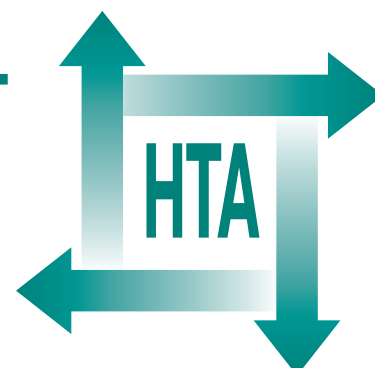# The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review

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

March 2006

**Health Technology Assessment
NHS R&D HTA Programme**

HTA

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

M Connock,[1] E Frew,[2] B-W Evans,[3] S Bryan,[2] C Cummins,[4] A Fry-Smith,[1] A Li Wan Po[5] and J Sandercock[1]*

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

* Corresponding author

Declared competing interests of authors: none

NHS R&D HTA Programme

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

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

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

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

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

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Peter Davidson, Dr Chris Hyde, Dr Ruairidh Milne,
                        Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

Abstract

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

M Connock,[1] E Frew,[2] B-W Evans,[3] S Bryan,[2] C Cummins,[4] A Fry-Smith,[1] A Li Wan Po[5] and J Sandercock[1*]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK

[2] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK

[3] Department of Medicine Management, Keele University, UK

[4] Institute of Child Health, Birmingham, UK

[5] Centre for Evidence-Based Pharmacotherapy, Aston University, Birmingham, UK

* Corresponding author

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.

Data sources: Electronic databases. Drug company submissions.

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.

Contents

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.

Glossary

Computed tomography   A non-invasive imaging technique using X-rays to produce pictures as though they were successive slices through the body.

Cytochrome P monooxygenase   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.

Electroencephalogram   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.

Magnetic resonance imaging   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.

Positron emission tomography   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.

Single photon emission computed tomography   SPECT imaging involves the rotation of a photon detector array around the body to acquire data from multiple angles.

List of abbreviations

A&E	accident and emergency		ICER	incremental cost-effectiveness ratio
ACTH	adrenocorticotrophic hormone		ILAE	International League Against Epilepsy
AED	antiepileptic drug			
ARIF	Aggressive Research Intelligence Facility		ITT	intention-to-treat
			JME	juvenile myoclonic epilepsy
BECTS	benign (partial) epilepsy with centrotemporal (rolandic) spikes		MHD	monohydroxy derivative
			MRI	magnetic resonance imaging
CAE	childhood absence epilepsy		NGPSE	National General Practice Study of Epilepsy
CCTR	Controlled Clinical Trials Register (Cochrane)		NICE	National Institute for Health and Clinical Excellence
CI	confidence interval			
CRD	Centre for Reviews and Dissemination		NMDA	N-methyl-D-aspartate
			ONS	Office of National Statistics
CT	computed tomography		PEM	prescription event monitoring
DARE	Database of Reviews of Effectiveness		PET	positron emission tomography
			QALY	quality-adjusted life-year
DCE	discrete choice experiment		QoL	quality of life
EED	Economic Evaluation Database		RCT	randomised controlled trial
EEG	Electroencephalogram		SD	standard deviation
EL	executive letter		SPECT	single photon emission computed tomography
GABA	γ-aminobutyric acid			
GPRD	General Practice Research Database		SUDEP	sudden unexpected death in epilepsy
HEED	Health Economic Evaluation Database		TTO	time trade-off
HRQoL	health-related quality of life		VNS	vagus nerve stimulation

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.

Executive summary

Description of proposed service

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

Epidemiology and background

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

Methods

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

Number and quality of studies and direction of evidence

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

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

Summary of benefits

For each of the epilepsy subtypes considered in RCTs identified for this review (partial epilepsy with or without secondary generalisation, Lennox–Gastaut syndrome, infantile spasms, absence epilepsy and BECTS), there is some evidence from placebo-controlled trials that the newer agents tested are of some value in the

treatment of these conditions. Where active controls have been used, the limited evidence available does not indicate a difference in effectiveness between newer and older drugs. The data are not sufficient to inform a prescribing strategy for any of the newer agents in any of these conditions. In particular, there is no clinical evidence to suggest that the newer agents should be considered as a first-choice treatment in any form of epilepsy in children.

Costs

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

Cost per quality-adjusted life-year (QALY)

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

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

Other issues

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

Conclusions

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

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

Need for further research

Better information is required from RCTs before any rational evidence-based prescribing strategy could be developed. Ideally, RCTs should be conducted from a 'public health' perspective, making relevant comparisons and incorporating outcomes of interest to clinicians and patients,

with sufficiently long-term follow-up to determine reliably the clinical utility of different treatments, particularly with respect to treatment retention and the balance between effectiveness and tolerability. RCTs should mirror clinical practice with respect to diagnosis, focusing on defined syndromes or, where no syndrome is identified, on groups defined by specific seizure type(s) and aetiology.

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

Chapter 1

Aim of the review

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 (refractory) 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.[1] Synchronised high firing rate of populations of neurons is in itself a normal brain activity, but the following distinguishing features characterise an epileptic event:[2]

- 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.[3]

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'.[3] 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 1981[4] and 1989[5] 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 2001[8] 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[5] 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 children[3] 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 spasms[16,17] 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 years[3] 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,[19] 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.[3] 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.[3] *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[23] 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 with, 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[24] 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[25] 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.*

	Prevalence					Incidence			
	Endziniene,[20] Lithuania, 1995			Eriksson,[21] Finland, 1992		Freitag,[22] Germany, 1999		Berg,[14] USA (CT), 1993–97	
	n	*%*	*Prevalence/ 1000*	*n*	*%*	*n*	*%*	*n*	*%*
Localisation-related epilepsies	189	50.0	2.13	134	41.0	21	58.3	359	58.6
Idiopathic	15	4.0	0.17	24	8.0	8	22.2	61	10
Symptomatic	63	17.7	0.71	35	11.0	4	11.1	195	31.8
Cryptogenic	111	29.4	1.25	75	22.0	9	25.0	103	16.8
Generalised epilepsies	113	29.9	1.27	158	48.0	14	38.9	126	20.6
Idiopathic	55	14.6	0.62	75	23.0	9	25.0		0.0
Cryptogenic/symptomatic	18	4.8	0.20	45	14.0	4	11.1	52	8.5
Symptomatic	35	9.3	0.39	38	12.0	1	2.8		0.0
Cryptogenic	5	1.3	0.06	–	–	0	0.0		0.0
Undetermined partial or generalised	60	15.9	0.68	5	2.0	1	2.8	76	12.4
Presumably symptomatic	16	4.2	16	4.2	0.18				0.0
Cryptogenic	44	11.6	44	11.6	0.50				0.0
Both partial and generalised	–	–						5	0.8
Unclassified	16	4.2	0.18					71	11.6
Total	378			32		36		613	
BECTS	–	–		16	5	7	19.4	–	
CAE	–	–		21	6	1	2.8	74	
West's/infantile spasms	–	–		25	8	0	0	24	
Lennox–Gastaut	–	–		6	2	0	0	4	

In their systematic review, Ross and colleagues[23] 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,[25] 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.[26]

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[27] and because of the inherent difficulties in distinguishing possible causes and types of seizure that occur in children,[28] misdiagnosis may possibly be frequent.[29,30] Grunewald and colleagues[31] 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[32] 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.[23]

Further to seizure description and EEG, imaging methods may be employed that can strengthen and or extend diagnosis. Their use depends on prognosis 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.[33]

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. tuberus sclerosis)[34]
- 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.[35] 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).[36] Such procedures offer the possibility of anticipating seizures and therefore ultimately of avoiding them.

It is possible that recurrent seizures may damage brain tissue.[37] 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 sclerotisation in particular brain regions. Hermann and colleagues[38] 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 compensatory 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.[3]

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[39] 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,[40] MacDonald and colleagues[41] and Heaney and colleagues[42] 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

TABLE 2 *Incidence of epilepsy in children of different age (new cases/100,000 person years[a])*

	Heaney et al., 2002[42] UK	MacDonald et al., 2000[41] UK	Wallace et al., 1998[39] UK	Kurtz et al., 1998[40] UK	Beilmann et al., 1999[44] Estonia	Freitag et al., 2001[22] Germany	Camfield et al., 1996[45] Nova Scotia
Study type/ population	Prospective 20 GPs	Prospective 13 urban GPs	GPRD Based on 294 GPs 2,052,922	Prospective Cohort at birth	Prospective 7 counties 581,887	Prospective 2 cities 448,553	Retrospective Province 850,000
Case definition[b]	≥ 1 unprovoked seizure	≥ 2 unprovoked seizures	Composite		≥ 2 unprovoked seizures	≥ 2 unprovoked seizures	≥ 2 unprovoked seizures
N or person years (py)[c]	56,615 py 0–14 y	100,230	380,360 5–19 y	17,414	161,202 < 20 y	59,647 <15 y	226,700 <16 y
Age band (years):							
0–4	190 (138–262)	86		58	76 (60–96)[d]	62 (30–114)[e]	62[f]
5–9		46	63 (50–79)	36	54 (42–68)	50 (24–91)	43
5–14	75 (52–109)			33			
10–14		94	54 (42–68)	29	44 (34–57)	56 (28–100)	27
15–19		52	101 (84–121)	26	13 (6–19)		

[a] All figures rounded to nearest whole number.
[b] Case definitions: Wallace *et al.*: person receiving any of 11 named anti-epileptic drugs and who was entered in the ONS GPRD under any diagnostic code denoting any epilepsy syndrome, seizure type, or a synonym for epilepsy (e.g. seizure); Kurtz *et al.*: child with recurrent paroxysmal disturbances of consciousness, sensation or movement that were primarily cerebral in origin and not associated with acute febrile episodes.
[c] Whole population (all ages) except where stated.
[d] Excluding 0–1 month.
[e] Data for 1–4 years. Separate data for 0–1 year (excluding first month life): 145.8 (47–340).
[f] 0–1 year 118 (93–143). For the 0–4 year age group the reports of Heaney *et al.* and MacDonald *et al.* differ by a factor of >2 (86 vs 190): the same ascertainment methods were used but case definitions differed.

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,[40] 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.[43] 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[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);[46] Sweden 4.2/1000 (0–16 year olds);[47] Finland 3.94/1000 (0–15 year olds);[21] Lithuania 4.25/1000 (0–15 year olds);[20] Estonia 4.3/1000 (5–9 year olds).[48] Based on a review of many studies Cowan and colleagues[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.[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.[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[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[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.[52]

Berg and colleagues[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[53] in which 25% of participants were <15 years old reported a modestly increased risk of accident [hazard ratio 1.6; 95% confidence internal (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,[54] 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[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.[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,[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[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,[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."[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,[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[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[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[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[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;[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[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*[74])

6. The necessity/desirability to consider the use of AEDs outside their licensed indications.

The systematic review by Ross and colleagues[23] 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.[10] 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[75] studied 392 children given long-term monotherapy with phenobarbitol, 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.[76] Facets of over-treatment include[77] 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[78] 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[79]). A report of postmarketing experience of topiramate with particular reference to cognition has also been published.[80] An unpublished PEM study failed to detect the visual field defects associated with vigabatrin,[81] yet a case–control study[82] estimated that 52% of vigabatrin patients had definite visual field defects (compared with 0% of control epileptics not taking vigabatrin) and a retrospective study[83] 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,[84] 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[61,85–88] 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).

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.[89]

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.[10,85,90] 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.[91]

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.[92]

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 extra-temporal 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[93] 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

significant numbers of refractory patients seizure free. An RCT published subsequent to the review[94] found that after 1 year 58% of patients (N = 40) receiving surgery for refractory temporal-lobe epilepsy were seizure free compared with 8% of patients (N = 40) who received medical management with AEDs (p < 0.001). Epilepsy-specific QoL scores were also significantly better in the surgery group (p < 0.001).

VNS involves an invasive procedure in which a programmable generator is implanted beneath the left collarbone and stimulates the left vagus nerve via an electrode implanted around the nerve. The mechanism of action is uncertain. Criteria for the selection of patients are lacking. In the USA up to January 2002, ~14,500 <18-year-olds had been implanted, of whom 70% had co-morbidity with mental retardation and developmental delay. In the USA, treatment must be used out of licence for children <12 years old. Side-effects, which include coughing and voice changes during stimulation and drooling and ear pain in a small proportion of children under 12 years old, appear appealingly mild compared with those associated with multiple AED therapies. Reductions in seizure frequency in refractory paediatric patients also appear promising and apparently improve with prolonged treatment. However, no RCT has been conducted in children comparing VNS with medical management or with surgery and quality information regarding continuation on therapy is lacking. For adult patients with refractory partial epilepsy, RCTs have been performed. VNS has been the subject of a Technology Assessment Report published in 1999[95] which concluded that for refractory partial epilepsy seizure relief was comparable to that of the newer AEDs. For less severely affected patients, efficacy was unknown. Cramer and colleagues[96] attempted a comparison of risk–benefit profiles of newer AEDs and VNS used as add-on therapy for adults with refractory partial epilepsy. Data from RCTs were synthesised into a success score (proportion achieving >50% reduction in seizure rate in active arm minus proportion in placebo arm) and a 'complaint score' (composite summing measure of all adverse events using COSTART or WHO-ART terms in active arm minus placebo arm). Of eight treatments (seven drugs + VNS), VNS registered the lowest 'success' score and the second worst 'complaint score'. The authors acknowledged that the 'success score' for VNS may be underestimated since the invasive nature of VNS dictated that RCTs have a pseudo-placebo arm that administered low-level stimulation from which some benefit might be derived.

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, β-hydroxybutyrate and acetone). The source of ketone bodies is hepatic acetate (acetyl-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 new intervention

Description of technologies
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. Levetiretecam 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.[100]

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 Economic Evaluation Database (EED)
   (d) NHS Database of Reviews of Effectiveness (DARE)
   (e) NHS CRD administration database (undertaken by NHS CRD)
   (f) Health Economic Evaluation Database (HEED) May 2002.
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 36[101–104] 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; one[105,106] considered drug treatment for infants and children with West's syndrome, another treatments for acute tonic-clonic convulsions including status epilepticus[107] 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			
No.	**Reference**	**Drug(s)**	**Mode**	**Epilepsy**
1	Castillo, 2000[109]	Oxcarbazepine	Add-on	Partial
2	Chaisewikul, 2001[110]	Levetiracetam	Add-on	Partial
3	Jette, 2000[111]	Topiramate	Add-on	Partial
4	Marson, 2000[112]	Gabapentin	Add-on	Partial
5	Marson, 2001[113]	Levetiracetam, oxcarbazepine	–	Partial
6	Mumford, 1989[569]	Vigabatrin	–	Epilepsy
7	Pereira, 2002[114]	Tiagabine	Add-on	Partial
8	Ramaratnam, 2000[115]	Lamotrigine	Add-on	Partial
9	Richens, 1991[570]	Lamotrigine	–	Various
	Other AEDs			
	Reference	**Drug(s)**	**Mode**	**Epilepsy**
10	Appleton, 2002[107]	Various	–	Tonic-clonic, status epilepticus
11	Baker, 2000[116]	Various	–	Various
12	Chadwick, 2001[117]	Zonisamide	Add-on	Partial
13	Chadwick, 1997[118]	Various	–	Various
14	Chaisewikul, 2001[119]	Various	Add-on	Various
15	Claassen, 2002[120]	Various	–	Status epilepticus
16	French, 2001[121]	Levetiracetam	–	Various
17	Leach, 2002[571]	Remacemide	Add-on	Partial
18	Marson, 1996[122]	Various	–	Various
19	Marson, 2001[123]	Carbamazepine and valproate	Mono	Epilepsy
20	Marson, 2002[124]	Carbamazepine and valproate	Mono	Partial
21	Priviter, 1999[125]	Various	–	Various
22	Ramsay, 1997[126]	Various	–	Tonic-clonic
23	Taylor, 2001[127]	Phenobarbitone and phenytoin	Mono	Partial or generalised
24	Tudur Smith, 2001[128]	Phenytoin and valproate	Mono	Partial or generalised
25	Tudur Smith, 2002[129]	Carbamazepine and phenytoin	Mono	Partial or generalised

TABLE 4 Systematic reviews in preparation

No.	Reference
1	Adab, 2001[130]
2	Hancock, 2001[131]
3	Kalviainen, 2001[132] (withdrawn in 2002)
4	Posner, 2001[133]
5	Preston, 2002[134]
6	Tudur Smith, 2001[135] (published 2003)[136]

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 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.

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

No.	Drug	Reference	N	Mean age[a]	Median age[a]	Age range[a]
1	Tiagabine	Aikia, 1999[137]	67	–	–	15–75
2	Gabapentin	Lindberger, 2000[138]	102	33.7	–	13–68
3	Lamotrigine	Binnie, 1989[139]	30	37.1	–	16–51
4	Levetiracetam	Cramer, 2000[140]	?	38.7	–	16–70
5	Oxcarbazepine	Barcs, 2000[141]	694	34.5	–	15–66
6	Tiagabine	Brodie, 1997[142]	?	–	–	12–85
7	Vigabatrin	Tanganelli, 1993[143]	11	29.5	–	17–58
8	Vigabatrin	Canger, 1997[144]	16	27.7	–	17–40
9	Vigabatrin	Chadwick, 1999[145]	446	35.5	–	12–75
10	Gabapentin	Andrews, 1990[146]	127	30.5	–	14–73
11	Gabapentin	Sivenius, 1991[147]	43	39	–	16–59
12	Gabapentin	McLean, 1993[148]	306	34.2	–	16–70
13	Gabapentin	Anhut, 1994[149]	272	32	–	12–67
14	Gabapentin	Leach, 1997[150]	27	–	–	16–67
15	Lamotrigine	Schapel, 1993[151]	41	31	28	17–63
16	Lamotrigine	Smith, 1993[152]	81	33.7	–	15–67
17	Lamotrigine	Severi, 1994[153]	27	39.7	–	17–58
18	Levetiracetam	Cereghino, 2000[154]	294	38	–	16–70
19	Levetiracetam	Cramer, 2000[155]	246	38.7	–	16–70
20	Levetiracetam	Shorvon, 2000[156]	324	36.7	–	14–68
21	Oxcarbazepine	Schachter, 1999[157]	102	33.5	–	11–65
22	Topiramate	Lee, 1999[158]	177	29.6	–	16–65
23	Vigabatrin	Grunewald, 1994[159]	45	–	27, 29	16–59
24	Vigabatrin	Brodie, 1999[160]	215	–	36, 37	12–78
25	Tiagabine	Dodrill, 1997[161]	297	34	–	12–77
26	Tiagabine	Dodrill, 2000[162]	277	37.5	–	<16–?[b]
27	Vigabatrin	Beran, 1996[163]	?	–	–	17–64
28	Gabapentin	Ben Menachem, 1995[164]	36	37	–	16–66
29	Levetiracetam	Ben Menachem, 2000[165]	286	36.5	–	16–70
30	Tiagabine	Sachdeo, 1997[166]	318	33.8	–	12–67
31	Vigabatrin	Rimmer, 1984[167]	?	33	–	16–61
32	Vigabatrin	Gram, 1985[168]	?	–	–	17–63
33	Vigabatrin	Cramer, 1995[169]	?	–	–	16–50
34	Vigabatrin	Provinciali, 1996[170]	40	36.5	–	17–66
35	Gabapentin	Chadwick, 1996[171]	129	29.5	–	13–62
36	Lamotrigine	Beran, 1998[172]	26	29	–	15–50
37	Topiramate	Biton, 1999[173c]	80	26.2	–	3–59
38	Gabapentin	Chadwick, 1998[174]	292	35.5	–	12–86
39	Lamotrigine	Brodie, 1995[175]	260	–	27, 28	13–81
40	Lamotrigine	Dam, 1996[176]	343	–	–	12–72
41	Lamotrigine	Steiner, 1999[177]	181	–	27, 28	13–74
42	Lamotrigine	Kalogjera, 2000[178]	133	–	–	12–?
43	Oxcarbazepine	Dam, 1989[179]	194	–	33, 32.5	14–63
44	Oxcarbazepine	Bill, 1997[180]	287	26.8	–	15–91
45	Oxcarbazepine	Christe, 1997[181]	249	32.5	–	15–65
46	Topiramate	Wheless, 2001[182]	626	–	–	6–?[d]
47	Vigabatrin	Kalviainen, 1995[183]	100	35	–	15–64
48	Lamotrigine	Binnie, 1987[184]	10	30.5	–	16–46
49	Levetiracetam	Betts, 2000[185]	119	38	–	16–70
50	Oxcarbazepine	Houtkooper, 1987[186]	?	–	29, 29	15–50
51	Vigabatrin	Loiseau, 1986[187]	22	28.9	24	10–58
52	Vigabatrin	Tartara, 1986[188]	23	30.5	30	17–50
53	Vigabatrin	Rimmer, 1987[189]	6	18	–	10–25
54	Vigabatrin	Tassinari, 1987[190]	31	28.9	–	10–58
55	Vigabatrin	Reynolds, 1991[191]; same as ref. 192	20	–	–	16–65
56	Vigabatrin	Gillham, 1993[193]	48	32.5	–	17–53
57	Lamotrigine	Carmant, 1999[194]	?	–	–	2–?
58	Lamotrigine	Montouris, 1999[195]	29	–	25, 26	12–?
59	Lamotrigine	Fakhoury, 2000[196]	?	–	–	16–?

[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.

TABLE 6 *Summary of trials and trial design (newly diagnosed partial seizures)*

	Nieto-Barrera, 2001	**Zamponi, 1999**
Newer drug(s) investigated	Lamotrigine	Vigabatrin
Target maintenance dose (mode)	Lamotrigine 2–15 mg/kg/day (oral); carbamazepine 5–40 mg/kg/day (oral)	Vigabatrin 50–60 mg/kg/day; carbamazepine 1520 mg/kg/day (oral) [typographical error in source?]
Seizure or syndrome	Newly diagnosed partial epilepsy	Newly diagnosed partial epilepsy
Type of trial design	Parallel	Parallel
Add-on or monotherapy?	Monotherapy	Monotherapy
Control(s)	Carbamazepine	Carbamazepine
Study start and end dates	Not stated	Not reported
Centres and location	Multicentre; Europe, Egypt and Mexico	1 centre in Italy
Baseline	None	None
Titration period	6 weeks (defined for lamotrigine arm only)	4 weeks
Maintenance	18 weeks	100 weeks (assumed from 2-year follow-up)
Withdrawal	None	None
Inclusion criteria	Newly diagnosed or currently untreated partial epilepsy; no age restrictions	Children with newly diagnosed partial epilepsy
Timing and additional eligibility for randomisation/continuation on study	NA (no baseline phase)	NA (no baseline period)
Comments on design	Titration schedule much more clearly defined for lamotrigine; patients on lamotrigine arm 'withdrawn' if dose reduction required during escalation phase or whilst on lowest maintenance dose, but no similar criteria given for carbamazepine	Very poor quality of reporting; not clear that trial was randomised.

