Chiron, 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newer drug(s) investigated</strong></td>
</tr>
<tr>
<td><strong>Target maintenance dose (mode)</strong></td>
</tr>
<tr>
<td><strong>Seizure or syndrome</strong></td>
</tr>
<tr>
<td><strong>Type of trial design</strong></td>
</tr>
<tr>
<td><strong>Add-on or monotherapy?</strong></td>
</tr>
<tr>
<td><strong>Control(s)</strong></td>
</tr>
<tr>
<td><strong>Study start and end dates</strong></td>
</tr>
<tr>
<td><strong>Centres and location</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Titration period</strong></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td><strong>Timing and additional eligibility for randomisation/continuation on study</strong></td>
</tr>
<tr>
<td><strong>Comments on design</strong></td>
</tr>
</tbody>
</table>
**TABLE 39 Quality assessment (mixed population)**

<table>
<thead>
<tr>
<th>Chiron, 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of treatment described as random?</td>
</tr>
<tr>
<td>Was method of randomisation described?</td>
</tr>
<tr>
<td>Was the method really random?</td>
</tr>
<tr>
<td>Was allocation of treatment concealed?</td>
</tr>
<tr>
<td>Who was blinded to treatment?</td>
</tr>
<tr>
<td>Was method of blinding adequately described?</td>
</tr>
<tr>
<td>Were eligibility criteria described?</td>
</tr>
<tr>
<td>Were groups comparable at study entry?</td>
</tr>
<tr>
<td>Were groups treated identically apart from the intervention?</td>
</tr>
<tr>
<td>Was ITT used?</td>
</tr>
<tr>
<td>Were withdrawals stated?</td>
</tr>
<tr>
<td>Were reasons for withdrawals stated?</td>
</tr>
<tr>
<td>Was a power calculation done?</td>
</tr>
<tr>
<td>Was monitoring of plasma levels done (including study drug)?</td>
</tr>
<tr>
<td>Were arrangements to blind plasma monitoring results mentioned?</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>

**TABLE 40 Results (mixed population)**

<table>
<thead>
<tr>
<th>Chiron, 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Number randomised</td>
</tr>
<tr>
<td>Number analysed</td>
</tr>
<tr>
<td>Maintenance dose achieved</td>
</tr>
<tr>
<td>Withdrawals including reasons where specified</td>
</tr>
<tr>
<td>Results (difference, or by arm)</td>
</tr>
<tr>
<td>CI for difference; p-value</td>
</tr>
<tr>
<td>Primary outcome(s)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>‘Ad hoc’ outcomes</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>
Fifteen of the 20 trials identified used placebo as comparator. In most cases these trials used the newer drug as add-on to existing therapy; some trials used a ‘responder enriched’ design where all patients were initially started on the newer drug and ‘responders’ were then randomised to ‘withdraw’ or ‘continue’. Most of the placebo-controlled trials were in previously diagnosed populations, but two were in newly diagnosed patients, one in infantile spasms with very short (5-day) follow-up and the other in benign epilepsy where active treatment is not considered necessary for all patients. These trials provide reasonably convincing evidence that the newer agents have some beneficial impact on the disease but offer little information as to how, and when, they are best used, and in particular how they compare to alternative drug treatments.

Five of the 20 trials identified employed active comparator treatments: two in newly diagnosed partial epilepsy (both using carbamazepine as comparator), one in a mixed population with partial or generalised seizure types (using phenytoin as comparator) and two in infantile spasms (one using ACTH and the other hydrocortisone). One very small trial suggested that vigabatrin was considerably more effective than hydrocortisone in the treatment of infantile spasms due to tuberous sclerosis, but this was based on data from just 22 patients. None of the other four trials found any clear evidence of a difference in effectiveness between the older and newer drugs compared, but in each case there was some evidence that the newer drugs might be better tolerated than the comparator treatments. Interpretation of these comparisons is complicated by variations in the choice of comparator, choice of drug doses and titration schedules and the lack of any confirmatory data from trials using similar designs and comparators.

Hence 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 each of the newer agents tested is of some value in the treatment of these conditions. Where active controls have been used, the newer agents appear no more effective but with better tolerability. 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 evidence to suggest that the newer agents should be considered as a first-choice treatment in any form of epilepsy in children.

Ongoing trials
Relevant ongoing RCTs (Table 42) were identified by contact with experts, from industrial submissions to NICE and by searching the National Research Register and the Clinical Trials Meta Register.

### Table 41 Adverse events (mixed population)

<table>
<thead>
<tr>
<th>Criteria for reporting</th>
<th>Placebo</th>
<th>Vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>None reported</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

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### TABLE 42 Relevant ongoing trials identified

<table>
<thead>
<tr>
<th>Start/finish; N</th>
<th>Population; age range</th>
<th>Intervention/comparator</th>
<th>Outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SANAD</strong>&lt;sup&gt;a&lt;/sup&gt; Long-term clinical outcomes and cost-effectiveness of standard and new AEDs 1998/2004 N = 3150 (450 in each of 7 arms)</td>
<td>Patients with epilepsy managed by monotherapy ≥ 5 years</td>
<td>Monotherapy. (a) Carbamazepine vs lamotrigine or topiramate or gabapentin (b) Valproate vs lamotrigine or topiramate</td>
<td>(a) Time to withdraw (lack of efficacy, intolerability, addition of other AED) (b) Time to 1 year seizure-free Others include: (a) Time to first seizure (b) Psychosocial functioning (c) Analysis of costs</td>
<td>Largest AED RCT undertaken. Economic study included. Head-to-head study of AEDs. Clinically meaningful outcomes, likely to yield best available evidence on new AEDs.</td>
</tr>
<tr>
<td><strong>MESS. Multicentre Study of Early Epilepsy and Single Seizures 1999/2002</strong> N = target 1800; recruited 1443</td>
<td>Recent history 7, 1 unprovoked seizure 5 months–85 years</td>
<td>Immediate vs delayed intervention with AED</td>
<td>(a) Time to seizure recurrence (b) Proportion to long-term remission (c) Psychosocial function</td>
<td></td>
</tr>
<tr>
<td><strong>UKISS&lt;sup&gt;b&lt;/sup&gt;. United Kingdom Infantile Spasm Study</strong> N = target 250; recruited 107 April 1998/August 2003 final follow-up</td>
<td>Infants with infantile spasms (not tuberous sclerosis)</td>
<td>Vigabatrin vs prednisolone or ACTH</td>
<td>(a) No. seizure-free for a minimum of 48 h at 14 days treatment (b) Psychomotor development at age 12–14 months (c) Epilepsy outcome at age 12–14 months</td>
<td>Head-to-head trial</td>
</tr>
<tr>
<td><strong>Valproate vs lamotrigine (alone or in combination) in patients failing monotherapy N = 178 (by January 2003)</strong></td>
<td>Patients aged ≥ 13 years</td>
<td>Valproate vs lamotrigine as add-on or monotherapy</td>
<td>(a) Freedom from seizures (b) Side-effects</td>
<td>Head-to-head trial</td>
</tr>
<tr>
<td><strong>Topomax (Topiramate) as adjunctive therapy for partial seizures with or without secondary generalisation&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>Children with chronic epilepsy</td>
<td>Open-label Topiramate vs ?</td>
<td>(a) Efficacy (b) Side-effects</td>
<td></td>
</tr>
<tr>
<td><strong>VNS vs new AEDs 2000/2003</strong></td>
<td>Epilepsy refractory to 2 different AEDs (as monotherapy or add-on) 7–16 years</td>
<td>VNS vs new AED (gabapentin, lamotrigine, tiagabine, topiramate or vigabatrin)</td>
<td>(a) Reduction in seizure frequency (b) Reduction in seizure severity (c) Tolerability and safety (d) QoL (e) Cost</td>
<td>Economic study included. Proportion &lt;18 years old likely to be small</td>
</tr>
<tr>
<td><strong>Valproate vs lamotrigine or topiramate 2000/2004</strong></td>
<td>Women newly diagnosed with epilepsy requiring treatment 16–45 years</td>
<td>Valproate vs lamotrigine or topiramate</td>
<td>(a) Presence of polycystic ovaries on ultrasound (b) Change in biochemical parameters of hyperandrogenaemia</td>
<td>Proportion &lt;18 years old likely to be small</td>
</tr>
<tr>
<td><strong>Levetiracetam as add-on for idiopathic generalised epilepsy and PGTC seizures&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td>Adults and children</td>
<td>Levetiracetam vs placebo</td>
<td></td>
<td>Not head-to-head trial</td>
</tr>
</tbody>
</table>

<sup>a</sup> [http://www.liv.ac.uk/neuroscience/sanad/docs/protocol.pdf](http://www.liv.ac.uk/neuroscience/sanad/docs/protocol.pdf)
<sup>b</sup> RCT nested within epidemiological study.
<sup>c</sup> Limited details from National Research Register.
<sup>d</sup> PGTC, primary generalised tonic clonic.
Chapter 4
Economic analysis of newer antiepileptic drugs in children

Summary

Commentary on company submissions that modelled childhood epilepsy

GlaxoSmithKline submission
- The first analysis concerned the use of lamotrigine as monotherapy in patients ≥12 years of age, with either partial or generalised seizure types. The comparison is of lamotrigine (first-line) with two older AEDs (carbamazepine and sodium valproate). The results indicate an incremental cost-effectiveness ratio (ICER) for lamotrigine as first line monotherapy of £13,045 per quality-adjusted life-year (QALY) gained.
- The second analysis considered the use of lamotrigine as add-on therapy in children ≥2 years old. The comparison, drawing upon trial data, was with placebo add-on therapy. This analysis resulted in an ICER of £16,456 per QALY gained.