NA, not applicable.

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[197] compared lamotrigine and carbamazepine in a mixed age population. Zamponi, 1999[198] 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.[198] 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)*

	Nieto-Barrera, 2001	Zamponi, 1999
Was assignment of treatment described as random?	Yes	Yes
Was method of randomisation described?	No (except stratified by age and country)	No
Was the method really random?	Can't tell	Can't tell
Was allocation of treatment concealed?	Can't tell	Can't tell
Who was blinded to treatment?	Open label study	Open study
Was method of blinding adequately described?	NA	NA
Were eligibility criteria described?	Yes	No
Were groups comparable at study entry?	Yes (data not reported for children separately)	Can't tell; large imbalance in numbers randomised for a small single centre study, large age difference, patient characteristics poorly reported
Were groups treated identically apart from the intervention?	Can't tell	Can't tell
Was ITT used?	No	Can't tell
Were withdrawals stated?	Yes (but see comment)	Yes
Were reasons for withdrawals stated?	Information incomplete	Yes (but see comment)
Was a power calculation done?	No	No
Was monitoring of plasma levels done (including study drug)?	No	No
Were arrangements to blind plasma monitoring results mentioned?	NA	NA (open study)
Comments	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	Very poor quality of reporting Reasons for withdrawal were stated but cannot be certain that these were complete data

reports on both groups entirely separately and at no point attempts to compare the two groups directly.

The standard of reporting was better for Nieto-Barrera, 2001[197] 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[197] 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)*

	Nieto-Barrera, 2001				Zamponi, 1999			
	Carbamazepine	**Lamotrigine**			**Carbamazepine**	**Vigabatrin**		
Number randomised	75	153			32	38		
Number analysed	64	134			Not stated	Not stated		
Maintenance dose achieved	Mean 16.9 mg/day Median 16.0, 5.2–36.5 mg/day	Mean 3.4 mg/day Median 2.7, 0.05–10.5 mg/day			1520 mg/kg/day [typographical error in source?]	50–60 mg/kg/day		
Withdrawals including reasons where specified	Total withdrawals 11 (15) Adverse events 5 (7)	21 (13) 8 (5)		Total withdrawals Lack of efficacy Adverse events	8 2 6	6 5 1		
	Results	**CI; *p*-value**			**Results**			**CI; *p*-value**
Primary outcome(s)	1. Seizure free in last 16 weeks and follow-up to week 22 — CBZ: 48/64 (75%) LTG: 89/134 (66%)	–22 to 5%; *p* = 0.205		None stated	NA	NA		NA
	2. Seizure free in last 16 weeks and follow-up to week 18 — CBZ: 48/75 (64%) LTG 89/158 (56%)	–21 to 6%; *p* = ns						
Secondary outcomes (time to withdrawal from study)	Global effectiveness — Survival analysis not reported [proportions CBZ: 11 (15%) LTG: 21 (13%)]	Not reported Kaplan–Meier curves not given for 2–12 years age group		None stated	NA	NA		NA
'Ad hoc' outcomes	Proportion withdrawn for adverse events — CBZ: 5/75 (7%) LTG: 8/158[a] (5%)	*p* = 0.761		Number of relapses (not defined; assumed to be recurrence of seizures)	CBZ: 7/32 (21.9%) VBT: 9/38 (23.7%)			No comparative analysis reported

CBZ, carbamozepine; LTG, lamotrigine; ns, not significant.
[a] Not clear if this is a typographical error.

25

TABLE 9 Adverse events *(newly diagnosed partial seizures)*

		Nieto-Barrera, 2001		Zamponi, 1999	
		Carbamazepine	Lamotrigine	Carbamazepine	Vigabatrin
Criteria for reporting		Events in more than 6% of patients		None stated	
Events	Any AE	47 (63)	80 (51)		
	Infection	0 (–)	20 (13)		
	Headache	12 (16)	12 (8)		
	Asthenia	1 (1)	4 (3)		
	Somnolence	7 (9)	5 (3)		
	Pharyngitis	8 (11)	13 (8)		
	Rash	6 (8)	11 (7)		
	Dizziness	11 (15)	1 (<1)		
	Serious AE	1 (1)	9 (6)		
	Drug-related	30 (40%)	35 (22%)		
		112 events in 47/75 patients	206 events in 80/158 patients		
	Irritability/excitability			0	6 (15.7)
	Weight gain			3 (9.3)	10 (26.3)
	Excessive sedation			6 (18.7)	0 (–)
	Rash			6 (18.7)	0 (–)

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.

Previously 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, 2000[199] Litzinger, 1998[200] Valentine, 1998[201] and Van Orman, 1998,[202] were reported in abstract form only, hence there is very limited information available.

Duchowny, 1998[203] Glauser, 2000[204] and Elterman, 1999[205] all gave adequate descriptions of the method of randomisation and allocation concealment; Appleton, 1999[206] 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, 1999[203] 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, 1999[203] 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, 1999[206] 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, 1999[203] and Elterman, 1999[205] both report ITT analysis; Glauser, 2000[204] 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, 1999[203] Glauser, 2000[204] Elterman, 1999[205] Valentine, 1998[201] and Van Orman, 1998[202] 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, 2000[199] 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, 1999[206] 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, 1999[205] who reported no withdrawals due to adverse events on topiramate in this small trial.

Partial and generalised seizures (mixed population)

One RCT, by Guerreiro, 1997[207] 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.

27

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

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

	Glauser, 2000	Litzinger, 1998	Elterman, 1999
Newer drug(s) investigated	Oxcarbazepine	Tiagabine	Topiramate
Target maintenance dose (mode)	30–46 mg/kg/day (oral, tablets)	0.7 mg/kg/day (assumed /day)	125–400 mg/day (oral)
Seizure or syndrome	Partial seizures	Refractory partial seizures	Partial seizures
Type of trial design	Parallel	Parallel	Parallel
Add-on or monotherapy?	Add-on	Add-on	Add-on
Control(s)	Placebo	Placebo	Placebo
Study start and end dates	Not reported [May 1995 to September 1997 (independent submission)]	Not reported [abstract only]	Not reported
Centres and location	47 centres in Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, USA	Not reported [abstract only]	17 centres in USA, Costa Rica
Baseline	8 weeks	8 weeks	8 weeks
Titration period	2 weeks	Not reported [abstract only]	8 weeks
Maintenance	14 weeks	12 weeks	8 weeks

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

	Glauser, 2000	Litzinger, 1998	Elterman, 1999
Withdrawal	Not reported [abstract only]	Not reported [abstract only]	None
Inclusion criteria	Medically uncontrolled partial seizures; age 3–17 years	Not reported [abstract only]	Medically uncontrolled partial seizures, with or without secondarily generalised seizures; age between 1 and 16 years
Timing and additional eligibility for randomisation/ continuation on study	Postbaseline; patients experiencing at least 1 seizure every 4 weeks and at least 8 seizures in total during 8-week baseline period	Not reported [abstract only]	Postbaseline; patients experiencing at least 6 partial seizures (at least 1 every 4-week interval) during baseline
Comments on design	Dose titration refers explicitly to oxcarbazepine only; unclear how/if placebo was titrated in same way	Abstract with few details of design	Dose titration refers explicitly to topiramate only; not clear how/if placebo was titrated in same way

	Valentine, 1998	Van Orman, 1998
Newer drug(s) investigated	Vigabatrin	Vigabatrin
Target maintenance dose (mode)	1.5–4 g/day (oral)	20, 60, 100 mg/kg/day (?mode)
Seizure or syndrome	Uncontrolled complex partial seizures with or without secondary generalisation	Uncontrolled complex partial seizures with or without secondary generalisation
Type of trial design	Parallel	Parallel
Add-on or monotherapy?	Add-on	Add-on
Control(s)	Placebo	Placebo
Study start and end dates	Not reported	Not stated
Centres and location	Multicentre ($n = ?$)	Multicentre ($n = ?$)
Baseline	6 weeks	Not stated
Titration period	10 weeks	6 weeks
Maintenance	7 weeks	8 weeks
Withdrawal	Not stated	Not stated
Inclusion criteria	Not stated	Not stated
Timing and additional eligibility for randomisation/ continuation on study	Not stated	Not stated
Comments on design	Randomised only 75% of target of 120 patients	Dose–response study

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 11 *Quality assessment (previously diagnosed partial seizures)*

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

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

	Appleton, 1999 (1)	Shapiro, 2000	Duchowny, 1999[203]	Glauser, 2000
Comments	–	Abstract with few details	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	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)

	Litzinger, 1998	Elterman, 1999	Valentine, 1998	Van Orman, 1998
Was assignment of treatment described as random?	– [abstract only]	Yes	Yes	Yes
Was method of randomisation described?	– [abstract only]	Yes	No	Not stated
Was the method really random?	– [abstract only]	Yes	Can't tell	Can't tell
Was allocation of treatment concealed?	– [abstract only]	Yes	Can't tell	Can't tell
Who was blinded to treatment?	– [abstract only]	Patients, investigators, study monitors and observers	Not stated	Not stated
Was method of blinding adequately described?	– [abstract only]	No description	No description	No description
Were eligibility criteria described?	– [abstract only]	Yes	No	No
Were groups comparable at study entry?	– [abstract only]	Yes	Can't tell	Can't tell
Were groups treated identically apart from the intervention?	– [abstract only]	Can't tell; no description of blinding and dose titration refers to topiramate group only	Can't tell	Can't tell
Was ITT used?	– [abstract only]	Yes	Claimed	Claimed
Were withdrawals stated?	– [abstract only]	Yes	No	No
Were reasons for withdrawals stated?	– [abstract only]	Yes	No	No
Was a power calculation done?	– [abstract only]	Yes	Yes	Yes
Was monitoring of plasma levels done (including study drug)?	– [abstract only]	Yes; including study drug	No	No
Were arrangements to blind plasma monitoring results mentioned?	– [abstract only]	No	NA	NA
Comments	Abstract with few details	–	127 patients entered baseline; 88 were randomised Abstract with few details	Randomised only 63% of target of 200 patients Abstract with few details

32

TABLE 12 Results (previously diagnosed partial seizures)

	Appleton, 1999 (I)		Shapiro, 2000	
	Placebo	**Gabapentin**	**Placebo**	**Gabapentin**
Number randomised	Not stated	Not stated	38	38
Number analysed	128	119	Not reported	Not reported
Maintenance dose achieved	Not reported	Not reported	Not reported	Not reported
Withdrawals including reasons where specified			–	
Total withdrawals	28 (21.9)	21 (17.6)	Not reported	Not reported
Lack of efficacy	19 (14.8)	11 (9.2)		
Adverse events	3 (2.3)	6 (5.0)		
Change in AED	2 (1.6)	0 (–)		
Other	4 (3.1)	4 (3.4)		

	Results	**CI; *p*-value**	**Results**	**CI; *p*-value**
Primary outcome(s)	Response ratio — Placebo –0.079, Gabapentin –0.146	*p* = 0.1246 (see comment)	1. Response ratio — Placebo –0.048, Gabapentin +0.018	*p* = ns
			2. Responder rate — No data reported	*p* = ns
Secondary outcomes	>50% reduction — Placebo 18%, Gabapentin 21%	*p* = ns	–	–
'Ad hoc' outcomes	–	–	–	–
Comments (including results reported)	All results adjusted whether unadjusted for centre		Abstract only; very limited information	

No ITT results available. Report defined ITT as 'all patients treated' and even then, only reported most outcomes for 'modified ITT' population.

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

ANOVA, analysis of variance; ITT, intention to treat.

TABLE 12 Results (previously diagnosed partial seizures) (cont'd)

	Duchowny, 1999			Glauser, 2000		
	Placebo	**Lamotrigine**	**CI; p-value**	**Placebo**	**Oxcarbazepine**	**CI; p-value**
Number randomised	101	98		129	138	
Number analysed	101	98		128	136	
Maintenance dose achieved	Not reported	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		Not reported	Median 31.4 mg/kg/day (6.4–51.4)	
	Results		**CI; p-value**	**Results**		**CI; p-value**
Withdrawals including reasons where specified / Adverse events	Total withdrawals 18 (17.8); Poor response 8 (7.9); Withdrew consent 6 (5.9); Protocol violations 2 (1.9); 2 (1.9)			Total withdrawals 10 (7.8); Lack of efficacy 4 (3.1); Adverse events 4 (3.1); Non-compliance 0 (–); Withdrew consent 1 (0.8); Lost to follow-up 1 (0.8)	Total withdrawals 21 (15.2); Lack of efficacy 0 (–); Adverse events 14 (10.1); Non-compliance 4 (2.9); Withdrew consent 2 (4.3); Lost to follow-up 0 (–)	
Primary outcome(s)	Median % change in frequency of all partial seizures during:			% change in frequency of all partial seizures per 28 days during DB double-blind treatment		
1. entire 18-week follow-up	Placebo –6.7%, Lamotrigine –36.1%		p = 0.008	Placebo –9%, Oxcarbazepine –35% (median % change)		p = 0.0001
2. 12 week maintenance period	Placebo –12.8%, Lamotrigine –44%		p = 0.012			

EIAED, enzyme-inducing AED; VPA, valproate.

continued

33

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

	Duchowny, 1999		Glauser, 2000	
	Placebo	**Lamotrigine**	**Placebo**	**Oxcarbazepine**
Secondary outcomes	1. % change in frequency of secondarily generalised seizures: Not based on whole population	$p < 0.05$	1. ≥ 50% reduction in all partial seizure frequency: Placebo 22% Oxcarbazepine 41%	$p = 0.0005$
	2. Proportion of patients with ≤ 25%, 26–49% and ≥ 50% reduction in all partial seizures: Results available graphically only	$p < 0.05$	2. % change in frequency of: Simple partial 45% oxcarbazepine 16% / Complex partial 42% vs 10% / Secondarily generalised 78% vs 33%	Not reported / Not reported / $p = 0.0012$
	3. Number of days when each patients was seizure free (all partial seizures): Placebo +3.2% Lamotrigine +28.0% (median change)	$p = 0.003$		
'Ad hoc' outcomes	–	–	Seizure-free patients: Placebo 1/128 vs oxcarbazepine 5/136	Not reported
Comments (including whether unadjusted results reported)	% change in seizure frequency adjusted for centre effects. Percentage changes reported are median (weekly) % changes		50% responder rates reported for 135 (not ITT population of 136) oxcarbazepine patients (no explanation for missing patient). Changes reported for each seizure type apply only to patients with that type of seizure at baseline. Sample size slightly less than target given in power calculation (267 vs 274). Analysis of responder rate adjusted for centre, sex, age and weight	

TABLE 12 Results (previously diagnosed partial seizures) (cont'd)

	Litzinger, 1998				Elterman, 1999		
	Placebo	Tiagebine		CI; *p*-value	Placebo	Topiramate	CI; *p*-value
Number randomised	–	–			45	41	
Number analysed	–	–			45	41	
Maintenance dose achieved	–	-			Not reported	Median 5.9 mg/kg/day	
Withdrawals including reasons where specified	–	–			Total withdrawals 2 (4.4) / Adverse events 1 (2.2) / Patient choice 1 (2.2)	0 (–) / 0 (–) / 0 (–)	
	Results			**CI; *p*-value**	**Results**		**CI; *p*-value**
Primary outcome(s)	–			-	% change in frequency of all partial seizures (average monthly rate)	Placebo –10.5% / Topiramate –33.1% (median % reduction)	*p* = 0.034
Secondary outcomes	–			–	1. % change in secondarily generalised seizures / 2. % with ≥ 50% reduction in all partial seizures / 3. % with ≥ 75% reduction in all partial seizures / 4. % with 100% reduction in all partial seizures / 5. Parental global evaluation	Placebo + 10.6% Topiramate –31.6% / Placebo 9 (20.0) Topiramate 16 (39.0) / Placebo 1 (2.2) Topiramate 7 (17.0) / Placebo 0 (–) Topiramate 2 (4.8) / (Results not reproduced here)	Not reported / *p* = ns / *p* = 0.019 / *p* = ns / Results not reproduced (Results not reproduced here) / –
'Ad hoc' outcomes	–			–	–		
Comments (including whether unadjusted results reported)	Data reported on a subset of patients from a larger randomised trial; no data extractable				Results adjusted for centre only		

continued

35

TABLE 12 Results (previously diagnosed partial seizures) (cont'd)

	Valentine, 1998				Van Orman, 1998			
	Placebo	Vigabatrin			Placebo	Vigabatrin: 20, 60, 100 mg		
Number randomised	Total 88, not stated by arm				Total 126, not stated by arm			
Number analysed	88, not stated by arm				126 not stated by arm			
Maintenance dose achieved	Not stated	1.5–4 g/day			Not stated	Not stated		
Withdrawals including reasons where specified	Not reported	–	–		Not stated	–	–	
			Results	CI; *p*-value			Results	CI; *p*-value
Primary outcome(s)	≥ 50% reduction in seizure frequency		Placebo 26.7% Vigabatrin 55.8%	*p* = 0.0089	Reduction in patient mean monthly seizure frequency		Not stated	*p* = 0.0142 (100-mg group vs placebo) greater reduction for active arm
Secondary outcomes	–		–	–	–		–	–
'Ad hoc' outcomes	–		–	–	–		–	–
Comments (including whether unadjusted results reported)	–				–			

TABLE 13 Adverse events (previously diagnosed partial seizures)

		Appleton, 1999 (I)		Shapiro, 2000		
		Placebo	Gabapentin		Placebo	Gabapentin
Criteria for reporting	Events in ≥ 2% of patients in either group			Most frequent		
Events	Viral infection	4 (3.1)	13 (10.9)	Somnolence	Not reported	Not reported
	Fever	4 (3.1)	12 (10.1)	Nausea	Not reported	Not reported
	Nausea/vomiting	9 (7.0)	10 (8.4)	Vomiting	Not reported	Not reported
	Somnolence	6 (4.7)	10 (8.4)			
	Pharyngitis	11 (8.6)	10 (8.4)			
	Hostility	3 (2.3)	9 (7.6)			
	Upper RTI	8 (6.3)	7 (5.9)			
	Headache	8 (6.3)	6 (5.0)			
	Rhinitis	6 (4.7)	6 (5.0)			
	Emotional lability	2 (1.6)	5 (4.2)			
	Weight increase	1 (0.8)	4 (3.4)			
	Fatigue	2 (1.6)	4 (3.4)			
	Bronchitis	1 (0.8)	4 (3.4)			
	Diarrhoea	4 (3.1)	3 (2.5)			
	Convulsions	4 (3.1)	3 (2.5)			
	Dizziness	2 (1.6)	3 (2.5)			
	Hyperkinesia	1 (0.8)	3 (2.5)			
	Respiratory infection	1 (0.8)	3 (2.5)			
	Anorexia	3 (2.3)	2 (1.7)			
	Coughing	4 (3.1)	2 (1.7)			
	Otitis media	4 (3.1)	1 (0.8)			
	Considered related to study drug (% events or patients)	20%	34%			
	Severe AEs	3 patients (3 events)	14 patients (23 events)			

37

38

TABLE 13 *Adverse events (previously diagnosed partial seizures) (cont'd)*

Duchowny, 1999

		Placebo	Lamotrigine
Criteria for reporting	Events in >10% of patients in either group		
Events	Vomiting	19 (18.8)	22 (22.4)
	Somnolence	18 (17.8)	24 (24.4)
	Infection	22 (21.7)	21 (21.4)
	Dizziness	5 (4.9)	21 (21.4)
	Rash	18 (17.8)	16 (16.3)
	Headache	15 (14.8)	18 (18.3)
	Rhinitis	17 (16.8)	14 (14.2)
	Accidental injury	15 (14.8)	14 (14.2)
	Diarrhoea	13 (12.8)	13 (13.2)
	Fever	12 (11.8)	14 (14.2)
	Abdominal pain	7 (6.9)	13 (13.2)
	Tremor	2 (1.9)	12 (12.2)
	Nausea	2 (1.9)	11 (11.2)
	Otitis media	11 (10.8)	9 (9.1)
	Pharyngitis	10 (9.9)	11 (11.2)
	Ataxia	2 (1.9)	10 (10.2)
	Asthenia	6 (5.9)	11 (11.2)
	Proportion of patients reporting at least one AE	96 (95.0)	92 (93.8)

Glauser, 2000

	Placebo	Oxcarbazepine
Events in ≥ 10% of patients in either group		
Viral infection	21 (16.2)	19 (13.7)
Fever	20 (15.5)	21 (15.2)
Nausea/vomiting	26 (20.1)	80 (57.9)
Somnolence	18 (13.9)	48 (34.7)
Pharyngitis	15 (11.6)	12 (8.6)
Upper RTI	15 (11.6)	10 (7.2)
Headache	23 (17.8)	44 (31.8)
Rhinitis	11 (8.5)	16 (11.5)
Fatigue	11 (8.5)	18 (13.0)
Dizziness	10 (7.7)	40 (28.9)
Anorexia	13 (10.0)	9 (6.5)
Ataxia	6 (4.6)	19 (13.7)
Abnormal gait	4 (3.1)	14 (10.1)
Nystagmus	2 (1.5)	14 (10.1)
Diplopia	1 (0.7)	23 (16.6)
Abnormal vision	2 (1.5)	19 (13.7)
Abdominal pain	13 (10.0)	12 (8.6)
Proportion of patients reporting ≥ 1 adverse event	106 (82)	126 (91)

TABLE 13 *Adverse events (previously diagnosed partial seizures) (cont'd)*

	Litzinger, 1998			Elterman, 1999		
		Placebo	Tiagebine		Placebo	Topiramate
Criteria for reporting						
Events	–	–	–	Events in ≥ 10% of patients in topiramate group		
				Upper RTI	36%	41%
				Sinusitis	27%	17%
				Coughing	11%	15%
				Diarrhoea	22%	10%
				Somnolence	13%	12%
				Anorexia	11%	12%
				Emotional lability	4%	12%
				Difficulty concentrating	2%	12%
				Mood problems	11%	10%
				Aggressive reaction	7%	10%
				Nervousness	7%	10%
				Viral infection	4%	15%
				Otitis media	11%	10%
				Rash	9%	12%
				Purpura	4%	15%
				Fever	24%	29%
				Injury	9%	20%
				Fatigue	7%	15%
				Serious AEs	3 (6.6)	1 (2.4)

	Valentine, 1998			Van Orman, 1998		
		Placebo	Vigabatrin		Placebo	Vigabatrin: 20, 60, 100 mg
Criteria for reporting	Treatment-related adverse events			Treatment-related adverse events		
Events	All events	(66.7)	(65.9)	All events	(61.3)	(42.3), (65.5), (86.7)
	Somnolence	Not reported	Not reported	Somnolence	Not reported	Not reported
	Headache	Not reported	Not reported	Dizziness	Not reported	Not reported
	Dizziness	Not reported	Not reported	Increased seizure Frequency	Not reported	Not reported
	Increased seizure frequency	Not reported	Not reported			

RIT, respiratory tract infection.

TABLE 14 *Summary of trial and trial design (population with partial and generalised seizure types)*

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

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

Trial ID	Guerreiro, 1997
Was assignment of treatment described as random?	Yes
Was method of randomisation described?	Yes
Was the method really random?	Yes
Was allocation of treatment concealed?	Can't tell
Who was blinded to treatment?	Described as 'double-blind'
Was method of blinding adequately described?	'Tablets with identical appearance'
Were eligibility criteria described?	Yes
Were groups comparable at study entry?	Yes
Were groups treated identically apart from the intervention?	Can't tell
Was ITT used?	No (except for time to withdrawal outcome)
Were withdrawals stated?	Yes
Were reasons for withdrawals stated?	Yes
Was a power calculation done?	Yes
Was monitoring of plasma levels done (including study drug)?	Yes
Were arrangements to blind plasma monitoring results mentioned?	Yes (results reported only as zero, low, within range or high)
Comments	–

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

	Guerreiro, 1997		
		Phenytoin	**Oxcarbazepine**
Number randomised		96	97
Number analysed		77	81
Maintenance dose achieved		Mean 5.8 mg/kg/day (at start of maintenance period)	Mean 18.8 mg/kg/day (at start of maintenance period)
Withdrawals including reasons where specified	Total withdrawals	34	24
	Loss to follow-up	9	8
	Adverse events	14	2
	Non-compliance	5	6
	Poor efficacy	3	4
	Protocol violation	2	3
	Concomitant illness	0	1
	Discontinued at baseline	1	0
		Results	**CI; *p*-value**
Primary outcome(s)	Proportion of seizure-free patients (of those who reached maintenance period and had at least one seizure assessment during the maintenance period)	46/77 phenytoin 49/81 oxcarbazepine	$p = 0.91$ (by logistic regression) Not based on ITT population
Secondary outcomes	1. Seizure frequency during maintenance	PHT: mean 0.04 OXC: mean 0.07	p = ns (not based on ITT population)
	2. Overall evaluation (4-point ordinal scale)	No data reported; not clear if ITT analysis	p = ns
	3. Premature discontinuation due to poor therapeutic effect	3 PHT, 4 OXC	p = ns
	4. Premature discontinuation due to adverse events	14 PHT, 2 OXC	(Log-rank $p = 0.002$)
	5. Overall evaluation of tolerability (4-point ordinal scale)	Not reproduced here	$p = 0.001$ (physician assessment) $p = 0.038$ (patient assessment)
	6. Clinical utility (time to premature discontinuation for any reason)	34/96 PHT, 24/97 OXC OR (PHT vs OXC) 1.99	1.0 to 3.9; $p = 0.046$
'*Ad hoc*' outcomes	–	–	–
Comments (including whether unadjusted results reported)	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		
HR, hazards ratio; OR, odds ratio; OXC, oxcarbazepine; PHT, phenytoin.			

long (8-week) titration period used in Guerreiro, 1997[207] 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 17 *Adverse events (population with partial and generalised seizure types)*

	Guerreiro, 1997		
		Phenytoin	**Oxcarbazepine**
Criteria for reporting	>5% of patients in either group	Phenytoin	Oxcarbazepine
Events	Somnolence	(29.8)	(25.0)
	Dizziness	(22.3)	(9.4)
	Headache	(14.9)	(13.5)
	Gum hyperplasia	(25.5)	(2.1)
	Apathy	(10.6)	(11.5)
	Ataxia	(13.8)	(0)
	Nervousness	(11.7)	(2.1)
	Nausea	(7.4)	(5.2)
	Abnormal thinking	(6.4)	(5.2)
	Rash	(5.3)	(4.2)
	Abdominal pain	(4.3)	(5.2)
	Hypertrichosis	(8.5)	(0)
	Vomiting	(5.3)	(0)
	Increase in γ-glutamyl transferase	(5.3)	(0)
	At least one adverse event	84/94 (89.4%)	79/96 (82.3%)

Generalised seizures

One trial, by Eriksson, 1998,[208] 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 18 Summary of trials and trial design (generalised seizures)

	Eriksson, 1998
Newer drug(s) investigated	Lamotrigine
Target maintenance dose (mode)	Not reported
Seizure or syndrome	Generalised seizures
Type of trial design	'Response-mediated' withdrawal/cross-over trial
Add-on or monotherapy?	Add-on
Control(s)	Placebo
Study start and end dates	Not reported
Centres and location	1 centre, Scandinavia
Baseline	8 weeks
Titration period	Up to 12 months (mean 5 months)
Maintenance	2 × 12 weeks
Withdrawal	3-week washout in between titration and first 12-week period, and before second 12-week period
Inclusion criteria	Refractory or intractable generalised epilepsy; age >2 years
Timing and additional eligibility for randomisation/continuation on study	Patients experiencing ≥ 50% reduction in seizure frequency or in seizure severity (or both), or with definite improvements in behaviour or motor skills or both were randomised to continue lamotrigine or withdraw. Non-responders were defined as without positive effects of lamotrigine with plasma levels ≤ 10 μg/ml or children who had adverse events during the titration phase
Comments on design	The way in which improvement in behavioural skills or motor improvements were assessed is not explained, which makes the definition of responder very subjective, although it seems from the definition of 'non-responder' that responder was defined by default.

TABLE 19 Quality assessment (generalised seizures)

	Eriksson, 1998
Was assignment of treatment described as random?	Yes
Was method of randomisation described?	No
Was the method really random?	Can't tell
Was allocation of treatment concealed?	Can't tell
Who was blinded to treatment?	Described as 'double-blind'
Was method of blinding adequately described?	No
Were eligibility criteria described?	Yes
Were groups comparable at study entry?	Can't tell
Were groups treated identically apart from the intervention?	Can't tell (methods of blinding not clear)
Was ITT used?	Yes (2 patients withdrawn from lamotrigine arm at family request)
Were withdrawals stated?	Yes
Were reasons for withdrawals stated?	Yes
Was a power calculation done?	No
Was monitoring of plasma levels done (including study drug)?	Yes (including study drug)
Were arrangements to blind plasma monitoring results mentioned?	Results only known to a single coordinator (implies but does not state that this coordinator was not responsible for patient care or assessment)
Comments	–

TABLE 20 *Results (generalised seizures)*

	Eriksson, 1998		
		Placebo/lamotrigine	Lamotrigine/placebo
Number analysed		8	7
Maintenance dose achieved		Not reported	Not reported
Withdrawals including reasons where specified	Total withdrawals	0	2
	Consent withdrawn	–	2
		Results (difference or by arm)	CI for difference; *p*-value
Primary outcome(s)	% reduction in average monthly seizure frequency during double-blind phase	Results reported for each individual; 14/15 had lower seizure rate in lamotrigine period, 1/15 no change	$p < 0.0001$ order effect: $p = 0.13$ period $\times$ treatment: $p = 0.83$ Period effect: not mentioned
Secondary outcomes	1. Seizure severity	Not reported	Not reported
	2. Functional status of patients	Not reported	Not reported
'*Ad hoc*' outcomes	1. >50% reduction in seizure frequency on lamotrigine period compared with placebo period	9/15 patients	Not reported
	2. Analysis of results by seizure type and in patients with Lennox–Gastaut syndrome	Results not reproduced here	Not reported
Comments (including whether unadjusted results reported)	Atypical absences and myoclonic events excluded from analyses owing to difficulty identifying these events in this patient population; not clear what effect this might have, or whether this decision was made prior to unblinding data		
	2 patients experienced atonic seizures when lamotrigine was added		

TABLE 21 *Adverse events (generalised seizures)*

	Eriksson, 1998		
		Placebo	Lamotrigine
Criteria for reporting	Not stated		
Events	Fatigue	10 (58.8)	None
	More intense seizures	4 (23.5)	

Lennox–Gastaut syndrome

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, 1997[209] 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

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

	Motte, 1997	**Sachdeo, 1999**
Newer drug(s) investigated	Lamotrigine	Topiramate
Target maintenance dose (mode)	50–300 mg/day (oral)	6 mg/kg/day (oral assumed)
Seizure or syndrome	Lennox–Gastaut syndrome	Lennox–Gastaut
Type of trial design	Parallel	Parallel
Add-on or monotherapy?	Add-on	Add-on
Control(s)	Placebo	Placebo
Study start and end dates	1994–1995	Not reported
Centres and location	43 centres in USA, Europe	12 centres in USA
Baseline	4 weeks	4 weeks
Titration period	6 weeks	3 weeks
Maintenance	10 weeks	8 weeks
Withdrawal	None	None
Inclusion criteria	More than one type of predominantly generalised seizure including tonic–clonic seizures and drop attacks for at least 1 year; age <11 years at onset of epilepsy; intellectual impairment or a clinical impression of intellectual deterioration	Drop attacks (tonic–atonic) + history of or active atypical absence seizures; age 1–30 years; medically uncontrolled
Timing and additional eligibility for randomisation/continuation on study	Postbaseline; no additional eligibility criteria	Postbaseline; patients who 'qualified for entry' were randomised, but no specific criteria for this are mentioned
Comments on design	Dose titration refers explicitly to lamotrigine only; not clear how/if placebo doses titrated in same way	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

NICE, National Institute for Health and Clinical Excellence.

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)[211] was a placebo-controlled trial of vigabatrin as monotherapy in newly diagnosed and previously untreated patients. Vigevano, 1997[212] and

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

	Motte, 1997	Sachdeo, 1999
Was assignment of treatment described as random?	Yes	Yes
Was method of randomisation described?	No	Yes
Was the method really random?	Can't tell	Yes
Was allocation of treatment concealed?	Can't tell	Yes
Who was blinded to treatment?	Described as 'double-blind'	Investigators, patients, study monitors and observers
Was method of blinding adequately described?	No description	'Blinded medication'; no further details
Were eligibility criteria described?	Yes	Yes
Were groups comparable at study entry?	No; some imbalance in sex, and also a relatively large difference in the numbers randomised to the two groups (90 vs 79)	Yes
Were groups treated identically apart from the intervention?	Can't tell (no description of blinding and dose titration refers to gabapentin group only)	Yes
Was ITT used?	Not clear (see comment)	Yes
Were withdrawals stated?	Yes	Yes
Were reasons for withdrawals stated?	Yes	Yes
Was a power calculation done?	No	Yes
Was monitoring of plasma levels done (including study drug)?	Yes, including lamotrigine	Yes
Were arrangements to blind plasma monitoring results mentioned?	No	No
Comments	Two patients are excluded for 'lack of completeness'; the report does not state to which arm(s) these patients were allocated	Titration refers explicitly to both arms of trial (i.e. including placebo).

Chiron, 1997[213] 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)[211] 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 24 Results (Lennox–Gastaut syndrome)

		Motte, 1997				Sachdeo, 1999		
		Placebo	**Lamotrigine**			**Placebo**	**Topiramate**	
Number randomised		90	79			50	48	
Number analysed		89	78			50	48	
Maintenance dose achieved		Not reported	≤ 25 kg + VPA 13.0 (4.9) ≤ 25 kg no VPA 3.7 (0.9) >25 kg + VPA 8.4 (3.3) >25 kg no VPA 3.7 (1.5)			92% achieved target dose	Median 5.8 mg/kg/day 71% achieved target dose (6 mg/kg/day)	
Withdrawals including reasons where specified	Total withdrawals Adverse events Worse seizure control Protocol violation Loss to follow-up Withdrew consent	14 (15.5) 7 (7.7) 2 (2.2) 3 (3.3) 1 (1.1) 1 (1.1)	7 (8.8) 3 (3.7) 0 (–) 4 (5.0) 0 (–) 0 (–)		Total withdrawals Patient choice	0 0	– –	
		Results	**CI; *p*-value**			**Results**	**CI; *p*-value**	
Primary outcome(s)	% change in frequency of major motor seizures (drop attacks and tonic–clonic seizures)	Placebo ~9% Lamotrigine ~32% (median reduction)	*p* = 0.002		1. % reduction in average monthly seizure rate 2. Composite: % reduction in average monthly drop attack rate and PGE	Placebo ~8.8% Topiramate ~20.6% Drop attacks: Placebo +5.1% Topiramate ~14.8% PGE: Data not reproduced Composite	*p* = ns *p* = 0.041 *p* = 0.037 *p* < 0.01	

continued

TABLE 24 *Results (Lennox–Gastaut syndrome) (cont'd)*

	Motte, 1997		Sachdeo, 1999	
	Results	**CI**	**Results**	**CI**
Secondary outcomes	1. % change in frequency of drop attacks		1. % reduction average monthly seizure rate (tonic, atonic and tonic–clonic only)	
	Placebo –9%		Placebo median 5.2%	
	Lamotrigine –34%	*p* = 0.01	Topiramate median 25.8%	*p* = 0.015
	2. % change in frequency of tonic–clonic seizures		2. % responders	
	Placebo +10%		Drop attacks:	
	Lamotrigine –36%	*p* = 0.03	≥ 50% reduction	
			14% placebo vs 28%	*p* = 0.071
	3. % change in frequency of atypical absences		≥ 75% reduction	
	Placebo –38%		6% vs 17%	Not reported
	Lamotrigine –13%	*p* = 0.96	100% reduction	
			0 vs 1 patient	Not reported
	4. Responder rate, defined as ≥ 50% reduction in major motor seizures		Drop attacks or tonic–clonic:	
	Placebo 16%		≥ 50% reduction	
	Lamotrigine 33%	*p* = 0.01	8% placebo vs 33%	*p* = 0.002
			≥ 75% reduction	
			4% vs 17%	Not reported
			100% reduction	
			0 vs 1 patient	Not reported
			All seizure types:	
			≥ 50% reduction	
			'No difference'	*p* = ns
			≥ 75% reduction	
			0 vs 4 patients	Not reported
			100% reduction	
			Not reported	Not reported
'Ad hoc' outcomes	–	–	–	–
Comments (including whether unadjusted results reported)	Results adjusted for country effects		Results adjusted for investigator	

PGE, parental global evaluation.

TABLE 25 *Adverse events (Lennox–Gastaut syndrome)*

	Motte, 1997		Sachdeo, 1999		
	Placebo	Lamotrigine		Placebo	Topiramate
Criteria for reporting			>10% greater incidence in top arm (i.e. treatment-emergent events)		
Events					
Infection	7 (7.7)	10 (12.6)	Somnolence	(22)	(42)
Fever	12 (13.3)	10 (12.6)	Anorexia	(20)	(40)
Nausea/vomiting	6 (6.6)	7 (8.8)	Nervousness	(10)	(21)
Somnolence	4 (4.4)	3 (3.7)	Behavioural	(10)	(21)
Pharyngitis	9 (10.0)	11 (13.9)	Fatigue	(4)	(19)
Cold/viral illness	0 (–)	4 (5.0)	Dizziness	(0)	(10)
Headache	6 (6.6)	3 (3.7)	Weight loss	(0)	(10)
Rhinitis	7 (7.7)	4 (5.0)			
Otitis media	4 (4.4)	1 (1.2)	Severe adverse events	(10)	(23)
Bronchitis	6 (6.6)	7 (8.8)			
Constipation	2 (2.2)	4 (5.0)			
Convulsions	6 (6.6)	1 (1.2)			
Rash	6 (6.6)	7 (8.8)			
Injury/accident	6 (6.6)	7 (8.8)			

TABLE 26 *Summary of trials and trial design (infantile spasms/West's syndrome)*

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

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[214] (*Tables 30–33*). A 'withdrawal' or 'responder-enriched' design was used; all patients were initially treated with lamotrigine with those achieving complete seizure

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

	Appleton, 1999 (2)	Vigevano, 1997	Chiron, 1997
Was assignment of treatment described as random?	Yes	Yes	Yes
Was method of randomisation described?	Yes	No	No
Was the method really random?	Yes	Can't tell	Can't tell
Was allocation of treatment concealed?	Yes	Can't tell	Can't tell
Who was blinded to treatment?	Described as 'double-blind'	Open-label study	Open-label study
Was method of blinding adequately described?	No	NA	NA
Were eligibility criteria described?	Yes	Not in any detail	Yes
Were groups comparable at study entry?	Yes	Some imbalance in sex ratios	No; differences compatible with chance in a such a small trial (see comment)
Were groups treated identically apart from the intervention?	Yes (if blinding adequate)	Can't tell	Can't tell
Was ITT used?	Yes	Yes	Can't tell; possibly not (see comment)
Were withdrawals stated?	Yes	Yes	Yes
Were reasons for withdrawals stated?	Yes	Yes	Yes
Was a power calculation done?	Yes	No	No
Was monitoring of plasma levels done (including study drug)?	No	No	No
Were arrangements to blind plasma monitoring results mentioned?	NA	NA	NA
Comments	–	–	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

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,[215] comparing gabapentin monotherapy against placebo in newly diagnosed patients. The trial was reported in

TABLE 28 *Results (infantile spasms/West's syndrome)*

	Appleton, 1999 (2)			Vigevano, 1997		
	Placebo	**Vigabatrin**		**ACTH**	**Vigabatrin**	
Number randomised	20	20		19	23	
Number analysed	20	20		19	23	
Maintenance dose achieved	Mean 148 mg/kg	Mean 133 mg/kg		10 IU/day	100–150 mg/kg/day	
Withdrawals including reasons where specified	None stated	–	Total withdrawals	–	–	
			Irritability/agitation	0	–	
			Irritability/raised blood pressure	–	0	
	Results	**CI; *p*-value**		**Results**	**CI; *p*-value**	
Primary outcome(s)				–	–	
1. % change spasm frequency:						
24-h assessment	Placebo –25.9% Vigabatrin –77.9%	95% CI –56 to 65% 95% CI 55 to 89%, *p* = 0.02				
2-h assessment	Placebo –54.6% Vigabatirn –71.9%	95% CI 4 to 78% 95% CI 42 to 86%, *p* = 0.342				
2. Seizure (spasm)-free patients	Placebo 2 (10%) Vigabatrin 7 (35%)	*p* = 0.063				

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

| | Appleton, 1999 (2) | | Vigevano, 1997 | |
	Placebo Results	**Vigabatrin** CI; *p*-value	**Placebo** Results	**Vigabatrin** CI; *p*-value
Secondary outcomes			–	–
	1. Investigator 'global assessment'	Placebo: 3 (15%) marked/moderate improvement 4 (20%) patients deteriorated Vigabatrin: 16 (80%) marked/moderate improvement 0 deteriorated	*p* < 0.0001	1. Proportion spasm-free in phase 1	14/19 (74) ACTH 11/23 (48) vigabatrin	*p* = 0.12
	2. Repeated EEG recordings	Hypsarrhythmia resolved in 1/2 seizure-free placebo patients vs 5/7 on vigabatrin	–		
'Ad hoc' outcomes	>70% improvement: 24-h assessment	Placebo 3/20 (15%) Vigabatrin 8/20 (40%)	Not reported		
	2-h assessment	Placebo 11/20 (55%) Vigabatrin 13/17 (76%)	Not reported		
	No change or worse 24-h	Placebo 9/20 (45%) Vigabatrin 4/20 (20%)	Not reported		
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				

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

Chiron, 1997		Hydrocortisone	Vigabatrin
Number randomised		Not stated	Not stated
Number analysed		11	11
Maintenance dose achieved		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
Withdrawals including reasons where specified	Total withdrawals	2 (18.2)	0
	Lack of efficacy	0	0
	Adverse events	2 (18.2)	0
	Change in AED	0	0
	Other	0	0

		Results	CI; p-value
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 29 *Adverse events (infantile spasms/West's syndrome)*

	Appleton, 1999 (2)		Vigevano, 1997	
	Placebo	**Vigabatrin**	**ACTH**	**Vigabatrin**
Criteria for reporting	Not stated		Not stated	
Events			All events	7 (37)	3 (13)
Drowsiness	Not reported	8	Drowsiness	–	2 (9)
Behaviour change (irritability)	Not reported	1	Hypotonia	–	2 (9)
Number reporting ≥ 1 AE	6 (30%)	12 (60%)	Irritability	7 (37)	1 (4)
			Hypertension	7 (37)	–

(Vigevano, 1997 columns: All events ACTH 7 (37) / Vigabatrin 3 (13); Drowsiness – / 2 (9); Hypotonia – / 2 (9); Irritability 7 (37) / 1 (4); Hypertension 7 (37) / –)

	Chiron, 1997	
	Hydrocortisone (n events)	**Vigabatrin (n events)**
Criteria for reporting	Events reported to or observed by investigator; data relate to both study periods	
Events		
Adverse events (all)	17	8
Drowsiness	–	3
Hyperexcitability/kinesia	5 (1 severe)	3 (1 severe)
Sleep disorders	3 (1 severe)	–
Weight	3	–
Abdominal distension	2 (1 severe)	–
Axial hypertonia	1	1 (severe)
Hypotonia	–	1
Hypertension	2	–
Cushing syndrome	1	–

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

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

TABLE 31 *Quality assessment (absence epilepsy)*

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

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 32 Results (absence epilepsy)

	Frank, 1999	
	Placebo	**Lamotrigine**
Number randomised	14	15
Number analysed	14	14
Maintenance dose achieved	Not reported	Median 5.0 mg/kg/day (range 2–15 mg/kg/day)
Withdrawals including reasons where specified	0 –	1 (6.6) 1 (6.6)
	Results (difference or by arm)	**CI for difference; *p*-value**
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)