Janssen–Cilag submission
- The main analysis presented in this report concerned the use of topiramate as adjunctive therapy in patients with partial seizure types. The comparison was of adjunctive topiramate with adjunctive lamotrigine (i.e. one newer AED is being compared with a second newer AED). The results indicate that topiramate dominates lamotrigine; it is associated with a lower mean cost and greater level of benefit.

Summary of the Birmingham epilepsy model
- A simulation model was constructed that considered the use of the newer AEDs as part of the drug sequence that a child might experience over the course of their childhood with epilepsy.
- Clearly each patient can potentially be subject to many different treatments during their time in the model, depending on the success or otherwise of their current treatment. In order to reflect this complexity, the analysis considered a predefined sequence and strategy for the use of drugs and drug combinations. The policy change considered was the introduction of each of the new drugs in turn, in line with its licensed indications.
- Data to populate the model were sparse. Where available, data were drawn from RCTs but there remain assumptions and judgements that had to be made given the paucity of data relating to the use of newer AEDs in children.
- The expected total cost of caring for the average child diagnosed with epilepsy, managed according to a no new drug therapy strategy, is just under £5000 (from the age of diagnosis through to 18 years of age). This includes both the cost of the drugs plus the costs of other health service resources. Such a patient is expected to experience just under 7.5 QALYs from this strategy, again through to the time when they reach the age of 18 years.

The analysis that considered the use of lamotrigine as monotherapy (either first- or second-line) indicated a positive incremental cost but no strong evidence of important health benefits. For the analyses looking at the use of the newer AEDs as add-on therapies, the findings were again of positive incremental costs and no strong evidence of important health benefits.

Introduction

In line with the objectives stated in the protocol for this review, the economic analysis has addressed the following question concerning the use of AEDs: what is the cost effectiveness of newer AEDs used in monotherapy, and/or combination therapy, when compared with other drug treatments for epilepsy in children?

There were two components to the economics aspects of this work: a review of existing economic analyses (including the analyses reported in the sponsor submissions) and a new model-based analysis. These are described in detail in the following sections.

Systematic review of existing economic analyses

The details of the literature search are provided earlier in the report.
It was clear at the outset that a review of the cost-utility of using AED therapy in children with epilepsy was going to be unachievable given the lack of published studies with utility-based QoL data in this age group. In fact, no published economic studies reviewing the use of AED therapy in the treatment of epilepsy in childhood were identified. The reason for exclusion in the majority of articles reviewed was that the AEDs were being used in a study population that did not match the age range specified in the review inclusion criteria. Therefore, the focus of this review is on the economic evidence submitted to NICE by the manufacturers of newer AEDs for treatment of epilepsy in childhood. Only two of the manufacturer submissions included an analysis of the use of the AED in children: the submissions by GlaxoSmithKline and Janssen–Cilag. Given that the analyses relating to the use of AEDs in adults is the subject of a separate review, we chose to focus solely on the submissions from GlaxoSmithKline and Janssen–Cilag.

**Review of submission models**

The two submissions are reviewed with respect to the appropriateness and the accuracy of the economic analyses presented. The quality of the economic data is appraised according to the following categories detailed in the cost-effectiveness review outlined in the protocol:

- Details of the study characteristics such as form of economic analysis, comparators, perspective, time horizon and modelling used.
- Details of the effectiveness and cost parameters such as effectiveness data, health state valuations, resource use data, unit cost data, price year, discounting assumptions and productivity costs.
- Details of the results and sensitivity analyses.

*Tables 43 and 44* provide an overall summary of the methods and results of the economic analyses reported in the manufacturer submissions.

**GlaxoSmithKline submission**

GlaxoSmithKline manufacture lamotrigine. Two economic analyses are reported in their submission, following the licensing restrictions on the use of lamotrigine.

- The first (and most substantial) analysis concerns the use of lamotrigine as monotherapy in patients ≥ 12 years of age with either partial or generalised seizure types. The comparison is of lamotrigine (first-line) with two older AEDs (carbamazepine and sodium valproate). The results indicate an ICER for lamotrigine as first-line monotherapy of £13,045 per QALY gained.
- The second analysis considered the use of lamotrigine as add-on therapy in children ≥ 2 years old. The comparison, drawing upon trial data, was with placebo add-on therapy. This analysis resulted in an ICER of £16,456 per QALY gained.

A simple decision tree was constructed that considered first- and second-line treatments only. The model followed patients for a period of 1 year only. An interesting aspect of the analysis was the primary research that involved the collection of new utility-based health-related quality of life (HRQoL) data. Epilepsy-specific health states were defined and participants in the survey were asked to complete a series of standard gamble exercises in order that a utility score could be derived. The states included reference to the drugs in question in order that issues of side effects would also be captured. However, the data were collected from adults who were asked to imagine themselves in the states in question and so the relevance of such data to an analysis of the use of lamotrigine in children has to be questioned.

**Janssen–Cilag submission**

Janssen–Cilag manufacture topiramate. Several economic analyses are reported in their submission, considering the use of topiramate as adjunctive therapy and as monotherapy, for patients with partial seizures and patients with generalised seizures. Given that topiramate is not licensed for use as monotherapy in children, we shall not review this aspect of the analysis reported in the submission.

For the analysis concerning the use of topiramate as adjunctive therapy in patients with partial seizure types, the comparison is of adjunctive topiramate with adjunctive lamotrigine. Therefore, one newer AED is being compared with a second newer AED. It is clearly important to consider whether this is the appropriate comparison to be making from a policy perspective; is the suggestion that topiramate would be used in place of lamotrigine?

The results indicate that topiramate dominates lamotrigine; it is associated with a lower mean cost and greater level of benefit. A Markov model was constructed that considered an initial period following start of drug therapy (to assess level of response in terms of seizure frequency) followed by a maintenance period on the drug, if at least partially effective. Where no response was
<table>
<thead>
<tr>
<th>TABLE 43 Review of economic analyses within the GlaxoSmithKline submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
</tr>
<tr>
<td><strong>Patient group</strong></td>
</tr>
<tr>
<td><strong>Treatment comparison</strong></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
</tr>
<tr>
<td><strong>Model</strong></td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
</tr>
<tr>
<td><strong>Model description</strong></td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
</tr>
<tr>
<td><strong>Health state valuation</strong></td>
</tr>
<tr>
<td><strong>Source of resource data</strong></td>
</tr>
<tr>
<td><strong>Discounting</strong></td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
</tr>
<tr>
<td><strong>Model base case results</strong></td>
</tr>
</tbody>
</table>
### TABLE 44 Review of economic analyses within the Janssen–Cilag submission

<table>
<thead>
<tr>
<th></th>
<th>Topiramate</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Janssen–Cilag</td>
<td>Janssen–Cilag</td>
</tr>
<tr>
<td><strong>Patient group</strong></td>
<td>Patients with partial seizure types</td>
<td>Patients with partial seizure types and, separately, patients with generalised seizure types</td>
</tr>
<tr>
<td><strong>Treatment comparison</strong></td>
<td>Adjunctive therapy with topiramate compared with adjunctive therapy with lamotrigine</td>
<td>For partial seizure patients: comparison of two monotherapies – topiramate and carbamazepine For generalised seizure patients: comparison of two monotherapies – topiramate and sodium valproate Note: topiramate not licensed for use as monotherapy in children</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Cost–utility analysis</td>
<td>Cost–utility analysis</td>
</tr>
<tr>
<td><strong>Model</strong></td>
<td>Markov model</td>
<td>Markov model</td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
<td>15 years</td>
<td>15 years</td>
</tr>
<tr>
<td><strong>Model description</strong></td>
<td>Markov model with 3 health states defined by response to treatment: seizure free (complete response), response but continuing to have seizures and no response. 3 monthly cycles Assumptions: All patients have one additional GP visit during titration period. Assumed an average weight of the child to be 34.5 kg. Assumed QoL issues and scores to be the same for adults and children. Health state utilities assumed to be the same during initial period and maintenance phase</td>
<td>Markov model with 3 health states defined by response to treatment: seizure free (complete response), response but continuing to have seizures and no response. 3 monthly cycles Assumptions: All patients have one additional GP visit during titration period. Assumed an average weight of the child to be 34.5 kg. Assumed QoL issues and scores to be the same for adults and children. Health state utilities assumed to be the same during initial period and maintenance phase</td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
<td>QALYs</td>
<td>QALYs</td>
</tr>
<tr>
<td><strong>Health state valuation</strong></td>
<td>Utility data taken from Selai et al. (1999),572 which gives adult data on utilities according to seizure frequency and response to treatment</td>
<td>Utility data taken from Selai et al. (1999),572 which gives adult data on utilities according to seizure frequency and response to treatment</td>
</tr>
<tr>
<td><strong>Source of resource data</strong></td>
<td>Data taken from a UK cost of illness study (Jacoby et al.573). This reports costs of adult epilepsy Cost data from published sources</td>
<td>Data taken from a UK cost of illness study (Jacoby et al.573). This reports costs of adult epilepsy Cost data from published sources</td>
</tr>
<tr>
<td><strong>Discounting</strong></td>
<td>1.5% for QALYs 6% for costs</td>
<td>1.5% for QALYs 6% for costs</td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td>QoL data varied – new data reported form a discrete choice experiment Time horizon and discounting rate also varied Results not highly sensitive to these variations</td>
<td>QoL data varied – new data reported form a discrete choice experiment Time horizon and discounting rate also varied Results not highly sensitive to these variations</td>
</tr>
<tr>
<td><strong>Model base case results</strong></td>
<td>Topiramate dominates lamotrigine</td>
<td>For partial seizure patients (topiramate vs carbamazepine): £734 per QALY For generalised seizure patients (topiramate vs sodium valproate): £635 per QALY</td>
</tr>
</tbody>
</table>
obtained from the use of the drug, switches were considered to other AEDs. Some consideration was therefore given to drug sequences. QALYs were estimated, drawing on QoL data collected in an adult epilepsy population. The assumption is made that QoL data for adults are similar to those for children. However, the sensitivity analysis did pick up the issue of QoL and demonstrated little sensitivity of the analysis results to variation in this parameter. In addition, a probabilistic sensitivity analysis was conducted allowing cost-effectiveness acceptability curves to be plotted.