	Frank, 1999		
		Placebo	**Lamotrigine**
Criteria for reporting	Events reported by ≥ 5% of patients		
Events	Nervous system complaints (e.g. asthenia, headache, dizziness, hyperkinsia) Rash Events related to infections, ailments common to childhood, or flu syndromes	Not reported	Frequencies not reported

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 34 *Summary of trials and trial design (BECTS)*

	Bourgeois, 1998
Newer drug(s) investigated	Gabapentin
Target maintenance dose (mode)	30 mg/kg/day
Seizure or syndrome	Benign partial epilepsy with centro-temporal spikes
Type of trial design	Parallel
Add-on or monotherapy?	Monotherapy
Control(s)	Placebo
Study start and end dates	Not reported
Centres and location	Not clear
Baseline	Not reported
Titration period	Not reported
Maintenance	36 weeks
Withdrawal	None
Inclusion criteria	At least one and not more than 10 partial or generalised seizures within 6 months of entry; age 4–13 years
Timing and additional eligibility for randomisation/continuation on study	–
Comments on design	Abstract with few details of design

TABLE 35 *Quality assessment (BECTS)*

	Bourgeois, 1998
Was assignment of treatment described as random?	Yes
Was method of randomisation described?	No
Was the method really random?	Can't tell
Was allocation of treatment concealed?	Can't tell
Who was blinded to treatment?	Described as double-blind
Was method of blinding adequately described?	No description
Were eligibility criteria described?	Yes
Were groups comparable at study entry?	Not reported
Were groups treated identically apart from the intervention?	Can't tell
Was ITT used?	Yes
Were withdrawals stated?	Yes
Were reasons for withdrawals stated?	Yes
Was a power calculation done?	Not reported
Was monitoring of plasma levels done (including study drug)?	No
Were arrangements to blind plasma monitoring results mentioned?	NA
Comments	Abstract with very limited information

TABLE 36 *Results (BECTS)*

		Bourgeois, 1998	
		Placebo	**Gabapentin**
Number randomised		112	113
Number analysed		112	113
Maintenance dose achieved		Not reported	Not reported
Withdrawals including reasons where specified	Adverse events	0 (0)	(3.5%)
		Results (difference, or by arm)	**CI for difference; *p*-value**
Primary outcome(s)	Time to treatment failure	No data	*p* = 0.06 for difference by log-rank test
Secondary outcomes	–	–	–
'Ad hoc' outcomes	–	–	–
Comments (including whether unadjusted results reported)	–		

TABLE 37 *Adverse events (BECTS)*

	Bourgeois, 1998		
		Placebo	Gabapentin
Criteria for reporting	None reported		
Events	–	–	–

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

	Chiron, 1996
Newer drug(s) investigated	Vigabatrin
Target maintenance dose (mode)	No dose information (not stated)
Seizure or syndrome	Any
Type of trial design	Withdrawal
Add-on or monotherapy?	Add-on
Control(s)	Placebo
Study start and end dates	Not stated (patients selected from cohort treated in vigabatrin trials 1987–1990)
Centres and location	1 centre; France
Baseline	2 months (possibly retrospective)
Titration period	NA (patients on vigabatrin for 3–39 months prior to entry)
Maintenance	None
Withdrawal	2 months
Inclusion criteria	Partial improvement in terms of seizure frequency or severity, or parental perception of benefit despite lack of response, after at least 3 months on vigabatrin as add-on therapy
	Note: patients selected from a total of 196 included in various vigabatrin trials at one hospital
Timing and additional eligibility for randomisation/continuation on study	None stated
Comments on design	Not clear if the 2-month baseline phase was retrospective. Placebo patients were withdrawn from vigabatrin during the first 2 months; the remaining patients were withdrawn over the following 2 months (described as 'single-blind', implying that the patients were not informed that all active treatment would be withdrawn during this period). The data extracted here are from the first 2-month (double-blind) period.
	Patients were 'dropped' and the randomisation code broken if seizure frequency increased by >50% or increased in severity compared with baseline

59

TABLE 39 *Quality assessment (mixed population)*

	Chiron, 1996
Was assignment of treatment described as random?	Yes
Was method of randomisation described?	No
Was the method really random?	Can't tell
Was allocation of treatment concealed?	Can't tell
Who was blinded to treatment?	Described as 'double-blind'
Was method of blinding adequately described?	No
Were eligibility criteria described?	Yes
Were groups comparable at study entry?	No; 7/9 patients with infantile spasms were allocated 'continue vigabatrin', 'continue vigabatrin' group had a longer mean duration of vigabatrin treatment at entry (12.2 vs 8.6 months) but a shorter median (7 vs 9 months), with standard deviations 10.2 vs 4.1 months
Were groups treated identically apart from the intervention?	Can't tell
Was ITT used?	Yes (for primary outcome; see comment)
Were withdrawals stated?	Yes
Were reasons for withdrawals stated?	Yes
Was a power calculation done?	No
Was monitoring of plasma levels done (including study drug)?	No
Were arrangements to blind plasma monitoring results mentioned?	NA
Comments	The policy of 'dropping' patients if they experienced a worsening of seizure frequency or severity makes ITT impossible for most end-points except for the primary end-point used here (proportion of patients completing phase)

TABLE 40 *Results (mixed population)*

	Chiron, 1996		
		Placebo	Vigabatrin
Number randomised		13	15
Number analysed		13	15
Maintenance dose achieved		Not reported	Not reported
Withdrawals including reasons where specified	Not reported	Not reported	Not reported
		Results (difference, or by arm)	**CI for difference; *p*-value**
Primary outcome(s)	Number of patients completing first phase	Placebo 7 (46.1) Vigabatrin 12 (93.3)	$p < 0.01$
Secondary outcomes	Seizure frequency	Placebo median 95 Vigabatrin median 46	$p < 0.05$
'Ad hoc' outcomes	–	–	0
Comments	–		

TABLE 41 *Adverse events (mixed population)*

	Chiron, 1996		
		Placebo	**Vigabatrin**
Criteria for reporting	None reported	Placebo	
Events	–	–	

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 42 Relevant ongoing trials identified

Start/finish; N	Population; age range	Intervention/comparator	Outcomes	Comment
SANAD[a]. Long-term clinical outcomes and cost-effectiveness of standard and new AEDs 1998/2004 N = 3150 (450 in each of 7 arms)	Patients with epilepsy managed by monotherapy ≥ 5 years	Monotherapy. (a) Carbamazepine vs lamotrigine or topiramate or gabapentin (b) Valproate vs lamotrigine or topiramate	(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	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.
MESS. Multicentre Study of Early Epilepsy and Single Seizures 1999/2002 N = target 1800; recruited 1443	Recent history 7, 1 unprovoked seizure 5 months–85 years	Immediate vs delayed intervention with AED	(a) Time to seizure recurrence (b) Proportion to long-term remission (c) Psychosocial function	
UKISS[b]. United Kingdom Infantile Spasm Study N = target 250; recruited 107 April 1998/August 2003 final follow-up	Infants with infantile spasms (not tuberous sclerosis)	Vigabatrin vs prednisolone or ACTH	(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	Head-to-head trial
Valproate vs lamotrigine (alone or in combination) in patients failing monotherapy N = 178 (by January 2003)	Patients aged ≥ 13 years	Valproate vs lamotrigine as add-on or monotherapy	(a) Freedom from seizures (b) Side-effects	Head-to-head trial
Topomax (Topiramate) as adjunctive therapy for partial seizures with or without secondary generalisation[c]	Children with chronic epilepsy	Open-label Topiramate vs ?	(a) Efficacy (b) Side-effects	
VNS vs new AEDs 2000/2003	Epilepsy refractory to 2 different AEDs (as monotherapy or add-on) 7–16 years	VNS vs new AED (gabapentin, lamotrigine, tiagabine, topiramate or vigabatrin)	(a) Reduction in seizure frequency (b) Reduction in seizure severity (c) Tolerability and safety (d) QoL (e) Cost	Economic study included. Proportion <18 years old likely to be small
Valproate vs lamotrigine or topiramate 2000/2004	Women newly diagnosed with epilepsy requiring treatment 16–45 years	Valproate vs lamotrigine or topiramate	(a) Presence of polycystic ovaries on ultrasound (b) Change in biochemical parameters of hyperandrogenaemia	Proportion <18 years old likely to be small
Levitiracetam as add-on for idiopathic generalised epilepsy and PGTC seizures[d]	Adults and children	Levetiracetam vs placebo		Not head-to-head trial
Confidential information removed				

[a] http://www.liv.ac.uk/neuroscience/sanad/docs/protocol.pdf
[b] RCT nested within epidemiological study.
[c] Limited details from National Research Register.
[d] 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 43 *Review of economic analyses within the GlaxoSmithKline submissions*

	Lamotrigine	Lamotrigine
Manufacturer	GlaxoSmithKline	GlaxoSmithKline
Patient group	Patients with either partial or generalised seizure types, aged ≥ 12 years	Patients with either partial or generalised seizure types, aged ≥ 2 years
Treatment comparison	Comparison of three drugs as first-line monotherapy: lamotrigine vs carbamazepine vs sodium valproate	Comparison of lamotrigine as add-on therapy with placebo add-on therapy
Analysis	Cost–utility analysis	Cost–utility analysis
Model	Simple decision tree	No formal decision model reported
Time horizon	1 year	1 year
Model description	This is a simple decision tree that models first- and second-line treatments. If a patient remains refractory after second-line treatment, no further treatment is considered The model includes states relating to seizures and states relating to drug side effects. The model assumes that partial control of seizures or unacceptable side-effects result in a change of treatment. If the patient experiences unacceptable side-effects from the second drug, the model assumes that no further treatment is considered	No model is reported The analysis simply used efficacy data from placebo-controlled trials and applied utility weights to the main trial outcome (i.e. reduction in seizures). Side-effects were not considered
Outcome measure	QALYs	QALYs
Health state valuation	New utility data are reported. Utility data collected using a standard gamble question from 64 adults (none of whom had epilepsy themselves). The data relate to 7 states in the model described in terms of seizure control and associated side-effects (with the drug name stated in the state description). Respondents asked to consider themselves in the states	New utility data are reported. Utility data collected using a standard gamble question from 64 adults (none of whom had epilepsy themselves). The data relate to 7 states in the model described in terms of seizure control and associated side-effects (with the drug name stated in the state description). Respondents asked to consider themselves in the states
Source of resource data	Initial mean and titration doses derived from published references Other resource use data generated from Delphi panel of experts	Resource use data focused solely on drugs. Initial mean and titration doses derived from published references
Discounting	N/A	N/A
Sensitivity analyses	Effectiveness data varied (data from different trials used) Time to discontinuation of therapy varied Utility scores varied within 95% CIs Results not highly sensitive to these variations	Effectiveness data varied (data from different trials used), allowing comparison of different seizure types Results not highly sensitive to these variations
Model base case results	Mean ICER for lamotrigine (compared with either carbamazepine or sodium valproate) is £13,045 per QALY gained	Mean ICER for lamotrigine (compared with placebo) is £16,456 per QALY gained

65

TABLE 44 *Review of economic analyses within the Janssen–Cilag submission*

	Topiramate	Topiramate
Manufacturer	Janssen–Cilag	Janssen–Cilag
Patient group	Patients with partial seizure types	Patients with partial seizure types and, separately, patients with generalised seizure types
Treatment comparison	Adjunctive therapy with topiramate compared with adjunctive therapy with lamotrigine	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
Analysis	Cost–utility analysis	Cost–utility analysis
Model	Markov model	Markov model
Time horizon	15 years	15 years
Model description	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	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
Outcome measure	QALYs	QALYs
Health state valuation	Utility data taken from Selai *et al.* (1999),[572] which gives adult data on utilities according to seizure frequency and response to treatment	Utility data taken from Selai *et al.* (1999),[572] which gives adult data on utilities according to seizure frequency and response to treatment
Source of resource data	Data taken from a UK cost of illness study (Jacoby *et al.*[573]). This reports costs of adult epilepsy Cost data from published sources	Data taken from a UK cost of illness study (Jacoby *et al.*[573]). This reports costs of adult epilepsy Cost data from published sources
Discounting	1.5% for QALYs 6% for costs	1.5% for QALYs 6% for costs
Sensitivity analyses	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	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
Model base case results	Topiramate dominates lamotrigine	For partial seizure patients (topiramate vs carbamazepine): £734 per QALY For generalised seizure patients (topiramate vs sodium valproate): £635 per QALY
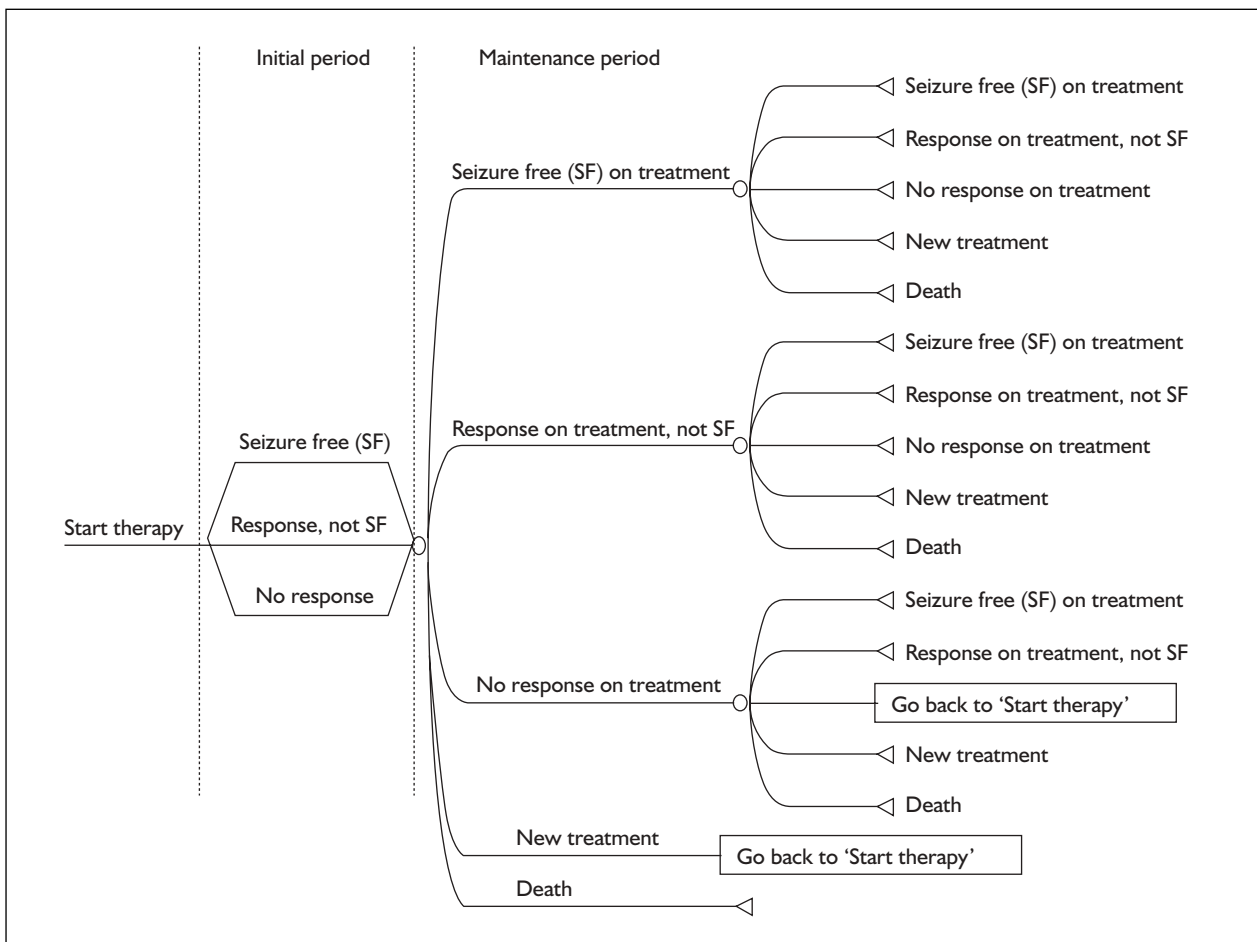
FIGURE 1 *Markov model depicted in the submission document*

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).

67

Example of a choice set

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

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)*

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

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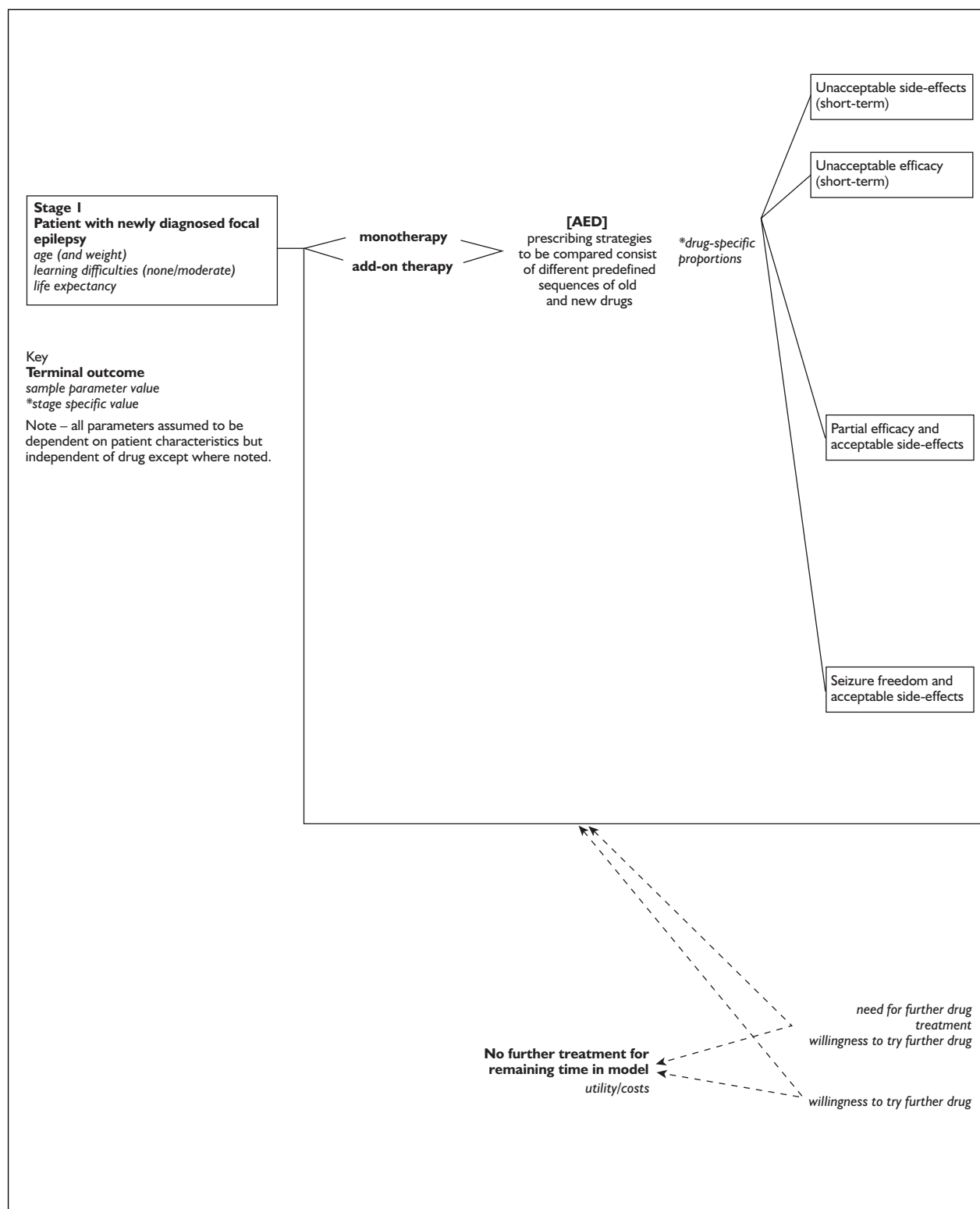
FIGURE 3 *Patient pathway for a child with newly diagnosed partial epilepsy*

time on drug
utility/cost
*willingness to try further treatment → **No further treatment for remaining time in model**

time on drug
utility/cost
*willingness to try further treatment

| Remain on drug and try further adjunctive therapy | *utility/cost* *time to try further treatment* |

*willingness to remain on drug
*willingness to try further treatment

| Reluctant to try further treatment or attempt withdrawal | *utility/cost* ----→ **On drug for remaining time in model** |

| Reluctant to remain on drug | *utility/cost* *time on drug* |

| Reluctant to remain on drug or try any further treatment | *utility/cost* *time on drug* ----→ **No further treatment for remaining time in model** *utility/costs* |

| Reluctant to attempt withdrawal | *utility/cost* ----→ **On drug for remaining time in model** |

willingness to withdraw
successful withdrawal

| Unsuccessful attempt to withdraw | *utility/cost* *time to reintroduce drug* ----→ **On drug for remaining time in model** |

| Successful withdrawal | *utility/cost on drug* *utility/cost off drug* *time to achieve withdrawal* ----→ **No further treatment for remaining time in model** *utility/costs* |

*likelihood surgery considered

Not considered for surgery

Rediagnosed (not epilepsy)
utility/costs

No further treatment for remaining time in model
utility/costs

willingness to try further drug

| Unsuitable for surgery |

suitability for surgery
rediagnosis at investigation

Considered for surgery

| Surgery successful |

| Surgery unsuccessful |

success of surgery

| Surgery |

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 45 *Model parameter list*

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

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
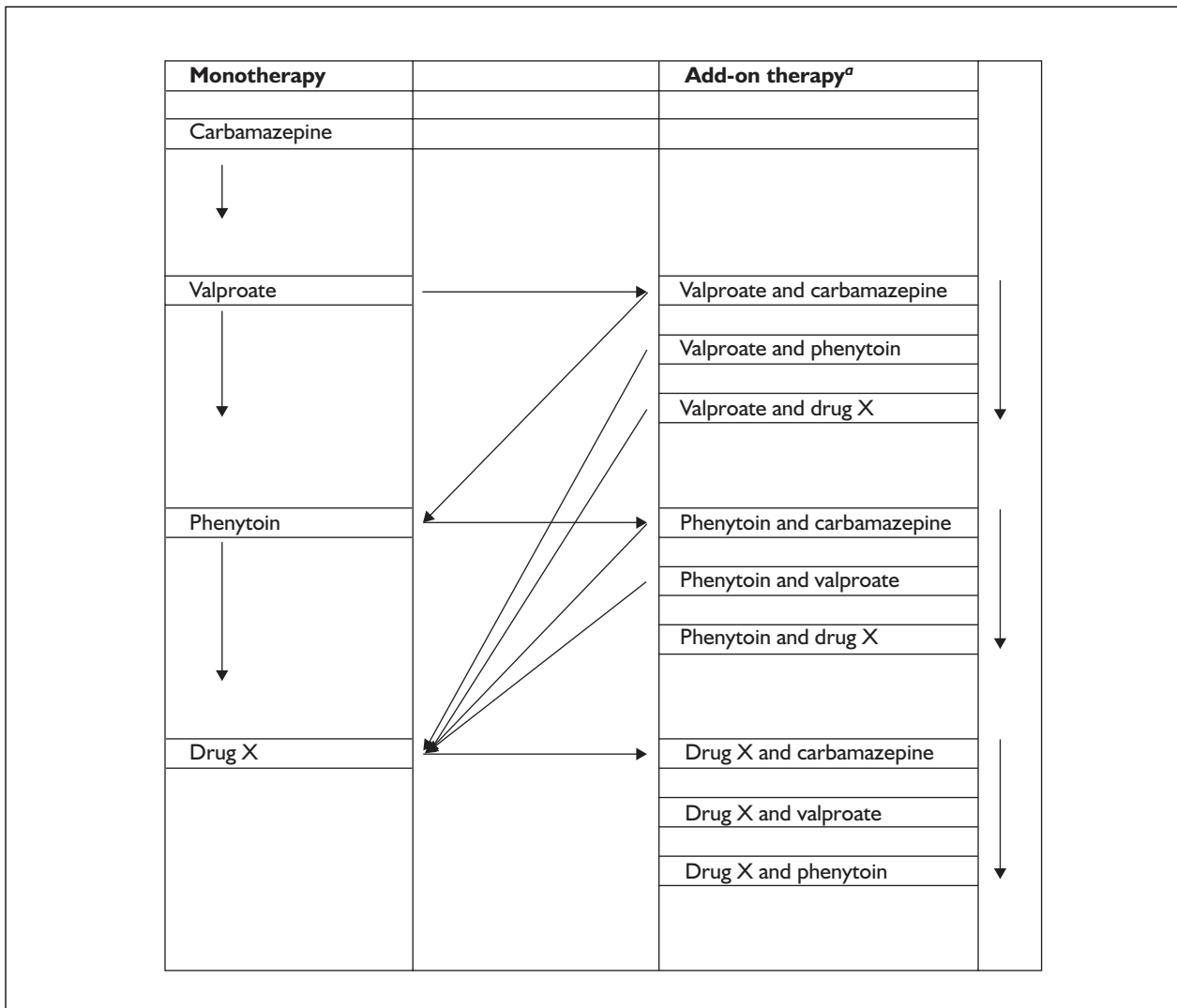
FIGURE 4 *'No new drug' strategy. ªDrug only used in combination if, in earlier use in this patient, it was not associated with unacceptable side-effects or unacceptable efficacy.*

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*.