The submission report Markov model was developed on behalf of the company by MEDTAP. The structure of the model is shown in Figure 1.

The model simulates a cohort of 1000 children over 2 years of age over a 15-year period. A cycle length of 3 months is used. Children are allocated to the model states according to their response to AED treatment. Response was estimated using data derived largely from RCTs. We are told that two UK-based neurologists validated the model structure and assumptions.

The first 3-month period was considered separately for a number of reasons: new treatments are unlikely to be offered, resource use is increased owing to intensive monitoring of the patient and QoL is likely to be diminished owing to a high incidence of side-effects. After the initial period, children not experiencing a >50% reduction in seizure frequency were switched to a new treatment. However, patients starting a new therapy were excluded from further analysis. Data sources and the key assumptions were outlined in the submission. An important weakness of the base-case analysis reported in the submission concerns the handling of side-effects. The authors of the report acknowledge this limitation: “The utility data used in the base-case analysis of the models does not allow for modelling the impact of side effects on utility values associated with health states.” (p. 124).

FIGURE 1 Markov model depicted in the submission document
Given that side-effects play an important part in the choice of AED therapy, especially for child patients, the company commissioned a new empirical study on this issue. The further piece of work sought to elicit values or disutilities associated with the most common side-effects of AEDs and seizure frequency. The study was a discrete choice experiment (DCE), sometimes referred to as a conjoint analysis, that involved respondents considering choices between two alternative drugs. An example choice is given above (Figure 2; taken from p. 175 of the submission).

Questionnaires were distributed to 1000 members of the ‘Epilepsy Action’ organisation and the questionnaire was available on the organisation’s website. The analysis is based on 94 responses. Concerns must be expressed about the apparently poor response. It would also be important to establish whether the data relate solely to adults. This is the implication of the report since there is no explicit statement that respondents were asked to consider the choice acting as a parent or guardian of a child with epilepsy.

The DCE data were transformed into time trade-off (TTO) utility scores (on a 0–1 scale) using the life expectancy payment vehicle. The scenarios presented to respondents included an attribute ‘Months given up’. This was expressed, for example, as: ‘The drug reduces your length of life by 6 months (out of every 30 years you live)’.

It seems reasonable to be highly cautious in the interpretation of the data generated through such an exercise. Before placing too much weight on such data, it would be important to explore the interpretation being placed on this attribute by respondents and that the conversion of such data into TTO utility scores is a reliable and valid estimation approach.

It is fair to say that the DCE results are used cautiously and do not feature in the base-case analyses. They are used as part of the sensitivity analysis but only for the analysis of topiramate as monotherapy. However, it should be remembered that topiramate is not licensed as monotherapy for the treatment of children with epilepsy. The QALY estimates for the analysis using the DCE data are

---

**Example of a choice set**

<table>
<thead>
<tr>
<th>Choice 1</th>
<th>Add-on Drug A</th>
<th>Add-on Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change?</td>
<td>Gain 12 kg (26 lbs)</td>
<td>Gain 6 kg (13 lbs)</td>
</tr>
<tr>
<td>Chance of skin rash?</td>
<td>1 in 5 chance (20%)</td>
<td>1 in 10 chance (10%)</td>
</tr>
<tr>
<td>Concentration affected?</td>
<td>1 in 10 chance (10%)</td>
<td>Your concentration is unaffected</td>
</tr>
<tr>
<td>Hair loss?</td>
<td>You have no hair loss</td>
<td>You have no hair loss</td>
</tr>
<tr>
<td>Reduction in seizures?</td>
<td>Your seizures are reduced by more than half (75%)</td>
<td>Your seizures are reduced by more than half (75%)</td>
</tr>
<tr>
<td>Monthly cost to you?</td>
<td>£50</td>
<td>£25</td>
</tr>
<tr>
<td>Feeling sick?</td>
<td>1 in 3 chance (33%)</td>
<td>You do not feel sick</td>
</tr>
</tbody>
</table>

Which drug would you prefer? Prefer Drug A [ ] Prefer Drug B [ ]

**FIGURE 2** Example of a choice set taken from the submission document (p. 175)
very similar to those using Selai and colleagues’ QoL data only.572

**Birmingham economic analysis**

Given the paucity of published economic analyses of treatments for children with epilepsy, we chose to undertake a new analysis using a cost–utility approach, with QALYs as the outcome measure. We constructed a decision-analytic model and used this as the framework through which to explore both the effectiveness and cost-effectiveness of the newer AEDs. The details of the model structure and the information used to populate it are described in the following sections.

**Overview of decision–analytic model**

The model is an individual sampling model whereby individual simulated patients progress through the model along the patient pathways illustrated in Figure 3. The model follows individual newly diagnosed patients with partial epilepsy from the point of diagnosis. The youngest patients at entry into the model are 3 years (infantile epilepsy is not considered in the model) and the oldest are just under 18 years. This represents a model of epilepsy in childhood and so patients exit on reaching the age of 18 years. Therefore, the longest simulated time period a patient can be in the model for is 15 years and the shortest period is a matter of days. As patients progress through the model, their treatment pathways and experience of epilepsy are monitored. The cohort of patients followed in the model includes some patients with neurological impairment and some without.

It is not possible to model every form of childhood epilepsy within this assessment, and no model could reasonably cope with too broad a range of diagnoses. We therefore decided to model those conditions which:

- account for a substantial proportion of diagnoses
- have been adequately addressed within RCTs, and
- for which there are clearly a number of alternative prescribing strategies

We therefore modelled partial seizures (with or without secondarily generalised seizures). A similar model structure could be employed to model generalised tonic–clonic seizures, although cost and utility data would have to be obtained separately for this patient group. However, only two RCTs included patients with generalised tonic–clonic seizures; one studied a mixed population including patients with partial seizures and the other recruited a broad range of patients, with 70% having Lennox–Gastaut syndrome. The only substantial RCT data available in generalised seizures are for patients with Lennox–Gastaut syndrome, which is a relatively rare and very severe syndrome and would require more substantial amendment of the model structure. Given the poor quality and small quantity of the data available for Lennox–Gastaut syndrome, it is not clear that decision-analytic modelling would add anything. The only remaining licensed indication for any of the newer drugs is vigabatrin for infantile spasms, which would require a completely different model structure, given the evolving nature of the syndrome (with many patients going on to develop different forms of epilepsy, including Lennox–Gastaut syndrome). Again, it is not clear that modelling could add substantially to the currently available clinical evidence for this diagnosis.

A patient enters the model with a new diagnosis of partial epilepsy. Personal characteristics for the individual (i.e. sex, age and the presence of neurological impairment) are then assigned to the patient through a process of repeated samplings from appropriate distributions for these characteristics. The patient is initially prescribed monotherapy with an AED (with the choice of drug defined by the fixed sequence described in the next section). There are then four broadly defined outcomes of drug treatment:

- intolerable side-effects, leading to early discontinuation (outcome 1)
- lack of effect on seizure rate, leading to early discontinuation (outcome 2)
- partial efficacy with tolerable side-effects (outcome 3)
- complete seizure freedom with tolerable side-effects (outcome 4).

Patients discontinuing early (i.e. moving into outcomes 1 and 2) go on to receive alternative treatment if they wish; we assume that further drug treatment is likely to involve a (gradual) switch rather than an adjunctive therapy for these outcomes.

Patients with some reduction in seizure frequency (outcome 3) may or may not go on to receive adjunctive therapy. It is assumed that willingness to try adjunctive treatment, and willingness to continue on drug treatment at all, will depend on...
Economic analysis of newer antiepileptic drugs in children

Stage 1
Patient with newly diagnosed focal epilepsy
- age (and weight)
- learning difficulties (none/moderate)
- life expectancy

[FIGURE 3] Patient pathway for a child with newly diagnosed partial epilepsy

Key
- Terminal outcome
- Sample parameter value
- *Stage specific value

Note – all parameters assumed to be dependent on patient characteristics but independent of drug except where noted.