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.[12,217–226] 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

TABLE 46 *EuroQol EQ-5D states and scores for the six epilepsy model states (without learning difficulties)*

Health states	Without learning difficulties				
	Utility values				
	Average (SD)	Quartile range			
		25	50	75	Borda ranking score[a]
Unacceptable side-effects (AES)	0.767 (0.1825)	0.6890	0.8120	0.8830	6
Unacceptable efficacy (USF)	0.782 (0.1972)	0.7430	0.8120	0.8830	5
Partial efficacy and partial side-effects (the drug is continued) (PAR)	0.908 (0.1144)	0.8830	0.8830	1.0000	3
Seizure freedom and acceptable side-effects (the drug is continued) (EFFd)	0.981 (0.0525)	1.0000	1.0000	1.0000	2
Seizure freedom following withdrawal (EFFw)	1.000 (0.0000)	1.0000	1.0000	1.0000	1
Untreated state (UNT)	0.846 (0.1375)	0.7655	0.8830	1.0000	4

[a] 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)*

Health states	With learning difficulties				
	Utility values				
	Average (SD)	Quartile range			
		25	50	75	Borda ranking score[a]
Unacceptable side-effects (AES)	0.603 (0.2416)	0.4213	0.7080	0.7790	6
Unacceptable efficacy (USF)	0.675 (0.1830)	0.5850	0.7790	0.7790	5
Partial efficacy and partial side-effects (the drug is continued) (PAR)	0.782 (0.09)	0.7613	0.7790	0.8320	3
Seizure freedom and acceptable side-effects (the drug is continued) (EFFd)	0.830 (0.1016)	0.7790	0.7790	0.8830	2
Seizure freedom following withdrawal (EFFw)	0.857 (0.1000)	0.7790	0.8150	1.0000	1
Untreated state (UNT)	0.707 (0.1938)	0.1938	0.5865	0.7790	4

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 UK[228]).

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 48 *Costs[a] associated with all AEDs considered in the model*

AEDs	Cost per mg (pence)	Titration dose (per day)	Maintenance dose (per day)
Newer AEDs			
Gabapentin	0.0023	Age >12 years: 20 mg/kg Others: 275 mg	Age >12 years: 30 mg/kg Others: 1100 mg
Lamotrigine	0.016	Age < 12 years: 1.5 mg/kg Others: 75 mg	Age < 12 years: 3 mg/kg Others: 150 mg
Oxcarbazepine	0.0013	20 mg/kg	30 mg/kg
Topiramate	0.0146	2 mg/kg	7 mg/kg
Older AEDs			
Carbamazepine	0.00028	200 mg/day	1–5 years: 300 mg/day 6–10 years: 500 mg/day 11–18 years: 800 mg/day
Valproate	0.00028	Up to 20 kg: 20 mg/kg Over 20 kg: 30 mg/kg	Up to 20 kg: 20 mg/kg Over 20 kg: 35 mg/dkg
Phenytoin	0.00089	6 mg/kg	6 mg/kg

[a] These unit costs are taken from the BNF (September 2002).

(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 49 *Cost information for patients with and without neurological impairment (£ per annum)*

Health states	Without learning difficulties				With learning difficulties			
	Average per annum	Quartile range			Average per annum	Quartile range		
		25	50	75		25	50	75
Unacceptable side-effects (AES)	1113	520	894	1328	1832	804	1130	2321
Unacceptable efficacy (USF)	1450	374	757	1944	1750	541	1300	2532
Partial efficacy and partial side-effects (the drug is continued) (PAR)	321	145	281	411	343	196	327	438
Seizure freedom and acceptable side-effects (the drug is continued) (EFFd)	322	151	223	363	273	201	244	411
Seizure freedom following withdrawal (EFFw)	291	130	155	369	227	109	175	348
Untreated state (UNT)	1001	152	218	564	2969	135	218	789

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, 30–40% 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[232] report that higher starting doses of lamotrigine resulted in worse treatment retention, reflecting the need for careful dose titration.

Wong and colleagues[232] 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,[231] 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[230] 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;[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,[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[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.
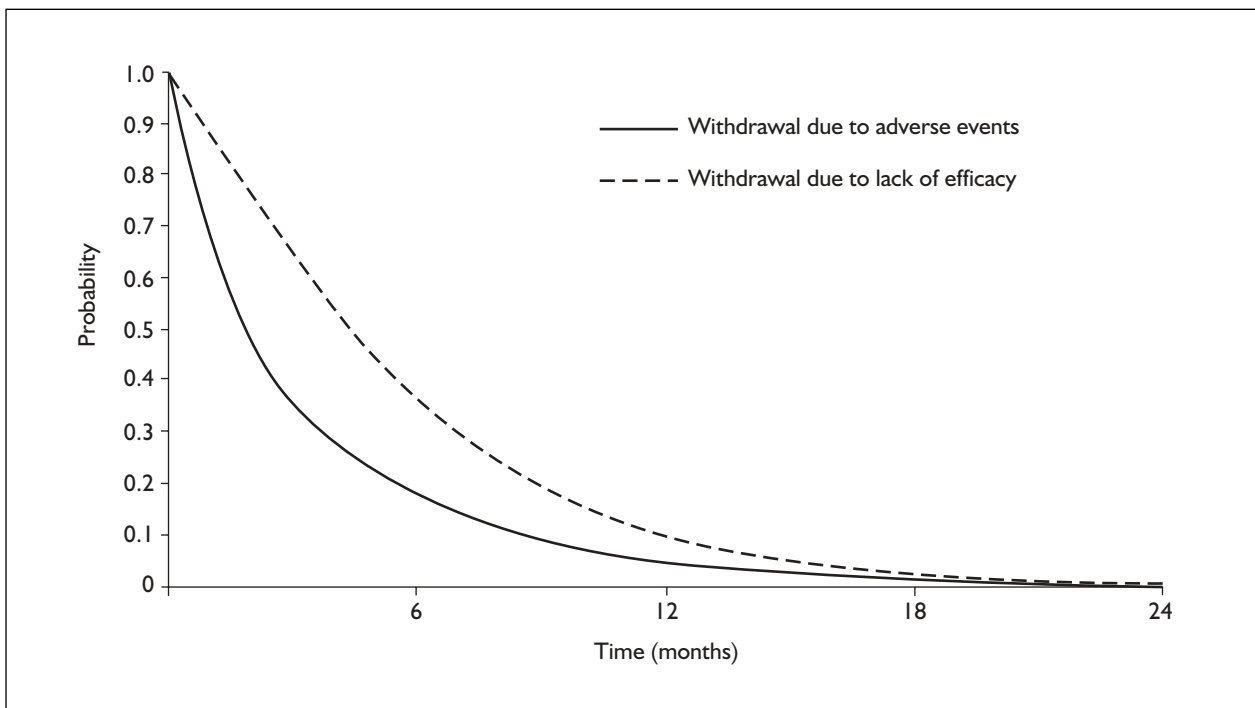
FIGURE 5 *Treatment retention curves for withdrawal due to side-effects and lack of efficacy*

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[145] and remission rates over time are also reported in the National General Practice Study of Epilepsy.[234] 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, 2001[197] and Zamponi, 1999[198] combined (the results for carbamazepine for both trials are similar). Meta-analyses of the older drugs[123,129] 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 '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)*

Treatment	First-line treatment Proportion	SD	Second-line treatment Proportion	SD	Third-line treatment Proportion	SD	Fourth-line + Proportion	SD
Carbamazepine								
USE	**0.113**	**0.029**	0.113		0.113		0.113	
UE	**0.107**	**0.029**	0.107		0.107		0.107	
PE	**0.153**		0.529		0.679		0.739	
CSF	**0.626**	**0.047**	0.250		0.100		0.040	
Valproate								
USE	0.119		0.119		0.119		0.119	
UE	0.113		0.113		0.113		0.113	
PE	0.174		0.531		0.673		0.730	
CSF	0.595		0.238		0.095		0.038	
Phenytoin								
USE	0.125		0.125		0.125		0.125	
UE	0.119		0.119		0.119		0.119	
PE	0.192		0.531		0.666		0.721	
CSF	0.565		0.226		0.090		0.036	
Lamotrigine								
USE	**0.062**	**0.019**	0.062	0.019	0.062	0.019	0.062	0.019
UE	**0.131**	**0.027**	0.131	0.027	0.131	0.027	0.131	0.027
PE	**0.238**		0.579		0.716		0.770	
CSF	**0.569**	**0.040**	0.227	0.040	0.091	0.040	0.036	0.040
Valproate + old								
USE	*0.131*		*0.131*		*0.131*		*0.131*	
UE	*0.105*		*0.105*		*0.105*		*0.105*	
PE	*0.110*		*0.503*		*0.660*		*0.723*	
CSF	*0.654*		*0.262*		*0.105*		*0.042*	
Phenytoin + old								
USE	*0.137*		*0.137*		*0.137*		*0.137*	
UE	*0.110*		*0.110*		*0.110*		*0.110*	
PE	*0.131*		*0.504*		*0.653*		*0.713*	
CSF	*0.622*		*0.249*		*0.099*		*0.040*	
Generic old drug								
USE	*0.131*		0.131		0.131		0.131	
UE	*0.124*		0.124		0.124		0.124	
PE	*0.208*		0.530		0.659		0.710	
CSF	*0.537*		0.215		0.086		0.034	
Gabapentin + old								
USE	0.081	0.025	0.081	0.025	0.081	0.025	**0.081**	**0.025**
UE	0.266	0.041	0.266	0.041	0.266	0.041	**0.266**	**0.041**
PE	0.252		0.492		0.588		**0.627**	
CSF	0.401	0.015	0.160	0.015	0.064	0.015	**0.026**	**0.015**
Lamotrigine + old								
USE	0.069	0.026	0.069	0.026	0.069	0.026	**0.069**	**0.026**
UE	0.123	0.033	0.123	0.033	0.123	0.033	**0.123**	**0.033**
PE	0.186		0.560		0.709		**0.769**	
CSF	0.622	0.020	0.249	0.020	0.100	0.020	**0.040**	**0.020**
Oxcarbazepine + old								
USE	0.143	0.030	0.143	0.030	0.143	0.030	**0.143**	**0.030**
UE	0.062	0.014	0.062	0.014	0.062	0.014	**0.062**	**0.014**
PE	0.225		0.567		0.704		**0.759**	
CSF	0.570	0.016	0.228	0.016	0.091	0.016	**0.036**	**0.016**

continued

TABLE 50 *Proportions moving into the main model outcome states ('anchor points' marked in bold) (cont'd)*

Treatment	First-line treatment Proportion	SD	Second-line treatment Proportion	SD	Third-line treatment Proportion	SD	Fourth-line + Proportion	SD
Topiramate + old								
USE	0.120	0.044	0.124	0.044	0.124	0.044	**0.124**	**0.044**
UE	0.190	0.044	0.194	0.044	0.194	0.044	**0.194**	**0.044**
PE	0.010		0.377		0.560		**0.634**	
CSF	0.680	0.034	0.305	0.034	0.122	0.034	**0.049**	**0.034**

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*

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

[a] 10% not going on to any further drug treatment chosen to approximate proportion going on to have successful surgery.

Our plan was to consider the two new AEDs licensed as monotherapies for use in children: lamotrigine (for use in children over 12 years olds) and oxcarbazepine (for use in children over 6 years olds). 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
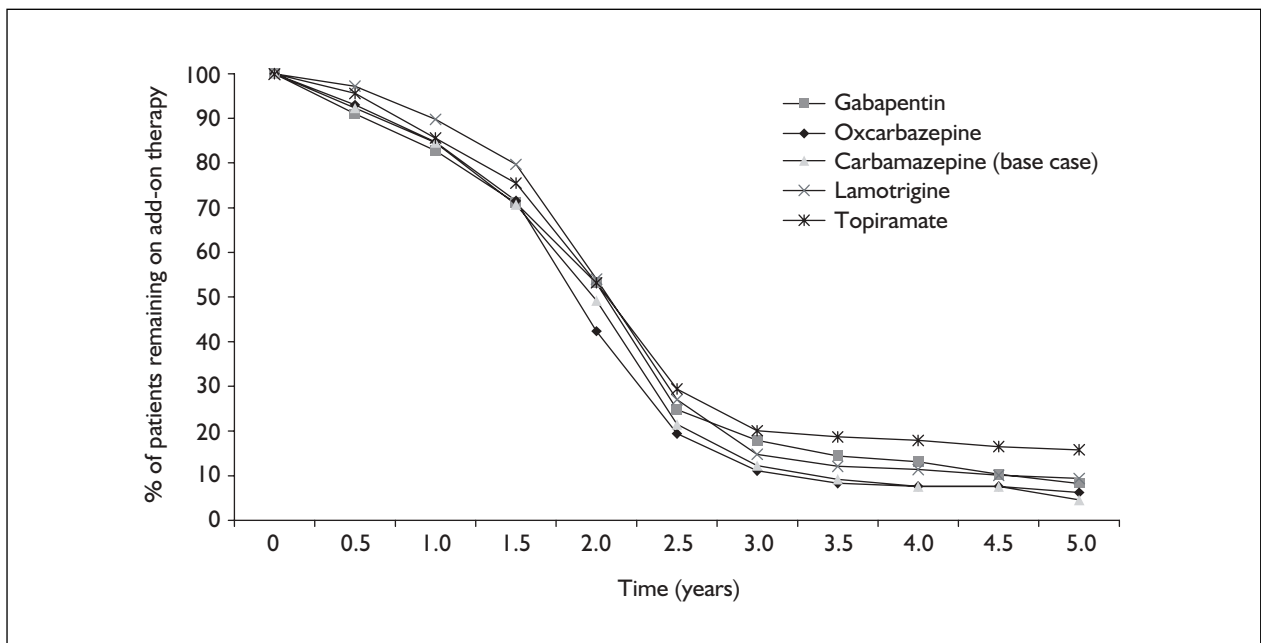
FIGURE 6 *First-choice add-on drug retention rate*

- 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

83
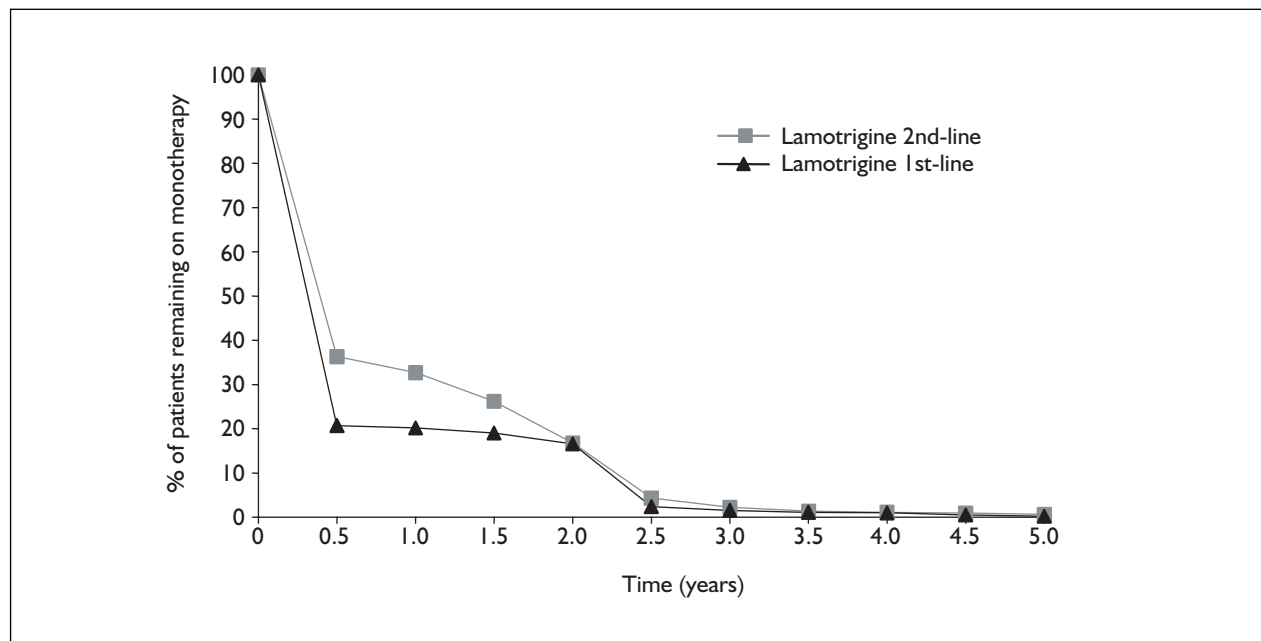
FIGURE 7 *Monotherapy drug retention rate*

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,
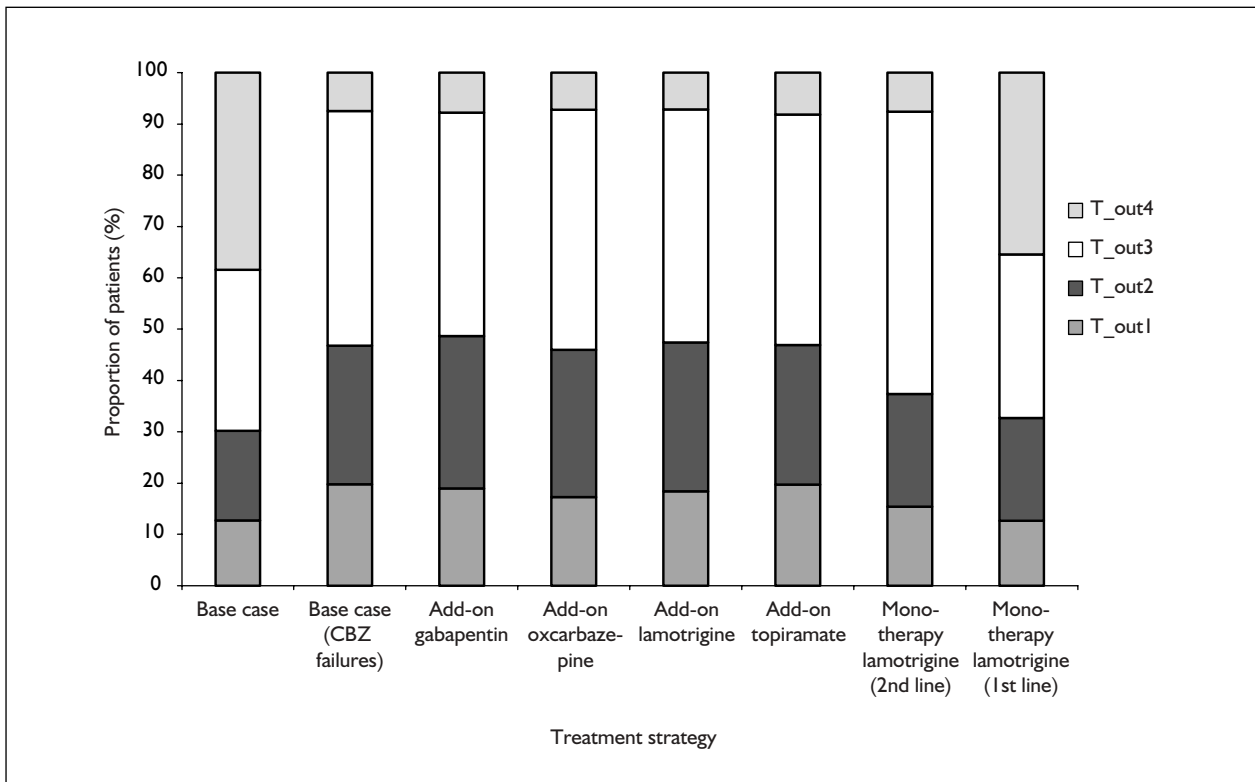
FIGURE 8 *Average time in model outcomes for all treatment strategies. T_out1, time with unacceptable side-effects; T_out2, time with unacceptable efficacy; T_out3, time with partial efficacy and acceptable side-effects; T_out4, time with seizure freedom and acceptable side-effects.*