Prescribing strategies to be compared consist of different predefined sequences of old and new drugs

- Unacceptable efficacy (short-term)
- Unacceptable side-effects (short-term)
- Partial efficacy and acceptable side-effects
- Seizure freedom and acceptable side-effects

No further treatment for remaining time in model

Need for further drug treatment

Willingness to try further drug

Utility/costs

Willingness to try further drug
the number of treatments already tried by this point. We have allowed for these patients to discontinue the drug and try alternative treatment at some stage (i.e. a different monotherapy).

It is assumed that patients achieving complete seizure freedom (outcome 4) would not go on to receive additional treatment, but that some would attempt to withdraw from drug therapy altogether after a certain period of seizure freedom. An unsuccessful withdrawal of the drug (i.e. experience of seizures after withdrawal) is assumed to be followed by reintroduction of the original drug. We have assumed that the proportion discontinuing due to late toxicity or reduction in efficacy over time is negligible.

We assume that the amount of time before discontinuing an unsuccessful drug (outcomes 1 and 2) is dependent on the reason for discontinuing rather than the drug. In other words, we assume that the average time to develop side-effects and/or time to establish lack of efficacy does not vary substantially by drug; differences between drugs are therefore mainly due to differences in the proportions experiencing each outcome. (We do recognise that patterns of early discontinuation due to side-effects will depend to some extent on starting dose and titration schedule; we have assumed ‘optimal’ titration schedules, which will vary by drug.)

On the basis of clinical advice, the model assumes a similar prescribing practice for boys and girls. That is, we have not built into the model a policy for young girls to be prescribed drugs thought to be less teratogenic in order to avoid the need for later treatment changes.

In addition, the policy on discontinuation and withdrawal of drugs is assumed to be the same for patients receiving monotherapy and adjunctive therapy. For example, we assume that a patient achieving complete seizure freedom on a two-drug combination would attempt to withdraw from both drugs.

As shown in Figure 3, we acknowledge that at any point after the first drug treatment patients may be referred for surgery or for confirmation of diagnosis (with the exception of those achieving complete seizure freedom with the first drug). However, we have worked on the assumption that the proportions referred for surgery or confirmation of diagnosis will not vary across the alternative AEDs and so these factors are not explicitly considered in the model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age distribution at diagnosis</td>
</tr>
<tr>
<td>Weight</td>
<td>Normal growth charts</td>
</tr>
<tr>
<td>Learning difficulties</td>
<td>Proportion of children with focal epilepsy experiencing learning difficulties</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Life expectancy for patients with diagnosis of epilepsy</td>
</tr>
<tr>
<td>Prescribing strategies</td>
<td>Ranked list of old drugs, and list of newer drugs which would be considered for inclusion in the strategy</td>
</tr>
<tr>
<td>Target doses and titration schedules</td>
<td>Target therapeutic dose, starting dose and dose increments</td>
</tr>
<tr>
<td>Licensed indications</td>
<td>Whether drug is licensed for newly-diagnosed and/or refractory partial epilepsy, as mono- and/or add-on therapy</td>
</tr>
<tr>
<td>Drug-specific proportions</td>
<td>Proportion expected to experience each of the 4 main outcomes on each of the old and new drugs considered</td>
</tr>
<tr>
<td>Time spent in each outcome</td>
<td>Survival distribution for time to discontinuation or planned withdrawal</td>
</tr>
<tr>
<td>Proportions withdrawing treatment, using add-on therapy, etc.</td>
<td>Proportions moving into secondary states from ‘partial efficacy’ and ‘seizure freedom’</td>
</tr>
<tr>
<td>QoL and utilities</td>
<td>Utility weights specific to this population and for each main outcome</td>
</tr>
<tr>
<td>Costs</td>
<td>Costs of drugs; and cost of management for each outcome</td>
</tr>
</tbody>
</table>

All costs and QoL effects in the model are discounted at the rate of 6% and 1.5%, respectively.

**Summary of model parameters**

A list of the parameters upon which data are required is given in Table 45. Further details on how these parameters were estimated for the model are given in subsequent sections of this report.

**Drug sequences compared in the analysis**

Clearly, each patient can potentially be subject to many different treatments during their time in the model, depending on the success or otherwise of current (and past) treatment. In order to reflect this complexity, the analysis considers a
The predefined sequence for the use of drugs and drug combinations. The sequences modelled are based on published prescribing guidance in childhood epilepsy, and advice from our clinical experts. In addition, despite the widespread use of AEDs outside of their licensed indication in childhood, we have only considered the use of drugs within licence. This is in line with restrictions on the scope of the NICE appraisal process, but our decision to restrict the scope of the modelling was due to the lack of RCT data in non-licensed indications.

First, we defined a ‘no new drug’ strategy of monotherapy and add-on therapies for the situation where the newer AEDs were not available. This is shown in Figure 4.

| Monotherapy | Add-on therapy
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Valproate and carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Valproate and phenytoin</td>
</tr>
<tr>
<td>Valproate</td>
<td>Valproate and drug X</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin and carbamazepine</td>
</tr>
<tr>
<td>Drug X</td>
<td>Phenytoin and valproate</td>
</tr>
<tr>
<td></td>
<td>Phenytoin and drug X</td>
</tr>
<tr>
<td></td>
<td>Drug X and carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Drug X and valproate</td>
</tr>
<tr>
<td></td>
<td>Drug X and phenytoin</td>
</tr>
</tbody>
</table>

*Drug only used in combination if, in earlier use in this patient, it was not associated with unacceptable side-effects or unacceptable efficacy.

All patients initially receive carbamazepine as monotherapy; those in outcome states 1, 2 or 3 then move on to sodium valproate, again as monotherapy. Failure on this will then lead either to a third monotherapy (i.e. phenytoin) or a combination involving valproate and either carbamazepine (if, and only if, carbamazepine was partially effective and well tolerated as a monotherapy) or phenytoin. For each patient in the model, a tracker variable monitors whether or not drugs used as monotherapies (earlier in the sequence) are partially effective (i.e. if outcome state 3 is experienced). If this is the case then the drug will be available for use as combination; otherwise any combination involving the drug is avoided. The fourth-line monotherapy for the base case is an unspecified generic older AED that...
has features of carbamazepine, valproate and phenytoin. If a patient exhausts all of the named drugs in the sequence then they will switch to another unspecified generic older AED. How the newer drugs enter the patient pathway (shown in Figure 3) to allow comparison with the ‘no new drug strategy’ is described in the section ‘Drug-specific proportions (for main outcome state)’ (p. 78).

Quality of life for children with epilepsy

The model seeks to compare the predicted outcomes of different prescribing strategies using older and newer agents, and takes into account effects on HRQoL in order that QALYs might be estimated. In the model we have made the assumption that the QoL associated with a particular outcome (e.g. partial efficacy and tolerable side-effects) is independent of the particular AED being used.

One of the principal difficulties we faced in this project was that we do not have access to data on HRQoL for children in a form that we require for the modelling work. For use in adult populations, generic utility-based HRQoL instruments (such as the EuroQol EQ-5D) have been developed that provide both a description of health but also information on how, in general, people value particular health states. Such utility measures can be used in economic analyses where the focus is on treatments for adult patient groups, but they have not been designed for use with children.

We searched for and identified many studies that have investigated the issue of QoL in epilepsy.12,127–226 A consistent finding is that epilepsy is associated with poorer academic performance and children with epilepsy score significantly lower on average on measures of intelligence, psychomotor speed, memory and behaviour. However, these studies do not provide the sort of information we require because they

- have either been conducted in adult populations exclusively (and we do not wish to rely solely on adult data for our review)
- have either used qualitative approaches, thereby not allowing a quantitative assessment of HRQoL
- have either used instruments that provide quantitative scores but not on a generic ‘utility-based’ scale.

The literature strongly supports the view that adult QoL estimates are wholly inadequate for modelling the experience of children with epilepsy. For example, complete seizure avoidance is reported to be of major importance in adult life given the adverse consequences of seizures for everyday activities such as holding a driver’s licence. The issue of drug side-effects associated with adverse impacts on educational achievements is viewed by some as a major issue in childhood. Hence, our aim was to explore the extent to which data relating to children with epilepsy might differ from those relating to adults.

Ideally, primary research would be conducted involving children and their parents. However, we were not in a position to conduct such work within the timescale and resources available. Given this, we sought views from clinical experts with experience in the care of children with epilepsy. In order, simply, to give us some QoL information for use in our analyses, we asked these experts to complete a modified version of the EuroQol EQ-5D instrument.227 This is an important area where data are lacking and we urge the Appraisal Committee to exercise appropriate caution in their interpretation of these results.

We approached 22 experts in paediatric neurology and asked them to consider six broadly defined outcomes of treatment for epilepsy in childhood (including no treatment) that related to states in our model:

- The patient experiences unacceptable side-effects of the drug (that cannot be controlled by adjusting the dose) such that the drug will be withdrawn (AES).
- After an adequate trial of the drug, the patient still experiences an unacceptable frequency of seizures such that a change of therapy will be initiated and the drug withdrawn (i.e. not considered to be having sufficient beneficial effect) (USF).
- The patient experiences an acceptable reduction in frequency of seizures and acceptable side-effects, such that the drug is continued (PAR).
- The patient experiences seizure freedom and acceptable side-effects, such that the drug is continued (EFFd).
- The patient experiences seizure freedom following withdrawal of a successful drug or successful surgery (EFFw).
- The patient is not seizure free but prefers to remain untreated (UNT).