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

	Costs and QALYs accrued from diagnosis of epilepsy				Costs and QALYs accrued from time of failure on carbamazepine			
	Costs (£)		QALYs		Costs (£)		QALYs	
Run	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	2320	1953	6.6352	3.6456	2102	2162	3.6599	2.9341
2	2327	2025	6.5936	3.131	2075	2151	3.5839	2.9013
3	2360	2029	6.6591	3.6403	2089	2183	3.6352	2.9239
4	2310	1965	6.5942	3.6316	2079	2181	3.6338	2.9106
5	2326	1971	6.6224	3.6552	2069	2128	3.6249	2.9389
6	2343	2000	6.6152	3.6328	2098	2212	3.615	2.9657
7	2288	1895	6.556	3.6436	2118	2240	3.5903	2.9273
8	2292	1963	6.6291	3.6336	2104	2191	3.6425	2.9388
9	2340	2068	6.645	3.618	2053	2143	3.5944	2.9212
10	2356	2044	6.7264	3.6565	2088	2191	3.5943	2.9201
11	2297	1964	6.5271	3.6643	2114	2171	3.6369	2.9577
12	2328	1966	6.661	3.6305	2103	2231	3.5813	2.9181
13	2345	2023	6.6433	3.6554	2091	2164	3.574	2.9121
14	2345	2049	6.5937	3.6389	2063	2120	3.635	2.9566
15	2281	1896	6.5886	3.6746	2060	2080	3.6434	2.9237
16	2315	1989	6.6137	3.6607	2098	2218	3.5936	2.9123
17	2341	1999	6.6276	3.6267	2079	2172	3.5933	2.9192
18	2327	2020	6.6176	3.6288	2088	2161	3.623	2.9275
19	2318	1992	6.6261	3.6568	2107	2229	3.6278	2.9381
20	2297	1956	6.6225	3.6644	2102	2193	3.6009	2.9237
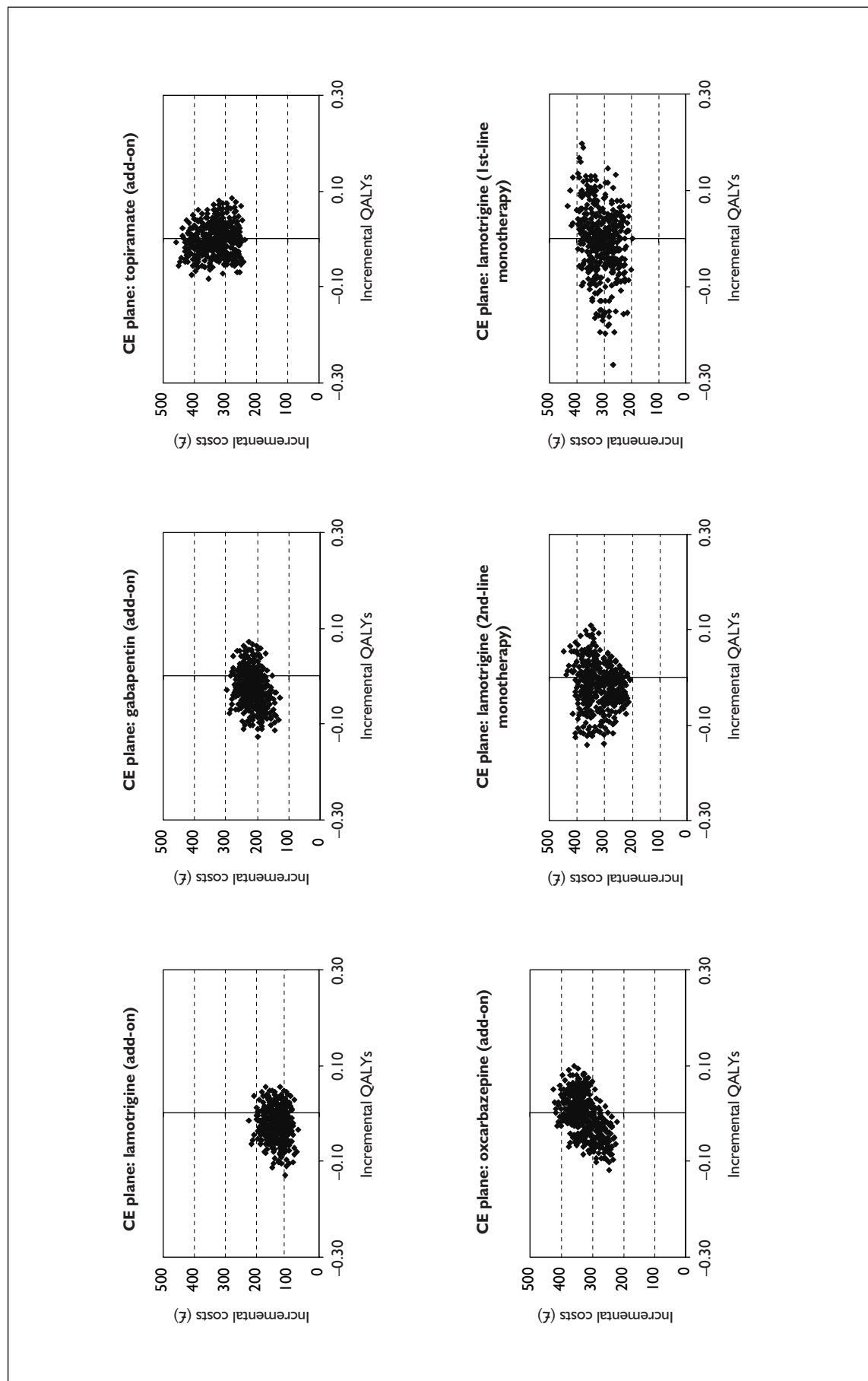
FIGURE 9 *Results for each new drug reported on cost-effectiveness (CE) planes*
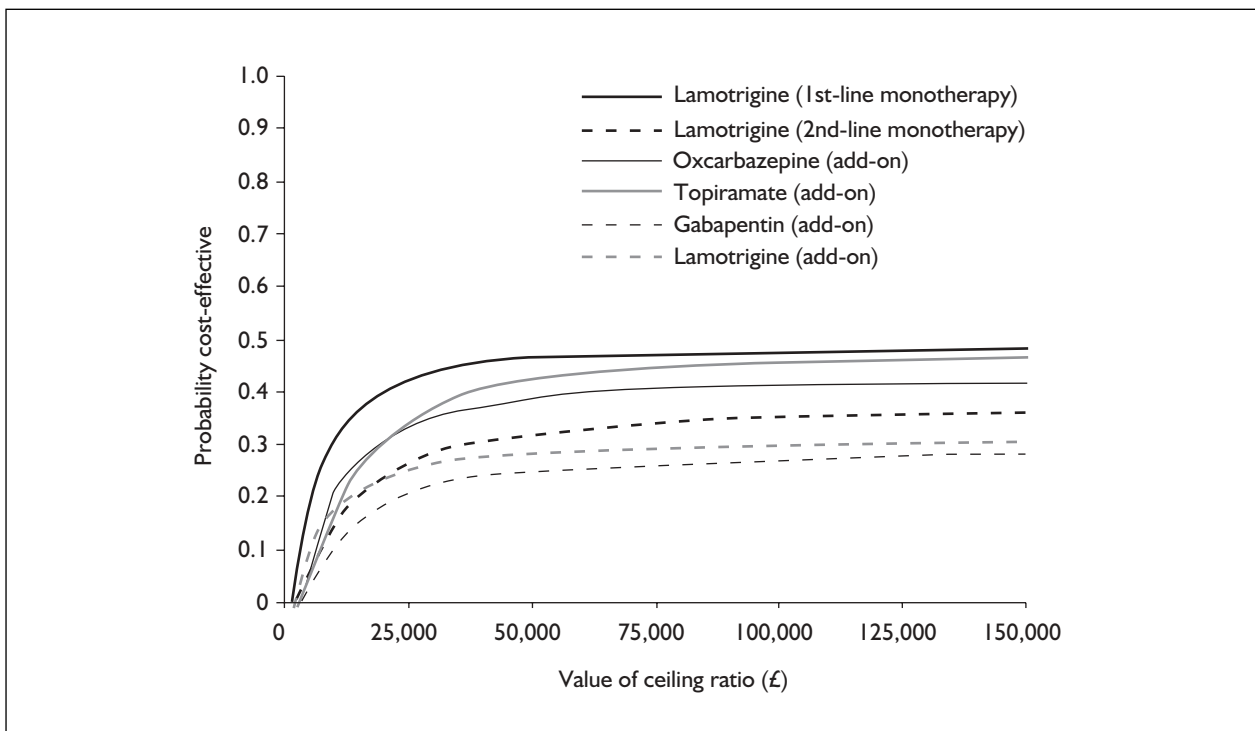
FIGURE 10 *CEACs for each new drug*

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 rediagnosed 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.

Chapter 5
Implications for other parties

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 to be 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 over-treatment 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.

93

Acknowledgements

References

1. Wallace SJ. Definitions. In Wallace SJ, editor. *Epilepsy in children*. London: Chapman and Hall; 1996. pp. 1–4.

2. Jefferys JGR, Traub RD. Cellular mechanisms of epilepsy pathogenesis. In Wallace SJ, editor. *Epilepsy in children*. London: Chapman and Hall; 1996. pp. 109–42.

3. Appleton R, Gibbs J. *Epilepsy in childhood and adolescence*. London: Martin Dunitz; 1995.

4. International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981;**22**:489–501.

5. International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;**30**:389–99.

6. Moreno G. Reflections on classification of epileptic seizures. *Rev Neurol* 2002;**34**:532–6.

7. Parra J, Augustijn PB, Geerts Y, van Emde B. Classification of epileptic seizures: a comparison of two systems. *Epilepsia* 2001;**42**:476–82.

8. Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; **42**:796–803.

9. Trevathan E. Epilepsy syndrome-specific anti-epileptic drug therapy for children. *Lancet* 2000;**356**:1623–4.

10. Pellock JM. Managing pediatric epilepsy syndromes with new antiepileptic drugs. *Pediatrics* 1999;**104**:1106–16.

11. Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. *Epilepsia* 2002; **43** Suppl 3:27–32.

12. Camfield C, Breau L, Camfield P. Impact of pediatric epilepsy on the family: a new scale for clinical and research use. *Epilepsia* 2001;**42**:104–12.

13. Sillanpaa M, Shinnar S. Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. *Ann Neurol* 2002;**52**:303–10.

14. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001;**56**:1445–52.

15. Glauser TA, Morita DA. Lennox–Gastaut syndrome. *e medicine* 2002. URL: http://www.emedicine.com/neuro/topic186.htm

16. Trevathan E. Infantile spasms and Lennox-Gastaut syndrome. *J Child Neurol* 2002;**17** Suppl 2: 2S9–2S22.

17. Appleton RE. West syndrome: long-term prognosis and social aspects. *Brain Dev* 2001;**23**:688–91.

18. Olsson I, Campenhausen G. Social adjustment in young adults with absence epilepsies. *Epilepsia* **34**:846–51.

19. Wirrell EC, Camfield CS, Camfield PR, Dooley JM, Gordon KE, Smith B. Long-term psychosocial outcome in typical absence epilepsy. Sometimes a wolf in sheeps' clothing. *Arch Pediatr Adolesc Med* 1997;**151**:152–8.

20. Endziniene M, Pauza V, Miseviciene I. Prevalence of childhood epilepsy in Kaunas, Lithuania. *Brain Dev* 1997;**19**:379–87.

21. Eriksson KJ, Koivikko MJ. Prevalence, classification, and severity of epilepsy and epileptic syndromes in children. *Epilepsia* 1997;**38**:1275–82.

22. Freitag CM, May TW, Pfafflin M, Konig S, Rating D. Incidence of epilepsies and epileptic syndromes in children and adolescents: a population-based prospective study in Germany. *Epilepsia* 2001;**42**:979–85.

23. Ross SD, Estok R, Chopra S, French J. Management of newly diagnosed patients with epilepsy: a systematic review of the literature. Evidence Report/Technology Assessment No. 39 (Contract 290-97-0016 to Metaworks Inc.) AHRQ Publication No. 01.E038. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

24. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults: A National Clinical Guideline recommended for use in Scotland. *Scottish Intercollegiate Guidelines Network* 1997;1–55. URL: http://www.sign.ac.uk/pdf/sign21.pdf

25. Frost S, Crawford P, Chappell B. *National statement of good practice for the treatment and care of people who have epilepsy*. London: Joint Epilepsy Council; 2002.

26. Nordli DR, Bazil CW, Scheuer ML, Pedley TA. Recognition and classification of seizures in infants. *Epilepsia* 1997;**38**:553–60.

27. Delanty N, Vaughan CJ, French JA. Medical causes of seizures. *Lancet* 1998;**352**:383–90.

97

28. Stephenson JBP. Nonepileptic seizure, anoxic–epileptic seizures, and epileptic–anoxic seizures. In Wallace SJ, editor. *Epilepsy in children*. London: Chapman and Hall; 1996. pp. 5–26.

29. Chadwick D, Smith D. The misdiagnosis of epilepsy. *BMJ* 2002;**324**:495–6.

30. Gibbs J, Appleton RE. False diagnosis of epilepsy in children. *Seizure* 1992;**1**:15–18.

31. Grunewald RA, Chroni E, Panayiotopoulos CP. Delayed diagnosis of juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry* 1992;**55**:497–9.

32. Appleton RE. Misdiagnosis of epilepsy. Misdiagnosis occurs particularly in children. *BMJ* 2002;**324**:1219.

33. British Paediatric Association Standing Committee on Paediatric Practice Guidelines. *Imaging in children with epilepsy (BPA (1995) June)*. Report CO/96/02. British Paediatric Association; 1995.

34. Slegtenhorst Mv, Hoogt Rd, Hermans C, Nellist M, Janssen B, Verhoef S, *et al*. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science* 1997;**277**:805–8.

35. Drury I. EEG in benign and malignant epileptic syndromes of childhood. *Epilepsia* 2002; **43** Suppl 3:17–26.

36. Navarro V, Pons A, Romero A, Bernardo M. Topiramate for clozapine-induced seizures. *Am J Psychiatry* 2001;**158**:968–9.

37. Duncan JS. Seizure-induced neuronal injury: human data. *Neurology* 2002;**59** (9 Suppl 5): S15–S20.

38. Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, *et al*. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. *Epilepsia* 2002;**43**:1062–71.

39. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998;**352**:1970–3.

40. Kurtz Z, Tookey P, Ross E. Epilepsy in young people: 23 year follow up of the British national child development study. *BMJ* 1998;**316**:339–42.

41. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;**123** (Pt 4):665–76.

42. Heaney DC, MacDonald BK, Everitt A, Stevenson S, Leonardi GS, Wilkinson P, *et al*. Socioeconomic variation in incidence of epilepsy: prospective community based study in south east England. *BMJ* 2002;**325**:1013–16.

43. Sander JW, Hart AP, Johnson AL, Shorvon S. National General Practice Study of Epilepsy: newly diagnosed epileptic seizures in a general population. *Lancet* 1990;**336**:1267–71.

44. Beilmann A, Napa A, Hamarik M, Soot A, Talvik I, Talvik T. Incidence of childhood epilepsy in Estonia. *Brain Dev* 1999;**21**:166–74.

45. Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley JM. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia* 1996;**37**:19–23.

46. Waaler PE, Blom BH, Skeidsvoll H, Mykletun A. Prevalence, classification, and severity of epilepsy in children in western Norway. *Epilepsia* 2000;**41**:802–10.

47. Sidenvall R, Forsgren L, Heijbel J. Prevalence and characteristics of epilepsy in children in northern Sweden. *Seizure* 1996;**5**:139–46.

48. Beilmann A, Napa A, Soot A, Talvik I, Talvik T. Prevalence of childhood epilepsy in Estonia. *Epilepsia* 1999;**40**:1011–19.

49. Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the epilepsies in children and adolescents. *Epilepsia* 1989;**30**:94–106.

50. Bouma PA, Bovenkerk AC, Westendorp RG, Brouwer OF. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. *Neurology* 1997;**48**:430–7.

51. Peters JM, Camfield CS, Camfield PR. Population study of benign rolandic epilepsy: is treatment needed? *Neurology* 2001;**57**:537–9.

52. Berg AT, Shinnar S, Levy SR, Testa FM, Smith R, Beckerman B, *et al*. Defining early seizure outcomes in pediatric epilepsy: the good, the bad and the in-between. *Epilepsy Res* 2001;**43**:75–84.

53. Beghi E, Cornaggia C. Morbidity and accidents in patients with epilepsy: results of a European cohort study. *Epilepsia* 2002;**43**:1076–83.

54. Breningstall GN. Mortality in pediatric epilepsy. *Pediatr Neurol* 2001;**25**:9–16.

55. Camfield CS, Camfield PR, Veugelers PJ. Death in children with epilepsy: a population-based study. *Lancet* 2002;**359**:1891–5.

56. Callenbach PM, Westendorp RG, Geerts AT, Arts WF, Peeters EA, van Donselaar CA, *et al*. Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. *Pediatrics* 2001;**107**:1259–63.

57. Donner EJ, Smith CR, Snead OC. Sudden unexplained death in children with epilepsy. *Neurology* 2001;**57**:430–4.

58. Cockerell OC, Hart YM, Sander JW, Shorvon SD. The cost of epilepsy in the United Kingdom: an

estimation based on the results of two population-based studies. *Epilepsy Res* 1994;**18**:249–60.

59. Jacoby A, Graham-Jones S, Baker G, Ratoff L, Heyes J, Dewey M, *et al*. A general practice records audit of the process of care for people with epilepsy. *Br J Gen Pract* 1996;**46**:595–9.

60. NHS Executive. *Burden of disease: a discussion document*. London: Department of Health; 1996.

61. Glauser TA. Integrating clinical trial data into clinical practice. *Neurology* 2002;**58**(12 Suppl 7):S6–12.

62. Lhatoo SD, Sander JWAS, Shorvon SD. The dynamics of drug treatment in epilepsy: an observational study in an unselected population based cohort with newly diagnosed epilepsy followed up prospectively over 11–14 years. *J Neurol Neurosurg Psychiatry* 2001;**71**:632–7.

63. Meads C, Bradley P, Burls A. *The effectiveness of specialist epilepsy services*. DPHE Report No. 27. Birmingham: West Midlands Health Technology Assessment Group; 2001.

64. Kitson A, Shorvon S. *Services for patients with epilepsy: a report of a CSAG Committee*. London, HMSO: 2000. URL: http://www.epilepsy.org.uk/action/reports.html

65. Hanna DJ, Black M, Sander JW, Smithson WH, Appleton R, Brown S, *et al*. National Sentinel Clinical Audit on Epilepsy-Related Death; epilepsy-death in the shadows. Norwich: The Stationary Office; 2002. URL: http://www.official-documents.co.uk/document/reps/nscaerd/nscaerd.pdf

66. NHS: *NHS Executive Letter EL(95)120*. Leeds: NHS; 1996.

67. Brown SW, Lee P. Developments in UK service provision for people with epilepsy: the impact of the NHS Executive Letter 95/120. *Seizure* 1998;**7**:185–7.

68. Brown SW, Lee P, Buchan S, Jenkins A. A 2 year follow-up of NHS Executive Letter 95/120: where is the commitment to quality? *Seizure* 1999;**8**:128–31.

69. Clinical Standards Advisory Group. *Services for people with epilepsy*. London: HMSO; 1999. URL: http://www.info.doh.gov.uk/doh/point.nsf/66b6f04b dca6defc0025693b0051ada0/f247dcff808e3032002 568b2005a39ca/$FILE/epile.pdf

70. Hart YM, Shorvon SD. The nature of epilepsy in the general population. II. Medical care. *Epilepsy Res* 1995;**21**:51–8.

71. Carpay HA, Arts WF, Geerts AT, Stroink H, Brouwer OF, Boudewyn P, *et al*. Epilepsy in childhood: an audit of clinical practice. *Arch Neurol* 1998;**55**:668–73.

72. Berg AT, Levy SR, Testa FM, Shinnar S. Treatment of newly diagnosed pediatric epilepsy: a community-based study. *Arch Pediatr Adolesc Med* 1999;**153**:1267–271.

73. Whitehouse W, Morris B. Paediatric out-patient antiepileptic drug doses recorded in the medical charts are not reliable: implications for the notion of noncompliance. *Seizure* 1997;**6**:41–2.

74. British Epilepsy Association. *Epilepsy care: making it happen. A tool kit for today*. Leeds: British Epilepsy Association; 1999.

75. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia* 1988; **29**:794–804.

76. Holmes GL. Overtreatment in children with epilepsy. *Epilepsy Res* 2002;**52**:35–42.

77. Perucca E. Overtreatment in epilepsy: adverse consequences and mechanisms. *Epilepsy Res* 2002; **52**:25–33.

78. MacDonald BK, Johnson AL, Sander JW, Shorvon SD. Febrile convulsions in 220 children – neurological sequelae at 12 years follow-up. *Eur Neurol* 1999;**41**:179–86.

79. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002;**43**:983–92.

80. Tatum WOI, French JA, Faught E, Morris GL III, Liporace J, Kanner A, *et al*. Postmarketing experience with topiramate and cognition. *Epilepsia* 2001;**42**:1134–40.

81. French JA. Postmarketing surveillance of new antiepileptic drugs: the tribulations of trials. *Epilepsia* 2002;**43**:951–5.

82. Lawden MC, Eke T, Degg C, Harding GFA, Wild JM. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999;**67**:716–22.

83. Nicolson A, Leach JP, Chadwick DW, Smith DF. The legacy of vigabatrin in a regional epilepsy clinic. *J Neurol Neurosurg Psychiatry* 2002;**73**:327–9.

84. Koul R, Chacko A, Ganesh A, Bulusu S, Al Riyami K. Vigabatrin associated retinal dysfunction in children with epilepsy. *Arch Dis Child* 2001;**85**:469–73.