Clinical experts were asked to consider how good or bad each state is for an average child with focal epilepsy, between the ages of 7 and 12 years, and with no motor impairments. Separate responses
were requested for children with moderate learning difficulties and children without such difficulties.

The first task was simply to rank the states, separately for a child with or without moderate learning difficulties. The second task was to classify each state using the EuroQol EQ-5D health state descriptor (modified slightly to consider childhood issues), again separately for a child with or without moderate learning difficulties. An example of the questions asked is shown in Appendix 12. The health states described were converted into ‘utility’ scores (on a 0–1 scale) using the MVH A1 tariff (derived from a TTO survey of the general population of the UK228).

The model provides an estimate of the time spent in each health state for all simulated patients. These time estimates were adjusted to reflect the QoL associated with each state, using the mean health state utility score from the data provided by the clinical experts, summarised in Table 46.

### Table 46: EuroQol EQ-5D states and scores for the six epilepsy model states (without learning difficulties)

<table>
<thead>
<tr>
<th>Health states</th>
<th>Utility values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (SD)</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Unacceptable side-effects (AES)</td>
<td>0.767 (0.1825)</td>
</tr>
<tr>
<td>Unacceptable efficacy (USF)</td>
<td>0.782 (0.1972)</td>
</tr>
<tr>
<td>Partial efficacy and partial side-effects (the drug is continued) (PAR)</td>
<td>0.908 (0.1144)</td>
</tr>
<tr>
<td>Seizure freedom and acceptable side-effects (the drug is continued) (EFFd)</td>
<td>0.981 (0.0525)</td>
</tr>
<tr>
<td>Seizure freedom following withdrawal (EFFw)</td>
<td>1.000 (0.0000)</td>
</tr>
<tr>
<td>Untreated state (UNT)</td>
<td>0.846 (0.1375)</td>
</tr>
</tbody>
</table>

* The Borda ranking score is a point-count system that provides each state with a score equal to the total number of times that a state is ranked over another minus the total number of times that state is ranked under another.

### Table 47: EuroQol EQ-5D states and scores for the six epilepsy model states (with learning difficulties)

<table>
<thead>
<tr>
<th>Health states</th>
<th>Utility values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (SD)</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Unacceptable side-effects (AES)</td>
<td>0.603 (0.2416)</td>
</tr>
<tr>
<td>Unacceptable efficacy (USF)</td>
<td>0.675 (0.1830)</td>
</tr>
<tr>
<td>Partial efficacy and partial side-effects (the drug is continued) (PAR)</td>
<td>0.782 (0.09)</td>
</tr>
<tr>
<td>Seizure freedom and acceptable side-effects (the drug is continued) (EFFd)</td>
<td>0.830 (0.1016)</td>
</tr>
<tr>
<td>Seizure freedom following withdrawal (EFFw)</td>
<td>0.857 (0.1000)</td>
</tr>
<tr>
<td>Untreated state (UNT)</td>
<td>0.707 (0.1938)</td>
</tr>
</tbody>
</table>
(without learning difficulties) and Table 47 (with learning difficulties). This allowed calculation of an individual QALY score for each simulated patient in the model.

Costs associated with care for children with epilepsy
The analysis of costs has been undertaken from the perspective of the NHS, so costs incurred by patients and costs falling on other agencies have not been included in the analysis. Given that costs are incurred over the course of a child’s treatment, which can happen over many years, discounting for the timing of costs was undertaken at the rate of 6%.

There are two principal components to the cost analysis:

- costs associated with drug therapy (and monitoring related to such therapy)
- other more general resource use and costs associated with a diagnosis of epilepsy and time spent in each of the model states.

The drug cost information and the dose information is reported in Table 48.

Data on the more general NHS resources associated with model states were gathered from a questionnaire completed by 18 clinical experts experienced in providing care for children with epilepsy. The questionnaire asked for the average use of services that would be expected for an average child within each health state. In line with the definition used in the QoL questionnaire, the experts were asked to consider an average child with focal epilepsy, between the ages of 7 and 12 years, and with no motor impairments. Data were gathered separately for the situation of a child with and a child without moderate learning difficulties. The resource use data for each state relate to the full breadth of treatment that a patient may have received in the time leading up to being in the health state in question (e.g. monitoring of patient during titration period of drug). The resource items upon which data were collected included: GP consultations, outpatient consultations, A&E visits, telephone calls to clinical departments from patients (and family) for advice and inpatient stays.

Average cost data are presented in Table 49 for children with and without learning difficulties.

Time spent in each model outcome
Time to withdrawal due to side-effects or poor efficacy
We identified several related population-based cohort studies which had attempted to estimate treatment retention for several newer AEDs and to examine the factors which influence treatment retention.229–232

These studies were all conducted to a high standard. Patients were identified retrospectively, but care was taken to exclude those who had started treatment with the newer AED outside the centre, avoiding referral and survival bias. Differences in drug doses were accounted for by

---

**TABLE 48 Costs associated with all AEDs considered in the model**

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Cost per mg (pence)</th>
<th>Titration dose (per day)</th>
<th>Maintenance dose (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newer AEDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0.0023</td>
<td>Age &gt; 12 years: 20 mg/kg</td>
<td>Age &gt; 12 years: 30 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: 275 mg</td>
<td>Others: 1100 mg</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0.016</td>
<td>Age &lt; 12 years: 1.5 mg/kg</td>
<td>Age &lt; 12 years: 3 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: 75 mg</td>
<td>Others: 150 mg</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0.0013</td>
<td>20 mg/kg</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0.0146</td>
<td>2 mg/kg</td>
<td>7 mg/kg</td>
</tr>
<tr>
<td><strong>Older AEDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.00028</td>
<td>200 mg/day</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>0.00028</td>
<td>Up to 20 kg: 20 mg/kg</td>
<td>Up to 20 kg: 20 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Over 20 kg: 30 mg/kg</td>
<td>Over 20 kg: 35 mg/dkg</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.00089</td>
<td>6 mg/kg</td>
<td>6 mg/kg</td>
</tr>
</tbody>
</table>

* These unit costs are taken from the BNF (September 2002).
using ‘defined daily doses’ to establish the relative dose levels for each drug, although these were not adjusted fully for concomitant medications (which will affect target doses).

Unfortunately, cohort studies of this type cannot be used to compare drugs directly and none of these studies report information on time to withdrawal due to specific reasons, although proportions withdrawing for various reasons are reported. There are, however, some useful general points which arise from these studies.

Remission rates in these (highly) refractory populations are low; 1–3% had been in complete remission for 6 months prior to being included in the studies.

Long-term treatment retention in this population is disappointing. For partial epilepsies retention rates are 50–60% at 1 year, 50–40% at 3 years and 10–20% at 5 years.

Higher maintenance doses are associated with lower drop-out for both adverse effects and lack of effectiveness, suggesting that higher doses achieved by those who tolerate the drugs well may result in better seizure control. Wong and colleagues reported that higher starting doses of lamotrigine resulted in worse treatment retention, reflecting the need for careful dose titration.

Wong and colleagues noted that 6% of patients had experienced a worsening of seizures on lamotrigine; most of these were discontinued within 3 months and the problem resolved. This phenomenon may account to some extent for the treatment retention curves in Lhatoo and colleagues, with the lamotrigine curve dipping sharply below topiramate early on but with the difference between the two then decreasing with time. This suggests that, ideally, the rare outcome of a worsening of seizures should be dealt with as a separate outcome for the purpose of estimating treatment retention, as a worsening of seizures is likely to be established earlier in the treatment course than a failure to substantially reduce seizure rates.

The number of concomitant AEDs influenced retention rates, with patients taking more AEDs more likely to discontinue, probably reflecting both side-effects and the severity of the condition.

Lhatoo and colleagues noted that patients with learning difficulties were less likely to discontinue owing to adverse events, probably reflecting the greater difficulty in identifying events in these patients. Similarly, patients with a younger age of onset were less likely to discontinue, which might reflect less severe epilepsy in this group or greater difficulty in identifying side-effects in young children.

All studies noted higher rates of discontinuation due to adverse events than noted in RCTs of these agents, which, at least in part, is likely to reflect the extent of follow-up in RCTs compared to these cohorts. The authors also note that the two key reasons for discontinuation, adverse events and lack of effect, cannot be precisely disaggregated; a patient may discontinue a drug owing to an unsatisfactory trade-off between side-effects and effect on seizure rate.
The only alternative source of treatment retention data that we identified is from the RCTs identified for the clinical effectiveness review. Although most of the RCTs do not report treatment retention as a ‘time to event’ outcome, four of the RCTs identified for the review of clinical effectiveness report some overall treatment retention data in the form of survival distributions.

One of these has been published (twice) in abstract form only,\textsuperscript{285,233} this is a placebo-controlled trial of gabapentin in BECTS and so the data available from this trial might be of limited value in informing a model for other conditions.

The three RCTs which reported treatment retention and have been published in full all give survival curves for this end-point. All three trials are in newly diagnosed epilepsy, two including children and adult patients with partial seizures, one including children with both partial and generalised seizures.

One of these trials, by Chadwick,\textsuperscript{145} comparing vigabatrin and carbamazepine in children and adults with newly diagnosed partial epilepsy, is particularly useful, giving separate survival curves for discontinuation due to adverse events and for overall time to ‘treatment failure event’ (withdrawal due to adverse event or lack of effect). The other two trials only give a composite survival curve based on all-cause withdrawal and are therefore less useful in informing survival estimates for specific withdrawal events.

There are two problems with the Chadwick trial data. The first is that the two survival curves are based on slightly different patient populations. According to the text, the only patients excluded from the ‘safety’ analysis were lost to follow-up at the start of the trial, contributing no follow-up, and therefore should make no difference to the estimated Kaplan–Meier survival curves. However, there are some small differences in the numbers of patients ‘at risk’ over time; it is not clear how these differences could have arisen. Although the discrepancies are small, they will have some effect on the survival estimates obtained from the plots.

The second problem is that the printed plots are small, with thick lines and a small gap between the axes, making it especially difficult to obtain accurate estimates of the survival rates. Estimates were obtained by measuring from the x axis to the centre of each curve, subtracting the size of the gap between the x and y axes and dividing the result by the height at \( t = 0 \) (i.e. 100%).

It was therefore not possible to use the Chadwick paper to estimate survival distributions accurately and so we chose distributions which were both consistent with the Chadwick data and which accorded with clinical advice, that is, that unacceptable side-effects will tend to lead to discontinuation earlier than discontinuation due to lack of effectiveness, often within the titration period, and that the majority of patients would discontinue by 1 year due to lack of effect. The distributions are both Weibull distributions with shape and location parameters 0.8 and 2.0 for side-effects and 1.2 and 6.0 for lack of effect. These are plotted in Figure 5.

**Time on treatment which is partially effective or gives complete freedom from seizure**

It is assumed that patients will continue on drugs which are beneficial with acceptable side-effects, but that at some point later on there will be further decisions to be made which may include discontinuation of the drug for various reasons (Figure 3). In the absence of better information, we have assumed that the time to make a change in treatment (switch, add-on or discontinue drug treatment) will follow a Weibull distribution with shape parameter 4 and location parameter 2; this distribution gives very few patients making a change within 6 months, with nearly two-thirds having made a change by 2 years.

We assume that patients achieving complete seizure freedom who are willing to try to withdraw from drug treatment will do so, on average, after 2 years of drug treatment.

**Drug-specific proportions (for main outcome states)**

**Proportions withdrawing early owing to side-effects or lack of efficacy**

These were estimated for each drug from the relevant RCT data available. The proportions were calculated from the trial data by obtaining the numbers withdrawing for these reasons, adjusting the sample size for other drop-outs (e.g. loss to follow-up) and for length of follow-up, to derive a predicted total proportion withdrawing for each reason.

For example, Nieto-Barrera\textsuperscript{197} reports eight and 13 patients on lamotrigine withdrawing for toxicity and lack of effect, respectively. The total sample size for this group was 158 with three patients lost to follow-up for other reasons. Assuming that these other patients were lost to follow-up at random time points during the follow-up, this gives an ‘effective sample size’ of 156.5.
Hence the proportions withdrawing owing to side-effects and lack of effect were 5.1% and 8.3%, respectively, during a follow-up period of 6 months. Based on our hypothetical treatment retention curves for these outcomes, we expect around 82% of withdrawals due to side-effects to have withdrawn by 6 months and around 63% of those withdrawing owing to lack of effect to have withdrawn by this time. Hence, we predict that the overall proportions eventually withdrawing for these reasons will be 6% and 13%, respectively.

Where a trial did not report any patients falling into a particular outcome (which is not plausible), we derived a proportion for this outcome which would be one standard deviation from zero. This solution is not unproblematic, but the alternative is to use data which we know cannot reflect the truth and which will give substantial advantage to the drugs concerned.

**Proportions achieving complete remission**

Time to achieve remission is reported by Chadwick and remission rates over time are also reported in the National General Practice Study of Epilepsy. Both publications suggest that those patients who will achieve complete remission do so quickly (usually within the titration period) and that most complete remissions are sustained in the long term. The proportions achieving complete remission will therefore be estimated from the proportions reported within the trials, on the assumption that no further complete remissions would have been achieved beyond the follow-up period of the trial and that all complete remissions would be successfully maintained while the patient remained on the drug treatment. The proportions were calculated using the numbers reported to be seizure free at the end of the trial, adjusting the sample size for losses to follow-up as previously described.

**Proportions achieving partial efficacy with acceptable side-effects**

This proportion is assumed to include all the remaining patients, that is, those who did not withdraw for adverse events or lack of efficacy and did not achieve complete seizure freedom.

**Drug-specific proportions entering each outcome at different stages of treatment**

The RCT data available for this model consist of a single trial for each newer drug used as add-on therapy in more or less refractory populations (but with insufficient data available from the trial using tiagabine), and a single trial using lamotrigine as first-line therapy in these patients; two trials of newer agents used carbamazepine as first-line monotherapy. Although oxcarbazepine is also licensed for use as monotherapy, the only RCT we
identified using oxcarbazepine monotherapy was based on a mixed patient population and therefore the results are not appropriate to populate this model. There are data for vigabatrin both as first-line monotherapy and as later add-on therapy, but current advice regarding the use of vigabatrin (except in infantile spasms) is that it should be considered only as a treatment of last resort owing to troublesome side-effects, particularly visual field defects.

The structure of this model allows different therapies to be introduced at a number of different stages, and so we need to be able to estimate the appropriate proportions to apply at different stages (i.e. after variable numbers of ‘failed’ treatments).

We used the RCT data available as ‘anchor points’, shown in Table 50 (marked in bold). The trials of add-on therapy all included patients with variable disease history, but the performance of placebo in these trials is broadly similar and so we have assumed that the trial data are reasonably representative of what will occur at fourth-line treatment.

Lamotrigine is the only agent for which we have trial data at two different time points, as first-line monotherapy and later use as add-on. This is a very sparse data set upon which to base assumptions about the changing effectiveness of AEDs as the patients become more heavily pretreated and more refractory to treatment. However, they are the best data that we have within the scope of this research. The proportions withdrawing owing to toxicity are very similar in the two lamotrigine trials, as are the proportions withdrawing owing to lack of effect. We have therefore kept these parameters constant across all stages for all drugs. Reducing the proportion achieving complete seizure freedom by a constant factor of 0.4 is consistent with the lamotrigine data, allowing for a small increase in efficacy when the drug is used in combination as compared with monotherapy.

The data for first-line carbamazepine monotherapy are based on the trial data from Nieto-Barrera, 2001197 and Zamponi, 1999198 combined (the results for carbamazepine for both trials are similar). Meta-analyses of the older drugs123,129 suggest that they are of similar effectiveness with some differences in toxicity, with the order of preference being carbamazepine, valproate, phenytoin and others. On the assumption that this is a rational order of preference, we have based estimates for valproate, phenytoin and a ‘generic older drug’ on a slight increase in toxicity and a slight decrease in effectiveness by comparison with the drug immediately before it in the sequence; we used a constant multiplier of 1.05 for withdrawal due to side-effects and lack of efficacy and 0.95 for complete seizure freedom to derive estimates for valproate, phenytoin and a ‘generic older drug’. Adjustments to toxicity and effectiveness were made in order to derive data for the older agents used in combination rather than as monotherapy; the multipliers used here were based on the differences in these proportions in the lamotrigine data.

This allowed us to build the data shown in Table 50, but it should be stressed that the trial data are very sparse and the means by which we filled in the gaps where there are no trials are essentially arbitrary.

**Proportions moving into secondary model states**

Table 51 shows the proportions that we used for the various decisions taken after the four main outcomes used in the model have occurred, with average time on drug also given where this is relevant.

These figures are based on the very limited literature that is available but, in truth, are more or less arbitrary (at the moment). Further work is being undertaken to improve these estimates where possible and clinical opinion will be sought on this.

The assumption has been made that these proportions do not vary by whether the patient has learning disabilities and are independent of patient age. In addition, the time to try alternative treatment strategy (after partial response) may vary over cycles.

**Methods of analysis**

The model was constructed and run using TreeAge DATA Professional (release 6). The results are based on a Monte Carlo simulation with a sample of 10,000 simulated patients.

Initially the model was run for the ‘no new drug’ sequence, and the costs and QALYs associated with this sequence were estimated.