85. Glauser TA. Expanding first-line therapy options for children with partial seizures. *Neurology* 2000; **55** (11 Suppl 3):S30–7.

86. Brodie MJ, Kwan P. The star systems: overview and use in determining antiepileptic drug choice. *CNS Drugs* 2001;**15**:1–12.

87. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology* 2002;**58**:2S–8.

88. French J. The long-term therapeutic management of epilepsy. *Ann Intern Med* 1994;**120**:411–22.

89. Neville BG. Epilepsy in childhood. *BMJ* 1997;**315**:924–30.

90. Pellock JM, Appleton R. Use of new antiepileptic drugs in the treatment of childhood epilepsy. *Epilepsia* 1999;**40** Suppl 6:S29–38.

91. Crumrine PK. Antiepileptic drug selection in pediatric epilepsy. *J Child Neurol* 2002;**17** Suppl 2:2S2–2S8.

92. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; **342**:314–19.

93. Chilcott J, Howell S, Kemeny A, Ritteu CDC, Richards C. *Effectiveness of surgery in the management of epilepsy*. InterDEC Report No. 15/1999. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield; 1999.

94. Wiebe S, Blume WT, Girvin JP, Eliasziw M, the Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; **345**:311–18.

95. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1999;**53**:666–9.

96. Cramer JA, Menachem EB, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res* 2001;**47**:17–25.

97. Freeman JM, Vining EPG, Pillas DJ, Pyzik PL, Casey JC, Kelly MT. The efficacy of the ketogenic diet – 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998; **102**:1358–63.

98. Nordli DR, Kuroda MM, Carroll J, Koenigsberger DY, Hirsch LJ, Bruner HJ, *et al*. Experience with the ketogenic diet in infants. *Pediatrics* 2001;**108**:129–33.

99. Magrath G, MacDonald A, Whitehouse W. Dietary practices and use of the ketogenic diet in the UK. *Seizure* 2000;**9**:128–30.

100. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the Fifth Eilat Conference (EILAT V). *Epilepsy Res* 2001; **43**:11–58.

101. O'Neill FF-G. Lamotrigine versus carbamazepine in adult and elderly patients with epilepsy. *J Neurol Sci* 2001;**187** (Suppl. 1).

102. Mecarelli O, de Feo MR, Del Priore D, Piacenti A, Pulitano P, Rinalduzzi S, *et al*. Adverse events and neurophysiological modifications induced by a single dose of topiramate in healthy volunteers: a placebo-controlled study. *Epilepsia* 2000; **41** Suppl Florence:106.

103. Remy C, Favel P, Tell G. Double-blind, placebo-controlled, crossover study of vigabatrin in drug-resistant epilepsy of the adult. *Boll Lega Ital Epilessia* 1986;**54**:241–3.

104. Belopitova L, Dimova P, Tomov V. Comparative study on the therapeutic effect of oxcarbazepine (trileptal) and carbamazepine (finlepsin) in children epilepsy. *Bulg Med* 2000;**8**:12–15.

105. Hancock E, Osborne JP, Milner P. The treatment of West syndrome: a Cochrane review of the literature to December 2000. *Brain Dev* 2001; **23**:624–34.

106. Hancock E, Osborne J, Milner P. Treatment of infantile spasms (Cochrane Review). *Cochrane Library* 2002 (4).

107. Appleton R, Martland T, Phillips B. Drug management for acute tonic–clonic convulsions including convulsive status epilepticus in children (Cochrane Review). *Cochrane Database Syst Rev* 2002;(4):CD001905.

108. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. *J Child Neurol* 1999;**14**:602–9.

109. Castillo S, Schmidt DB, White S. Oxcarbazepine add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev [Computer File]* 2000; (3):CD002028.

110. Chaisewikul R, Privitera MD, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. *Cochrane Database Syst Rev* 2001;(1):CD001901.

111. Jette NJ, Marson AG, Kadir ZA, Hutton JL. Topiramate for drug-resistant partial epilepsy. *Cochrane Database Syst Rev [Computer File]* 2000; (2):CD001417.

112. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. Gabapentin add-on for drug-resistant partial epilepsy [update of *Cochrane Database Syst Rev*. 2000;(2):CD001415]. *Cochrane Database Syst Rev Computer File]* 2000;(3):CD001415.

113. Marson AG, Hutton JL, Leach JP, Castillo S, Schmidt D, White S, *et al*. Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review. *Epilepsy Res* 2001;**46**:259–70.

114. Pereira J, Marson AG, Hutton JL. Tiagabine add-on for drug-resistant partial epilepsy. *Cochrane Library* 2002;(3):CD001908.

115. Ramaratnam S, Marson AG, Baker GA. Lamotrigine add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev [Computer File]* 2000;(3):CD001909.

116. Baker GA, Hesdon B, Marson AG. Quality-of-life and behavioral outcome measures in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards. *Epilepsia* 2000;**41**:1357–63.

117. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy (Cochrane Review). *Cochrane Library* 2001 (4).

118. Chadwick DW. An overview of the efficacy and tolerability of new antiepileptic drugs. *Epilepsia* 1997;**38** (Suppl 1):S59–62.

119. Chaisewikul R, Baillie N, Marson AG. Calcium antagonists as an add-on therapy for drug-resistant epilepsy. *Cochrane Database Syst Rev* 2001;(4):CD002750.

120. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002;**43**:146–53.

121. French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: A new antiepileptic drug. *Epilepsy Res* 2001;**47**:77–90.

122. Marson AG, Kadir ZA, Chadwick DW. New antiepileptic drugs: a systematic review of their efficacy and tolerability. *BMJ* 1996;**313**:1169–74.

123. Marson AG, Williamson PR, Hutton JL, Clough HE, Chadwick DW. Carbamazepine versus valproate monotherapy for epilepsy (Cochrane Review). *Cochrane Library* 2001 (4).

124. Marson AG, Williamson PR, Clough H, Hutton JL, Chadwick DW. Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis. *Epilepsia* 2002;**43**:505–13.

125. Privitera MD. Evidence-based medicine and antiepileptic drugs. *Epilepsia* 1999;**40** Suppl 5:S47–56.

126. Ramsay ER. Tonic–clonic seizures: a systematic review of antiepilepsy drug efficacy and safety. *Clin Ther* 1997;**19**:433–46.

127. Taylor S, Tudur Smith C, Williamson PR, Marson AG. Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalised onset tonic-clonic seizures (Cochrane Review). *Cochrane Library* 2001 (4).

128. Tudur Smith C, Marson AG, Williamson PR. Phenytoin versus valproate monotherapy for partial onset and generalised onset tonic-clonic seizures (Cochrane Review). *Cochrane Library* 2001 (4).

129. Tudur Smith C, Marson AG, Clough HE, Williamson PR. Carbamazepine versus phenytoin monotherapy for epilepsy (Cochrane Review). *Cochrane Library* 2002;(4):CD001911.

130. Adab N, Winterbottom J, Tudur Smith C, Williamson PR. Common antiepileptic drugs in pregnancy in women with epilepsy (protocol for a Cochrane Review). *Cochrane Library* 2001 (4).

131. Hancock E, Cross H. Treatment of Lennox–Gastaut syndrome (protocol for a Cochrane Review). *Cochrane Library* 2001 (4).

132. Kalviainen R, Chadwick DW. Vigabatrin versus carbamazepine monotherapy for epilepsy (protocol for a Cochrane Review). *Cochrane Library* 2001 (4).

133. Posner EB, Mohamed K. Ethosuximide, sodium valproate or lamotrigine for typical absence seizures of childhood and adolescence (protocol for a Cochrane Review). *Cochrane Library* 2001 (4).

134. Preston CL, Marson AG, Williamson PR. Lamotrigine versus carbamazepine monotherapy for epilepsy (protocol for a Cochrane Review). *Cochrane Library* 2002 (4).

135. Tudur Smith C, Marson AG, Williamson PR, Hutton JL, Chadwick DW. Carbamazepine versus phenobarbitone monotherapy for epilepsy (protocol for a Cochrane Review). *Cochrane Library* 2001 (4).

136. Tudur Smith C, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy (Cochrane Review). *Cochrane Database Syst Rev* 2003;(1):CD001904.

137. Aikia MM-K. The cognitive effects of initial tiagabine monotherapy. *Epilepsia* 1999;**40** Suppl 7:51.

138. Lindberger M, Alenius M, Frisen L, Johannessen SI, Larsson S, Malmgren K, *et al*. Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. GREAT Study Investigators Group. Gabapentin in Refractory Epilepsy Add-on Treatment. *Epilepsia* 2000;**41**:1289–95.

139. Binnie CD, Debets RM, Engelsman M, Meijer JW, Meinardi H, Overweg J, *et al*. Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. *Epilepsy Res* 1989;**4**:222–9.

140. Cramer JA, Arrigo C, Van Hammee G, Bromfield EB. Comparison between the QOLIE-31 and derived QOLIE-10 in a clinical trial of levetiracetam. *Epilepsy Res* 2000;**41**:29–38.

141. Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, *et al*. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 2000;**41**:1597–607.

142. Brodie MJ, Bomhof MAM, Kalviainen R, Beran R, Richens A, Edwards D, *et al*. Double-blind comparison of tiagabine and carbamazepine monotherapy in newly diagnosed epilepsy. *Epilepsia* 1997;**38** Suppl 3:66–7.

101

143. Tanganelli P, Ottonello G-A, Monzeglio R-M, *et al*. Vigabatrin vs carbamazepine in monotherapy in newly diagnosed patients with partial epilepsy: a randomized cross-over study (preliminary data). *Boll Lega Ital Epilessia* 1993;**82–83**:137–8.

144. Canger R, Saltarelli A. Vigabatrin versus carbamezapine as first line monotherapy in newly diagnosed patients: a double blind randomized parallel group study. *Boll Lega Ital Epilessia* 1997;**99**(Suppl. 1):33–6.

145. Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. *Lancet* 1999;**354**:13–19.

146. Andrews J, Chadwick D, Bates D, Cartlidge N, Boddie G, Bolel P, *et al*. Gabapentin in partial epilepsy. *Lancet* 1990;**335**:1114–17.

147. Sivenius J, Kalviainen R, Ylinen A, Riekkinen P. Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991;**32**:539–42.

148. McLean MJ, Ramsay RE, Leppik LE, Rowan AJ, Shellenberger MK, Wallace J. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993;**43**:2292–8.

149. Anhut H, Ashman P, Feuerstein TJ, Sauermann W, Saunders M, Schmidt B, *et al*. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994;**35**:795–801.

150. Leach JP, Girvan J, Paul A, Brodie MJ. Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1997;**62**:372–6.

151. Schapel GJ, Beran RG, Vajda FJ, Berkovic SF, Mashford ML, Dunagan FM, *et al*. Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures. *J Neurol Neurosurg Psychiatry* 1993;**56**:448–53.

152. Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993;**34**:312–22.

153. Severi S, Muscas GC, Bianchi A, Zolo P. Efficacy and safety of Lamotrigine monotherapy in partial epilepsy. *Boll Lega Ital Epilessia* 1994;**86–87**:149–51.

154. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;**55**:236–42.

155. Cramer JA, Arrigo C, Van Hammee G, Gauer LJ, Cereghino JJ. Effect of levetiracetam on epilepsy-related quality of life. *Epilepsia* 2000;**41**:868–74.

156. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 2000;**41**:1179–86.

157. Schachter SC, Vazquez B, Fisher RS, Laxer KD, Montouris GD, Combs-Cantrell DT, *et al*. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures [see comments]. *Neurology* 1999;**52**:732–7.

158. Korean Topiramate Study Group. Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. *Epilepsia* 1999;**40**:1767–74.

159. Grunewald RA, Thompson PJ, Corcoran R, Corden Z, Jackson GD, Duncan JS. Effects of vigabatrin on partial seizures and cognitive function. *J Neurol Neurosurg Psychiatry* 1994; **57**:1057–63.

160. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; **34**:199–205.

161. Dodrill CB, Arnett JL, Sommerville KW, Shu V. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. *Neurology* 1997; **48**:1025–31.

162. Dodrill CB, Arnett JL, Deaton R, Lenz GT, Sommerville KW. Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000;**42**:123–32.

163. Beran RG, Berkovic SF, Buchanan N, Danta G, Mackenzie R, Schapel G, *et al*. A double-blind, placebo-controlled crossover study of vigabatrin 2 g/day and 3 g/day in uncontrolled partial seizures. *Seizure* 1996;**5**:259–65.

164. Ben Menachem E, Soderfelt B, Hamberger A, Hedner T, Persson LI. Seizure frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures. *Epilepsy Res* 1995; **21**:231–6.

165. Ben Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000;**41**:1276–83.

166. Sachdeo RC, Leroy RF, Krauss GL, Drake MEJ, Green PM, Leppik IE, *et al*. Tiagabine therapy for complex partial seizures: a dose-frequency study. *Arch Neurol* 1997;**54**:595–601.

167. Rimmer EM, Richens A. Double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. *Lancet* 1984;**1**:189–90.

168. Gram L, Klosterskov P, Dam M. Gamma-Vinyl GABA: a double-blind placebo-controlled trial in partial epilepsy. *Ann Neurol* 1985;**17**:262–6.

169. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. *Epilepsia* 1995;**36**:1111–17.

170. Provinciali L, Bartolini M, Mari F, Del Pesce M, Ceravolo MG. Influence of vigabatrin on cognitive performances and behaviour in patients with drug-resistant epilepsy. *Acta Neurol Scand* 1996;**94**:12–18.

171. Chadwick D, Leiderman DB, Sauermann W, Alexander J, Garofalo E. Gabapentin in generalized seizures. *Epilepsy Res* 1996;**25**:191–7.

172. Beran RG, Berkovic SF, Dunagan FM, Vajda FJ, Danta G, Black AB, *et al*. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy. *Epilepsia* 1998;**39**:1329–33.

173. Biton V, Montouris GD, Ritter F, Riviello JJ, Reife R, Lim P, *et al*. A randomized, placebo-controlled study of topiramate in primary generalized tonic–clonic seizures. *Neurology* 1999;**52**:1330–7.

174. Chadwick DW, Anhut H, Greiner MJ, Alexander J, Murray GH, Garofalo EA, *et al*. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998;**51**:1282–8.

175. Brodie MJ, Richens A, Yuen AWC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995;**345**:467+476–467+479.

176. Dam M. Lamotrigine versus carbamazepine open-label comparative trial. In *Lamotrigine: A Brighter Future – International Congress and Symposium*. 1996;Series 214:17–21.

177. Steiner TJ, Dellaportas CI, Findley LJ, Gross M, Gibberd FB, Perkin GD, *et al*. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia* 1999;**40**:601–7.

178. Kalogjera SD, Sackellares C, Kwong J, Vuong A, Hammer AE, Barrett PS. Quality of life improvements with lamotrigine monotherapy: a randomized, double-blind comparison with valproate. *Epilepsia* 2000;**41** Suppl 7:116–17.

179. Dam M, Ekberg R, Loyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;**3**:70–6.

180. Bill PA, Vigonius U, Pohlmann H, Guerreiro CA, Kochen S, Saffer D, *et al*. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997;**27**:195–204.

181. Christe W, Kramer G, Vigonius U, Pohlmann H, Steinhoff BJ, Brodie MJ, *et al*. A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997;**26**:451–60.

182. Wheless JW, Neto W, Wang S. Topiramate, carbamazepine, and valproate in children with newly diagnosed epilepsy: a unique trial design. *Neurology* 2001;**56**(8)Suppl 3:A234–5.

183. Kalviainen R, Aikia M, Saukkonen AM, Mervaala E, Riekkinen PJ Sr. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy: a randomized, controlled study. *Arch Neurol* 1995;**52**:989–96.

184. Binnie CD, Beintema DJ, Debets RM, Van Emde BW, Meijer JW, Meinardi H, *et al*. Seven day administration of lamotrigine in epilepsy: placebo-controlled add-on trial. *Epilepsy Res* 1987;**1**:202–8.

185. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure Euro J Epilepsy* 2000;**9**:80–7.

186. Houtkooper MA, Lammertsma A, Meyer JW, Goedhart DM, Meinardi H, van Oorschot CA, *et al*. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? *Epilepsia* 1987;**28**:693–8.

187. Loiseau P, Hardenberg JP, Pestre M, Guyot M, Schechter PJ, Tell GP. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. *Epilepsia* 1986;**27**:115–20.

188. Tartara A, Manni R, Galimberti CA, Hardenberg J, Orwin J, Perucca E. Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study. *Epilepsia* 1986;**27**:717–23.

189. Rimmer EM, Milligan NM, Richens A. A comparison of the acute effect of single doses of vigabatrin and sodium valproate on photosensitivity in epileptic patients. *Epilepsy Res* 1987;**1**:339–46.

190. Tassinari CA, Michelucci R, Ambrosetto G, Salvi F. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. *Arch Neurol* 1987;**44**:907–10.

191. Reynolds EH, Ring HA, Farr IN, Heller AJ, Elwes RD. Open, double-blind and long-term study of vigabatrin in chronic epilepsy. *Epilepsia* 1991;**32**:530–8.

103

192. Reynolds EH, Ring H, Heller A. A controlled trial of gamma-vinyl-GABA (vigabatrin) in drug-resistant epilepsy. *Br J Clin Pract* 1988;**61** Suppl:33.

193. Gillham RA, Blacklaw J, McKee PJW, Brodie MJ. Effect of vigabatrin on sedation and cognitive function in patients with refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1993;**56**:1271–5.

194. Carmant L, Bryant CL, Moorat A. Switching patients to monotherapy: improved tolerability for Lamictal® compared to valproate. *Euro J Neurol* 1999;**6** (Suppl 3):72.

195. Montouris G, Mirza WU, Biton V, Vuong A, Barrett P, Hammer A. Effects of Lamictal® and Depakote® monotherapy on body weight in patients with epilepsy: interim analysis of a randomized, double-blind clinical trial. *Neurology* 1999;**52**:A523–4.

196. Fakhoury T, Gazda S, Nanry KP, Hammer AE, and-Barrett PS. Comparison of monotherapy with lamotrigine versus carbamazepine in patients with uncontrolled epilepsy with a broad spectrum of seizure types. *Epilepsia* 2000;**41** Suppl 7:107.

197. Nieto-Barrera M, Brozmanova M, Capovilla G, Christe W, Pedersen B, Kane K, *et al*. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. *Epilepsy Res* 2001;**46**:145–55.

198. Zamponi N, Cardinali C. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. *Arch Neurol* 1999;**56**:605–7.

199. Shapiro DY, Nordli D, Glauser TA, Knapp LE, Greiner M, Purcell TJ, *et al*. Gabapentin as add-on therapy for refractory partial seizures in children 1–36 months of age: a novel, short-term, placebo-controlled trial. *Epilepsia* 2000;**41** Suppl 7:106.

200. Litzinger MJ, Hanny A. Tiagabine therapy in a small group of pediatric patients with refractory partial seizure. *Ann Neurol* 1998;**44**:B16.

201. Valentine C, Mettert N, Mosier M, Michon AM. A parallel group study comparing oral adjunctive vigabatrin with placebo in children with uncontrolled complex partial seizures. *Epilepsia* 1998;**39** (Suppl 6):166.

202. Van Orman CB, Ruckh S, Mosier M. Efficacy and safety of vigabatrin in children with uncontrolled complex partial seizures: a dose response study. *Epilepsia* 1998; **39** (Suppl 6):166.

203. Duchowny M, Pellock JM, Graf WD, Billard C, Gilman J, Casale E, *et al*. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Lamictal Pediatric Partial Seizure Study Group. *Neurology* 1999;**53**:1724–31.

204. Glauser TA, Nigro M, Sachdeo R, Pasteris LA, Weinstein S, Abou-Khalil B, *et al*. Adjunctive therapy with oxcarbazepine in children with partial seizures. The Oxcarbazepine Pediatric Study Group. *Neurology* 2000;**54**:2237–44.

205. Elterman RD, Glauser TA, Wyllie E, Reife R, Wu SC, Pledger G. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. *Neurology* 1999;**52**:1338–44.

206. Appleton R, Fichtner K, LaMoreaux L, Alexander J, Halsall G, Murray G, *et al*. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. *Epilepsia* 1999;**40**:1147–54.

207. Guerreiro MM, Vigonius U, Pohlmann H, de Manreza ML, Fejerman N, Antoniuk SA, *et al*. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997; **27**:205–13.

208. Eriksson A-S, Nergardh A, Hoppu K. The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, cross over study. *Epilepsia* 1998; **39**:495–501.

209. Motte J, Trevathan E, Arvidsson JFV, Barrera MN, Mullens EL, Manasco P. Lamotrigine for generalized seizures associated with the Lennox–Gastaut syndrome. *N Engl J Med* 1997; **337**:1807–12.

210. Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G, *et al*. A double-blind, randomized trial of topiramate in Lennox–Gastaut syndrome. *Neurology* 1999;**52**:1882–7.

211. Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia* 1999;**40**:1627–33.

212. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38**:1270–4.

213. Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Res* 1997;**26**:389–95.

214. Frank LM, Enlow T, Holmes GL, Manasco P, Concannon S, Chen C, *et al*. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. *Epilepsia* 1999;**40**:973–9.

215. Bourgeois B, Brown LW, Pellock JM, Buroker M, Greiner M, Garofalo EA, *et al*. Gabapentin (Neurontin) monotherapy in children with benign childhood epilepsy with centrotemporal spikes (BECTS): a 36-week, double-blind, placebo-controlled study. *Epilepsia* 1998;**39** Suppl 6:163.

216. Chiron C, Dulac O, Gram L. Vigabatrin withdrawal randomized study in children. *Epilepsy Res* 1996;**25**:209–15.

217. Aldenkamp AP, Alpherts WC, Sandstedt P, Blennow G, Elmqvist D, Heijbel J, *et al*. Antiepileptic drug-related cognitive complaints in seizure-free children with epilepsy before and after drug discontinuation. *Epilepsia* 1998;**39**:1070–4.

218. Austin JK, Dunn DW. Children with epilepsy: quality of life and psychosocial needs. *Ann Rev Nurs Res* 2000;**18**:26–47.

219. Cramer JA, Westbrook LE, Devinsky O, Perrine K, Glassman MB, Camfield C. Development of the Quality of Life in Epilepsy Inventory for Adolescents: the QOLIE-AD-48. *Epilepsia* 1999; **40**:1114–21.