The policy change considered was the introduction of each of the new drugs in turn, in line with its licensed indications.
TABLE 50  Proportions moving into the main model outcome states ('anchor points' marked in bold)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
<th>Third-line treatment</th>
<th>Fourth-line +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>SD</td>
<td>Proportion</td>
<td>SD</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>USE</td>
<td>0.113</td>
<td>0.029</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.107</td>
<td>0.029</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.153</td>
<td>0.529</td>
<td>0.679</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.626</td>
<td>0.047</td>
<td>0.250</td>
</tr>
<tr>
<td>Valproate</td>
<td>USE</td>
<td>0.119</td>
<td>0.119</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.119</td>
<td>0.119</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.174</td>
<td>0.531</td>
<td>0.673</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.595</td>
<td>0.238</td>
<td>0.095</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>USE</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.119</td>
<td>0.119</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.192</td>
<td>0.531</td>
<td>0.666</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.565</td>
<td>0.226</td>
<td>0.090</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>USE</td>
<td>0.062</td>
<td>0.019</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.131</td>
<td>0.027</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.238</td>
<td>0.579</td>
<td>0.716</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.569</td>
<td>0.040</td>
<td>0.091</td>
</tr>
<tr>
<td>Valproate + old</td>
<td>USE</td>
<td>0.131</td>
<td>0.131</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.105</td>
<td>0.105</td>
<td>0.105</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.110</td>
<td>0.503</td>
<td>0.660</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.654</td>
<td>0.262</td>
<td>0.105</td>
</tr>
<tr>
<td>Phenytoin + old</td>
<td>USE</td>
<td>0.137</td>
<td>0.137</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.110</td>
<td>0.110</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.131</td>
<td>0.504</td>
<td>0.653</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.622</td>
<td>0.249</td>
<td>0.099</td>
</tr>
<tr>
<td>Generic old drug</td>
<td>USE</td>
<td>0.131</td>
<td>0.131</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.124</td>
<td>0.124</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.208</td>
<td>0.530</td>
<td>0.659</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.537</td>
<td>0.215</td>
<td>0.086</td>
</tr>
<tr>
<td>Gabapentin + old</td>
<td>USE</td>
<td>0.081</td>
<td>0.025</td>
<td>0.081</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.266</td>
<td>0.041</td>
<td>0.266</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.252</td>
<td>0.492</td>
<td>0.588</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.401</td>
<td>0.015</td>
<td>0.160</td>
</tr>
<tr>
<td>Lamotrigine + old</td>
<td>USE</td>
<td>0.069</td>
<td>0.026</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.123</td>
<td>0.033</td>
<td>0.123</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.186</td>
<td>0.560</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.622</td>
<td>0.020</td>
<td>0.249</td>
</tr>
<tr>
<td>Oxcarbazepine + old</td>
<td>USE</td>
<td>0.143</td>
<td>0.030</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.062</td>
<td>0.014</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.225</td>
<td>0.567</td>
<td>0.704</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.570</td>
<td>0.016</td>
<td>0.228</td>
</tr>
</tbody>
</table>
Our plan was to consider the two new AEDs licensed as monotherapies for use in children: lamotrigine (for use in children over 12 years old) and oxcarbazepine (for use in children over 6 years old). However, no data were available for the use of oxcarbazepine as monotherapy and so the focus for monotherapy use was exclusively lamotrigine. This drug was considered as first-line monotherapy and second-line monotherapy, after carbamazepine had failed. The costs and QALYs for the average patient were calculated for this monotherapy strategy. This then allowed the incremental cost (i.e. the cost of the new drug monotherapy strategy minus the cost of the ‘no new drug’ strategy) and the incremental QALYs (i.e. the QALYs for the new drug monotherapy strategy minus the QALYs for the ‘no new drug’ strategy) to be calculated.

The newer AEDs that can be used as add-on therapies are lamotrigine, gabapentin, topiramate, oxcarbazepine and tiagabine. Vigabatrin is licensed for use as an add-on therapy in partial epilepsy but is recommended for use only as a treatment of last resort owing to problematic side-effects; we therefore did not include it in this analysis. Each new drug was considered for use as the first choice add-on therapy following a decision to switch from monotherapy. Owing to lack of data, we were not able to consider tiagabine in our analysis. The costs and QALYs for the average patient were calculated for these five add-on strategies, again allowing the incremental cost and the incremental QALYs to be calculated.

To summarise, the strategies for which results are presented in this report are:

- ‘no new drug’ strategy
- first-line use of lamotrigine as monotherapy
- second-line use of lamotrigine as monotherapy
- use of lamotrigine as first-choice add-on therapy

### TABLE 50 Proportions moving into the main model outcome states (‘anchor points’ marked in bold) (cont’d)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
<th>Third-line treatment</th>
<th>Fourth-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>SD</td>
<td>Proportion</td>
<td>SD</td>
</tr>
<tr>
<td>Topiramate + old</td>
<td>USE</td>
<td>0.120</td>
<td>0.044</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>UE</td>
<td>0.190</td>
<td>0.044</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>0.010</td>
<td>0.377</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.680</td>
<td>0.034</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Tiagabine + old No data available from RCTs identified for the review
Oxcarbazepine No data available from RCTs identified for the review
CSF, seizure freedom and acceptable side-effects; PE, partial efficacy and acceptable side-effects; UE, unacceptable efficacy; USE, unacceptable side-effects.

### TABLE 51 Proportions moving into secondary model states

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
<th>Fourth-line and beyond (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unacceptable efficacy</td>
<td>Try another drug</td>
<td>90</td>
<td>95</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>No further drugs</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Unacceptable side-effects</td>
<td>Try another drug</td>
<td>90</td>
<td>95</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>No further drugs</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Partial efficacy, acceptable side-effects</td>
<td>Continue</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Add-on</td>
<td>0</td>
<td>30</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>No further drugs</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Try different drug</td>
<td>90</td>
<td>60</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Seizure freedom, acceptable side-effects</td>
<td>Continue indefinitely</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Withdraw unsuccessfully</td>
<td>50</td>
<td>50</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Withdraw successfully</td>
<td>50 at 2 years</td>
<td>50 at 2 years</td>
<td>45 at 2 years</td>
<td>40 at 2 years</td>
</tr>
</tbody>
</table>

*10% not going on to any further drug treatment chosen to approximate proportion going on to have successful surgery.*
use of gabapentin as first-choice add-on therapy
use of topiramate as first-choice add-on therapy
use of oxcarbazepine as first-choice add-on therapy.

For all strategies except the first-line use of lamotrigine, we decided to exclude the costs and QALYs accrued by patients successfully treated with carbamazepine. The reason for this is that these costs and effects are common to both the ‘no new drug’ strategy and the new drug strategies (when the new drugs are not used as first line) but add noise to the comparison of strategies. Hence the estimates of costs and effects presented for these strategies are estimates from the point of failure on carbamazepine.

Where first-line use is considered, the results for this analysis consider the costs and QALYs for patients from the point of initiation of drug therapy for epilepsy. The ‘no new drug’ strategy was then re-run to allow the incremental calculation of costs and effects to use comparable strategies.

Small differences in costs and effects between strategies were expected, given the results from the trial evidence. Runs of 10,000 simulated patients were used and these were repeated 20 times for each strategy to give some indication of the sampling variability in the results.

The comparison of the 20 mean estimates of the cost and QALY scores for each new drug with the 20 mean estimates for the baseline ‘no new drug’ strategy give a total of 400 estimates of the incremental cost, incremental QALY score and ICER. These are reported graphically as scatters on the cost-effectiveness plane and uncertainty in the appropriate threshold value of the ICER is explored using cost-effectiveness acceptability curves (CEACs).

**Drug retention rate**

For each of the drug strategies considered, costs and QoL effects are estimated for the time spent on each health state. Logically, it can be inferred that the longer a patient spends on a drug (or drug combination), then the more that drug is deemed to be effective and acceptable in terms of the efficacy and side-effect profile. Figure 6 displays the retention rate for each of the add-on therapy strategies considered in the model. Figure 7 displays the retention rate for each of the monotherapy strategies considered. It is clear from these diagrams that over 5 years, a similar proportion of patients in the different drug therapies have withdrawn from the first-choice add-on therapy and from each of the monotherapy strategies.

A similar analysis compares the average time on each model outcome across each of the treatment strategies. Again, logic can infer that the longer a patient spends on outcome 4 within the model then the more that drug has deemed to have...
achieved seizure freedom and acceptable side effects. Figures 8 displays the average time on each model outcome for each treatment strategy; the diagram clearly demonstrates that there is little difference between strategies.

**Cost-effectiveness results**

The results of the 20 runs of the baseline analysis for the ‘no new drug’ strategy are reported in Table 52. The expected total cost of caring for the average child diagnosed with epilepsy, managed according to the drug therapy strategy outlined in Figure 4, is just under £3000 (from the age of diagnosis through to 18 years of age). This includes both the cost of the drugs plus the costs of other health service resources. Such a patient is expected to experience just under 6.6 QALYs from this strategy, again through to the time when they reach the age of 18 years. As expected, when we focus on patients who fail on the first monotherapy (i.e. carbamazepine) and count costs and QALYs from the point of failure, the mean cost estimate is slightly lower and the mean QALY estimate is substantially lower (i.e. about 3.6 QALYs).

The incremental analysis always used the ‘no new drug’ strategy as the point of comparison. The results of the incremental analyses are reported in Figure 9 and Table 52 (the detailed results for each of the 20 runs of the model for each strategy are reported in Appendix 14). For all strategies, the incremental cost is clearly positive.

The analysis that considered the use of lamotrigine as monotherapy (either first- or second-line) produced results indicating a positive incremental cost. The results show that for some runs of the model the incremental QALY estimate is positive (indicating health benefits from the use of lamotrigine) and for other runs the incremental QALY estimate is negative. There is no strong evidence from this analysis that monotherapy use of lamotrigine is associated with important health benefits.

For the analyses looking at the use of the newer AEDs as add-on therapies, the findings in terms of incremental costs and the incremental QALY scores are similar to the results for lamotrigine monotherapy. Positive incremental costs are found and a mixture of positive and negative incremental QALY estimates. Therefore, there is no strong evidence from this analysis that add-on therapy use of the new drugs considered is associated with important health benefits.

**Conclusions**

The model that we have presented in this report has strengths and weaknesses. We have constructed an individual sampling model that considers simulated children over their childhood from the age at diagnosis through to 18 years. A particular advantage of this approach is that a cohort of patients can then be considered,
**FIGURE 8** Average time in model outcomes for all treatment strategies. $T_{out1}$, time with unacceptable side-effects; $T_{out2}$, time with unacceptable efficacy; $T_{out3}$, time with partial efficacy and acceptable side-effects; $T_{out4}$, time with seizure freedom and acceptable side-effects.

**TABLE 52** Baseline (‘no new drug’ strategy) results for 20 runs of the model

<table>
<thead>
<tr>
<th>Costs and QALYs accrued from diagnosis of epilepsy</th>
<th>Costs (£)</th>
<th>QALYs</th>
<th>Costs (£)</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>1</td>
<td>2320</td>
<td>1953</td>
<td>6.6352</td>
<td>3.6456</td>
</tr>
<tr>
<td>2</td>
<td>2327</td>
<td>2025</td>
<td>6.5936</td>
<td>3.131</td>
</tr>
<tr>
<td>3</td>
<td>2360</td>
<td>2029</td>
<td>6.6591</td>
<td>3.6043</td>
</tr>
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<td>4</td>
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</tr>
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<td>1971</td>
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</tr>
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<td>6</td>
<td>2343</td>
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</tr>
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<td>7</td>
<td>2288</td>
<td>1895</td>
<td>6.556</td>
<td>3.6436</td>
</tr>
<tr>
<td>8</td>
<td>2292</td>
<td>1963</td>
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</tr>
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<td>9</td>
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<td>3.6565</td>
</tr>
<tr>
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<td>2297</td>
<td>1964</td>
<td>6.5271</td>
<td>3.6643</td>
</tr>
<tr>
<td>12</td>
<td>2328</td>
<td>1966</td>
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<td>3.6305</td>
</tr>
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<td>2023</td>
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<td>3.6554</td>
</tr>
<tr>
<td>14</td>
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<td>2049</td>
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</tr>
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<td>2281</td>
<td>1896</td>
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</tr>
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<td>17</td>
<td>2341</td>
<td>1999</td>
<td>6.6276</td>
<td>3.6267</td>
</tr>
<tr>
<td>18</td>
<td>2327</td>
<td>2020</td>
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<td>3.6288</td>
</tr>
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<td>19</td>
<td>2318</td>
<td>1992</td>
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<td>3.6568</td>
</tr>
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<td>20</td>
<td>2297</td>
<td>1956</td>
<td>6.6225</td>
<td>3.6644</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs and QALYs accrued from time of failure on carbamazepine</th>
<th>Costs (£)</th>
<th>QALYs</th>
<th>Costs (£)</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run out1</td>
<td>Mean</td>
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FIGURE 9 Results for each new drug reported on cost-effectiveness (CE) planes
comprising individuals with a mix of personal characteristics. In the results we report here the cohorts include patients who vary in terms of the age at diagnosis (from 3 to 18 years), their sex and whether or not they experience learning difficulties. Other appropriate personal characteristics (for which data are available) could easily be incorporated into the model. The model does not work with a fixed cycle time, as would be required by a Markov process. The time spent in outcome states is sampled from distributions for every simulated patient. An assumption is made that longer durations in states with reasonable efficacy and side-effect profiles represent a positive outcome.

Drug sequences, and the introduction of the newer AEDs into an existing drug sequence, are explicitly considered. This mirrors clinical practice where, for patients not experiencing efficacy or experiencing unacceptable side-effects, new drugs (either as monotherapy or add-on therapy) will be introduced. However, additional variations in the sequences might be modelled. For example, the newer AEDs might be considered as last-resort therapy only; this scenario has not been considered in the analysis reported here. Drug sequences have been defined considering the use of all AEDs within their licence only. However, it is widely recognised that in childhood there is considerable use of AEDs outside of their licensed indications.

A weakness in the model is its limited scope, which results largely from data limitations. It does not consider the effect of AEDs on the likelihood of patients being referred for surgery, being re-diagnosed as not having epilepsy and mortality. The structure of the model is capable of accommodating all of these issues.

The results of the incremental analysis can be used to construct cost-effectiveness acceptability curves (CEACs) (Figure 10) for each new drug strategy. These indicate that, for a willingness to pay of £150,000 per QALY, the probability that any of the newer drugs is cost-effective is less than 50%.

Other limitations of the analysis reported here that should be highlighted are as follows:

- One of the more concerning data limitations that faced us related to the lack of reliable data on QoL issues in children (that can be used in a cost-utility analysis).
- The model currently assumes that the time in the outcome states (and the QoL experienced whilst in those states) is independent of the drug used. It is the likelihood of entering the states that varies by the AEDs.
An optimal prescribing strategy for children with epilepsy would improve outcomes for the patients, families and carers, and might reduce the burden on other services. However, it is clear from the available evidence that the differences between the various AEDs are small. What differences there are appear mainly in the trade-off between tolerability and effectiveness, with older drugs appearing generally more effective but with a less favourable side-effect profile. Further research, specific to the various epilepsy syndromes of interest, would be needed to determine how different prescribing choices might affect outcomes for other parties.

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 much smaller population with intractable epilepsy, who experience little or no benefit after trying a number of different treatments. For the latter group (that might be of the order of 20% of pediatric epilepsy patients attending a district general hospital), 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 is desirable that as many treatment options as possible remain available for this small group of patients. The cost of using the newer agents as a last resort for these patients is likely to be small, owing to the low 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.
Chapter 6

Discussion

Clinical effectiveness
The quality of the 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 on which to base a rational prescribing strategy.

Twenty trials were identified which reported outcome data for children with epilepsy; 18 of these were conducted exclusively in children. For each of the epilepsy subtypes considered in these RCTs (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 newer agents do not appear any more effective than older agents but seem to be better tolerated. 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 evidence to suggest that the newer agents should be considered as a first-choice treatment in any form of epilepsy in children.

Cost-effectiveness
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 a sufficient quantity and quality of trial data to inform a model. The model was based on a complex patient pathway which attempted to reflect the variety of treatment decisions made and outcomes experienced by patients treated for epilepsy in childhood. Even with a relatively simplified pathway and straightforward prescribing strategy, the complexity of the disease requires a large number of parameters to be estimated. Some parameters are specific to the drugs considered whereas others relate to more general clinical decisions, prognosis following different outcomes and patient preferences. 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 model was based on an individual patient sampling procedure, so the results obtained are subject to some random variation. We therefore obtained several sets of results for each scenario where a newer agent was introduced into the prescribing strategy. 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.

Assumptions, limitations and uncertainties
There are a number of assumptions and limitations in the decision-analytic model. We have not explicitly modelled the impact of surgery or other non-drug treatments or the effect of patients who have been misdiagnosed. Our model attempts to model a reasonable spread of ‘good clinical practice’, with respect to changes in treatment and the use of monotherapy or polytherapy, but there is no clear consensus regarding good clinical practice. Reports of clinical audits or population-based cohorts are of some use in determining what happens in practice, but the consensus is shifting and so these reports are of limited use in defining current practice, which is shifting away from overtreatment and the widespread use of polytherapy towards a preference for monotherapy unless there are clear reasons to add on rather than switch treatments.

The evidence base for AEDs, both newer and older agents, is weak; there are very few trials, a
number of methodological difficulties with most of the trials, few comparative trials against older AEDs and none comparing the newer AEDs with each other in children. In addition, the complexity of the model provides for many different patient pathways, each one subject to its own uncertainties in the parameters used. In these circumstances, obtaining an accurate estimate of cost-effectiveness is not a plausible aim, and we have attempted here only to quantify some of the uncertainty surrounding the true value.

**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 adequately to inform parameter values with respect to epidemiology and clinical practice.
Chapter 7

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.
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The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3–6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost–utility analysis) of the intervention.

Contribution of the authors
Josie Sandercock (Senior Reviewer) directed the review, assisted with the review of effectiveness, contributed to development of the decision-analytic model, wrote sections of the report.

Martin Connock (Systematic Reviewer) led the review of effectiveness, extracted data and wrote sections of the report.

Stirling Bryan (Senior Health Economist) helped direct the review, assessed industry models, conceived, developed and analysed the decision-analytic model, and wrote sections of the report.

Beti-Wynn Evans (Systematic Reviewer) developed and piloted the data extraction form, extracted data, and wrote sections of the report.

Emma Frew (Health Economist) assessed industry models, conceived, developed and analysed the model, and wrote sections of the report.

Anne Fry-Smith (Information Specialist) performed literature searches, and wrote sections of the report.

Carole Cummins (Paediatric Trials Adviser) wrote sections of the report and, advised on paediatric aspects of the report.

Alain Li Wan Po (Pharmacological Adviser) wrote sections of the report and, advised on pharmacology.
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M Connock, E Frew, B-W Evans, S Bryan, C Cummins, A Fry-Smith, A Li Wan Po and J Sandercock

March 2006