220. Hanai T. Quality of life in children with epilepsy. *Epilepsia* 1996;**37** Suppl 3:28–32.

221. Hoare P. The quality of life of children with chronic epilepsy and their families. *Seizure* 1993; **2**:269–75.

222. Jacoby A. Assessing quality of life in patients with epilepsy. *Pharmacoeconomics* 1996;**9**:399–416.

223. Norrby U, Carlsson J, Beckung E, Nordholm L. Self-assessment of well-being in a group of children with epilepsy. *Seizure* 1999;**8**:228–34.

224. Ronen GM, Rosenbaum P, Law M, Streiner DL. Health-related quality of life in childhood epilepsy: the results of children's participation in identifying the components. *Dev Med Child Neurol* 1999;**41**:554–9.

225. Sabaz M, Cairns DR, Lawson JA, Bleasel AF, Bye AM. The health-related quality of life of children with refractory epilepsy: a comparison of those with and without intellectual disability. *Epilepsia* 2001;**42**:621–8.

226. Wildrick D, Parker-Fisher S, Morales A. Quality of life in children with well-controlled epilepsy. *J Neurosc Nurs* 1996;**28**:192–8.

227. Hennessy S, Kind P. Measuring health status in children: developing and testing a child-friendly version of EQ-5D. Presented at EuroQol Scientific Meeting, York, 12 September 2002.

228. Dolan P. Modelling valuations for EuroQol Health States. *Med Care* 1997;**35**:1095–108.

229. Wong IC, Chadwick DW, Fenwick PB, Mawer GE, Sander JW. The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy. *Epilepsia* 1999;**40**:1439–45.

230. Lhatoo SD, Wong ICK, Sander JWAS. Prognostic factors affecting long-term retention of topiramate in patients with chronic epilepsy. *Epilepsia* 2000; **41**:338–41.

231. Lhatoo SD, Wong ICK, Polizzi G, Sander JWAS. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. *Epilepsia* 2000;**41**:1592–6.

232. Wong IC, Mawer GE, Sander JW, Lhatoo SD. A pharmacoepidemiologic study of factors influencing the outcome of treatment with lamotrigine in chronic epilepsy. *Epilepsia* 2001; **42**:1354–8.

233. Hes MS, Trudeau VL, Kilgore MB, Poulter CJ, Garofalo EA, Koto EP. A double-blind, placebo-controlled, randomized multicenter trial of gabapentin (GBP Neurontin) in pediatric-patients with benign childhood epilepsy with centrotemporal spikes (BECTS). *Epilepsia* 1995; **36**:531.

234. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995;**346**:140–4.

235. Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. *Epilepsia* 2002;**43** Suppl 3:53–9.

236. Morselli PL, Franco M, Bossi L. Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980;**5**:485–527.

237. Stewart CF, Hampton EM. Effect of maturation on drug disposition in pediatric patients. *Clin Pharm* 1987;**6**:548–64.

238. Painter MJ, Pippenger C, MacDonald H, Pitlick W. Phenobarbital and diphenylhydantoin levels in neonates with seizures. *J Pediatr* 1978;**92**:315–19.

239. Asconape JJ. Some common issues in the use of antiepileptic drugs. *Semin Neurol* 2002;**22**:27–39.

240. Gidal BE, Anderson GD, Spencer NW. Valproate-associated weight gain in patients with epilepsy: potential relationship to energy expenditure and metabolism. *J Epilepsy* 1996;**9**:234–41.

241. Gidal BE, Maly MM, Nemire RE, Haley K. Weight gain and gabapentin therapy. *Ann Pharmacother* 1995;**29**:1048.

242. Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. *Neurology* 2001;**56**:172–7.

243. Smith U, Axelsen M, Hellebö-Johanson E, Lundgren B, Ben-Menachem E. Topiramate a novel antiepileptic drug, reduces body weight and food intake in obesity. *Obes Res* 2000;**8** (Suppl 1):10S.

244. Sato Y, Kondo I, Ishida S, Motooka H, Takayama K, Tomita Y, *et al*. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. *Neurology* 2001; **57**:445–9.

245. Tsukahara H, Kimura K, Todoroki Y, Ohshima Y, Hiraoka M, Shigematsu Y, *et al*. Bone mineral

status in ambulatory pediatric patients on long-term anti-epileptic drug therapy. *Pediatr Int* 2002;**44**:247–53.

246. Pavlakis SG, Chusid RL, Roye DP, Nordli DR. Valproate therapy: predisposition to bone fracture? *Pediatr Neurol* 1998;**19**:143–4.

247. Ueberall MA. Normal growth during lamotrigine monotherapy in pediatric epilepsy patients – a prospective evaluation of 103 children and adolescents. *Epilepsy Res* 2001;**46**:63–7.

248. Bourgeois BF. Differential cognitive effects of antiepileptic drugs. *J Child Neurol* 2002; **17** Suppl 2:2S28–2S33.

249. Dodrill CB, Arnett JL, Sommerville KW, Sussman NM. Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy. *Epilepsia* 1995;**36**:164–73.

250. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 2002;**87**:462–6.

251. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllyla VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993;**329**:1383–8.

252. Herzog AG. Polycystic ovarian syndrome in women with epilepsy: epileptic or iatrogenic? *Ann Neurol* 1996;**39**:559–60.

253. Isojarvi JI, Rattya J, Myllyla VV, Knip M, Koivunen R, Pakarinen AJ, *et al*. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann Neurol* 1998;**43**:446–51.

254. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, *et al*. Population based prospective study of the care of women with epilepsy in pregnancy. *BMJ* 2000;**321**:674–5.

255. Orme M, Back DJ, Chadwick DJ, Crawford P, Martin C, Tjia J. The interaction of phenytoin and carbamazepine with oral contraceptive steroids. *Euro J Clin Pharmacol* 1990;**183**:1029–30.

256. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol* 1990; **30**:892–6.

257. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine. *Clin Pharmacokinet* 1996; **31**:198–214.

258. Grant SM, Faulds D. Oxcarbazepine – a review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. *Drugs* 1992;**43**:873–88.

259. Keranen T, Jolkkonen J, Jensen PK, Menge GP, Andersson P. Absence of interaction between oxcarbazepine and erythromycin. *Acta Neurol Scand* 1992;**86**:120–3.

260. Kramer G, Tettenborn B, Flesch G. Oxcarbazepine–verapamil drug interaction in healthy volunteers. *Epilepsia* 1991;**32** (Suppl 1):70–1.

261. Fattore C, Cipolla G, Gatti G, Limido GL, Sturm Y, Bernasconi C, *et al*. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia* 1999;**40**:783–7.

262. Doose D, Rosenfeld W, Schaefer P, Walker SA, Nayak RK. Evaluation of a potential pharmacokinetic interaction between topiramate and the oral contraceptive combination norethindrone ethinylestradiol. *J Clin Pharmacol* 1994;**34**:1031.

263. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 1997;**38**:317–23.

264. Odlind V, Olsson SE. Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with Norplant implants. *Contraception* 1986;**33**:257–61.

265. Haukkamaa M. Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. *Contraception* 1986;**33**:559–65.

266. Eldon MA, Underwood BA, Randinitis EJ, Posvar EL, Sedman AJ. Lack of effect of gabapentin on the pharmacokinetics of a norethindrone acetate/ethinyl estradiol-containing oral contraceptive. *Neurology* 1993; **43** (Suppl. 2):A307–8.

267. Eldon MA, Underwood BA, Randinitis EJ, Sedman AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. *Neurology* 1998;**50**:1146–8.

268. Holdich T, Whiteman P, Orme M, Black D, Ward S. Effect of lamotrigine on the pharmacology of the oral contraceptive pill. *Epilepsia* 1991;**32** Suppl. 1:96.

269. Crawford P, Chadwick D, Cleland P, Tjia J, Cowie A, Back DJ, *et al*. Sodium valproate and oral contraceptive steroids. *Br J Clin Pharmacol* 1985; **20**:288P–289P.

270. Mengel H, Houston A, Back DJ. An interaction of the interaction between tiagabine and oral contraceptives in female volunteers. *J Pharm Med* 1994;**4**:141–50.

271. Bartoli A, Gatti G, Cipolla G, Barzaghi N, Veliz G, Fattore C, *et al*. A double-blind, placebo-controlled study on the effect of vigabatrin on *in vivo* parameters of hepatic microsomal enzyme induction and on the kinetics of steroid oral contraceptives in healthy female volunteers. *Epilepsia* 1997;**38**:702–7.

272. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, *et al*. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001; **344**:1132–8.

273. Berg M, Fincham R, Ebert EB, Schottelius DD. Phenytoin pharmacokinetics before and after folic acid administration. *Epilepsia* 1992;**33**:712–20.

274. Mackay FJ, Wilton LV, Pearce GL, Freemantle SN, Mann RD. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997;**38**:881–6.

275. Hoyme HE, Hauck L, Quinn D. Minor abnormalities accompanying prenatal exposure to topiramate [abstract]. *Epilepsia* 1998;**56**:119A.

276. Friis ML, Kristensen O, Boas J, Dalby M, Deth SH, Gram Mikkelsen LM, *et al*. Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol Scand* 1993; **87**:224–7.

277. Lindhout D, Omtzigt JG. Teratogenic effects of antiepileptic drugs: implications for the management of epilepsy in women of the childbearing age. *Epilepsia* 1994;**45**:409–11.

278. McLean MJ. Gabapentin in the management of convulsive disorders. *Epilepsia* 1999;**40** Suppl **6**:S39–50.

279. Richens A. Safety of lamotrigine. *Epilepsia* 1994; **35** Suppl 5:S37–40.

280. Palmieri C, Canger R. Teratogenic potential of the newer antiepileptic drugs: what is known and how should this influence prescribing? *CNS Drugs* 2002;**16**:755–64.

281. Chang SI, McAuley JW. Pharmacotherapeutic issues for women of childbearing age with epilepsy. *Ann Pharmacother* 1998;**32**:794–801.

282. Isojarvi JIT, Pakarinen AJ, Myllyla VV. Basic haematological parameters, serum gammaglutamyl-transferase activity, and erythrocyte folate and serum vitamin B12 levels during carbamazepine and oxcarbazepine therapy. *Seizure* 1997;**6**:207–11.

283. Leppik IE, Gram L, Deaton R, Sommerville KW. Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 1999;**33**:235–46.

284. Glauser TA. Topiramate. *Epilepsia* 1999; **40** Suppl. 5:S71–80.

285. Meadow R. Anticonvulsants in pregnancy. *Arch Dis Child* 1991;**66** (1 Spec No):62–5.

286. British Epilepsy Association. *Epilepsy and pregnancy; the facts*. URL: http://www.epilepsy.org.uk/info/ pregnancy1.html

287. Cramer J, Ryan J, Chang J, Sommerville K, Study Group. The short-term impact of adjunctive tiagabine on health-related quality of life. *Epilepsia* 2001;**42** Suppl 3:70–5.

288. Lopes-Lima JM, Pereira H, Sol JM, Morralla C, Hernandez G. Gabapentin vs valproate in partial epilepsy uncontrolled by carbamazepin. *Eur J Neurol* 1999;**6** Suppl 3:17.

289. Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S. Dose–response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res* 2002;**48**:77–89.

290. Dodrill CB, Arnett JL, Sommerville KW, Sussman NM. Evaluation of the effects of vigabatrin on cognitive abilities and quality of life in epilepsy. *Neurology* 1993;**43**:2501–7.

291. Uthman BM, Rowan AJ, Ahmann PA, Leppik IE, Schachter SC, Sommerville KW, *et al*. Tiagabine for complex partial seizures: a randomized, add-on, dose–response trial. *Arch Neurol* 1998;**55**:56–62.

292. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Res* 1996;**23**:149–55.

293. Gillham R, Kane K, Bryant-Comstock L, Brodie MJ, *et al*. A double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure. *Seizure* 2000;**9**:375–9.

294. Edwards KR, Sackellares JC, Vuong A, Hammer AE, Barrett PS. Lamotrigine monotherapy improves depressive symptoms in epilepsy: a double-blind comparison with valproate. *Epilepsy Behav* 2001;**2**:28–36.

295. Aikia M, Kalviainen R, Sivenius J, Halonen T, Riekkinen PJ. Cognitive effects of oxcarbazepine and phenytoin monotherapy in newly diagnosed epilepsy: one year follow-up. *Epilepsy Res* 1992; **11**:199–203.

296. Coles H, Baker G, O'Donoghue M. Seizure severity in patients with partial onset (POS) or primary generalised tonic clonic (PGTC) seizures following treatment with topiramate. A comparison of two different methodologies in a randomised controlled trial. *Epilepsia* 1999;**40**:285.

297. McKee PJW, Blacklaw J, Friel E, Thompson GG, Gillham RA, Brodie MJ. Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients? *Epilepsia* 1993;**34**:937–43.

298. Kerr M, Kane K, Moorat A. Switching patients to monotherapy: efficacy and tolerability for Lamictal® compared to valproate. *Euro J Neurol* 1999;**6** Suppl 3:17.

299. French J, Pellock J, Ferrendelli J, Sommerville K, Sherry K, Ahlbrandt R, *et al*. Results of a multicenter, placebo-controlled, parallel study of vigabatrin (VGB, Sabril®) in patients with focal epilepsy whose seizures are difficult to control. *Neurology* 1993;**43**:A307.

107

300. Canger R, Saltarelli A. Vigabatrin versus carbamezapine as first line monotherapy in newly diagnosed patients: a double blind randomized parallel group study. *Boll Lega Ital Epilessia* 1997;**99**(Suppl 1):33–6.

301. Anon. Head-to-head epilepsy studies demonstrate benefits of switching to monotherapy with Lamictal. *Ir Med J* 2000;**93**:26.

302. Abdulrazzak M, Kutluay E, Passaro EA, Milling CJ, Minecan DN, Kothary S, *et al*. Long term efficacy and safety of oxcarbazepine as adjunctive therapy or monotherapy in patients with refractory partial onset seizures. *Epilepsia* 2000;**41** Suppl 7:228–9.

303. Aberg L, Kirveskari E, Santavuori P. Lamotrigine therapy in juvenile neuronal ceroid lipofuscinosis. *Epilepsia* 1999;**40**:796–9.

304. Aldenkamp AP, Baker G, Mulder OG, Rentmeester TW, Hulsman J, Overweg J, *et al*. A randomized observer-blind clinical study comparing the cognitive effects of topiramate versus valproate in a first-line add-on design. *Epilepsia* 1998;**39** Suppl 6:188–9.

305. Aldenkamp AP, Baker G, Mulder OG, Rentmeester TW, Hulsman J, Overweg J, *et al*. A randomized clinical study comparing the cognitive effects of topiramate versus valproate in a first-line add-on design. *Epilepsia* 1999;**40** Suppl 7:83–4.

306. Aldenkamp AP, Baker G, Mulder OG, Chadwick D, Cooper P, Doelman J, *et al*. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia* 2000;**41**:1167–78.

307. Aldenkamp AP, Arends J, Bootsma HP, Diepman L, Hulsman J, Lambrechts D, *et al*. Randomized double-blind parallel-group study comparing cognitive effects of a low-dose lamotrigine with valproate and placebo in healthy volunteers. *Epilepsia* 2002;**43**:19–26.

308. Anhut H, Greiner MJ, Murray GH. Double-blind, fixed-dose comparison study of gabapentin (GBP Neurontin®) and carbamazepine (CBZ) monotherapy in patients with newly-diagnosed partial epilepsy. *Epilepsia* 1995;**36**:341.

309. Anderson WT III, Sakhoury T, Nasreddine W, Abou KB, Beydoun A. Gabapentin monotherapy for newly diagnosed partial epilepsy. *Epilepsia* 1999;**40** Suppl 7:224.

310. Angeleri F, Scarpino O, Avanzini G, Binelli D, Baruzzi A, Procaccianti G, *et al*. Single-blind, placebo-controlled multicenter trial of vigabatrin in the treatment of epilepsy. *Ital J Neurol Sci* 1992;**13**:741–7.

311. Anhut H, Ashman PJ, Feuerstein TJ, Quebe-Fehling E, Saunders M, Baron BA, *et al*. Long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995;**8**:44–50.

312. Appleton R, Fichtner K, LaMoreaux L, Alexander J, Maton S, Murray G, *et al*. Gabapentin as add-on therapy in children with refractory partial seizures: a 24-week, multicentre, open-label study. *Dev Med Child Neurol* 2001;**43**:269–73.

313. Arteaga R, Herranz JL, Armijo JA. Add-on vigabatrin in children with refractory epilepsy. A 4-year follow-up study. *Clin Drug Invest* 1996;**12**:287–97.

314. Arteaga R, Herranz JL, Valdizan EM, Armijo JA. Gamma-vinyl GABA (vigabatrin): Relationship between dosage, plasma concentrations, platelet GABA-transaminase inhibition, and seizure reduction in epileptic children. *Epilepsia* 1992;**33**:923–31.

315. Arteaga R, Herranz JL, Armijo JA. Platelet gaba-transaminase in epileptic children – influence of epilepsy and anticonvulsants. *Epilepsy Res* 1993;**14**:73–85.

316. Arzimanoglou A, Kulak I, Bidaut-Mazel C, Baldy-Moulinier M. Optimal use of lamotrigine in clinical practice: results of an open multicenter trial in refractory epilepsy. *Rev Neurol (Paris)* 2001;**157**:525–36.

317. Banin E, Gross-Tsur V, Shachar E, Lahat E, Shalev RS. Impaired visual function in epileptic children treated with vigabatrin. *Invest Ophthalmol Vis Sci* 2000;**41**(4):S507.

318. Bartolini M, Del Pesce M, Mari F, Judice A, Quattrini A, Provinciali L. Influence of vigabatrin on cognitive functions and behaviour in patients with drug-resistant epilepsy. *Boll Lega Ital Epilessia* 1993;**84**:161–2.

319. Belmonte A, Ferrari R, Battini R, Guerrini R. Add-on lamotrigine treatment in children and young adults with severe partial epilepsy: an open, prospective study. *Epilepsia* 1999;**40**:236.

320. Ben Menachem E, Henriksen O, Dam M, Mikkelsen M, Schmidt D, Reid S, *et al*. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996;**37**:539–43.

321. Ben Menachem E. Clinical efficacy of topiramate as add-on therapy in refractory partial epilepsy: the European experience. *Epilepsia* 1997;**38** Suppl 1:S28–30.

322. Ben Menachem E, Topiramate YTC Group. A double-blind trial of topiramate in patients with generalised tonic–clonic seizures of non-focal origin. *Epilepsia* 1997;**38** Suppl 3:60.

323. Beran R, Berkovic S, Black A, Danta G, Dunne J, Frasca J, *et al*. Australian study of titration to effect profile of safety (AUS-STEPS): high-dose

gabapentin (Neurontin) in partial seizures. *Epilepsia* 2001;**42**:1335–9.

324. Bergey GK, Crockatt JG, Leiderman DB, Malicsi M, Garofalo EA. Multicenter double-blind-study of gabapentin (GBP Neurontin®) monotherapy in hospitalised patients with refractory epilepsy. *Epilepsia* 1995;**36**:344.

325. Bergey GK, Morris HH, Rosenfeld W, Blume WT, Penovich PE, Morrell MJ, *et al*. Gabapentin monotherapy: I. An 8-day, double-blind, dose-controlled, multicenter study in hospitalized patients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997;**49**:739–45.

326. Bernardina BD, Fontana E, Vigevano F, Fusco L, Torelli D, Galeone D, *et al*. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995;**36**:687–91.

327. Besag FMC, Dulac O, Alving J, Mullens EL. Long-term safety and efficacy of lamotrigine (Lamictal™) in paediatric patients with epilepsy. *Seizure* 1997;**6**:51–6.

328. Betts T, Laskar P, Crawford PM, Debrabandere L, Selak I. Efficacy and tolerability of levetiracetam (ucb L059) as add-on therapy in patients with refractory partial and generalized seizures. *Epilepsia* 1998;**39** Suppl 6:68.

329. Beydoun A, Fakhoury T, Nasreddine W, Abou KB. Conversion to high dose gabapentin monotherapy in patients with medically refractory partial epilepsy. *Epilepsia* 1998;**39**:188–93.

330. Beydoun A. Monotherapy trials with gabapentin for partial epilepsy. *Epilepsia* 1999;**40** Suppl 6: S13–16.

331. Beydoun AA, Sachdeo R, Rosenfeld W, D'Souza J, Kramer L. Safety and efficacy of oxcarbazepine monotherapy in patients with medically refractory partial epilepsy. *Epilepsia* 1998;**39** Suppl 6:48.

332. Bielicka-Cymerman J, Golebiwska M, Pakszys M. Clinical efficacy of topiramate as add-on therapy in refractory partial seizures in children. Preliminary report. *Epilepsia* 1999;**40**:178.

333. Birbeck GL, Kim S, Hays RD, Vickrey BG. Quality of life measures in epilepsy: how well can they detect change over time? *Neurology* 2000; **54**:1822–7.

334. Biton V, Montouris GD, YTC Study Team. Topiramate double-blind trial in patients with generalised tonic–clonic seizures of non-focal origin. *Epilepsia* 1997;**38** Suppl 3:59–60.

335. Biton V, Vasquez B, Sachdeo RC, Lenz GT, Deaton R, Sommerville KW. Adjunctive tiagabine compared with phenytoin and carbamazepine in the multicenter, double-blind trial of complex partial seizures. *Epilepsia* 1998;**39** Suppl 6:125–6.

336. Biton V, Rosenfeld WE, Twyman R, Lim P. Topiramate (TPM) in juvenile myoclonic epilepsy (JME): observations from randomized controlled trials in primary generalized tonic–clonic seizures (PGTCS). *Epilepsia* 1999;**40**:218.

337. Biton V, Mirza W, Montouris GD, Vuong A, Hammer AE, Barrett PS. Weight gain associated with valproate vs. lamotrigine monotherapy in patients with epilepsy: a randomized, double-blind clinical trial. *Epilepsia* 2000;**41** Suppl 7:89–90.

338. Biton V. Erratum: a randomized, placebo-controlled study of topiramate in primary generalized tonic–clonic seizures (*Neurology* (1999) **52** (1330–7)). *Neurology* 1999;**53**:1162.

339. Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS. Weight gain associated with valproate vs. lamotrigine monotherapy in patients with epilepsy: a randomized, double-blind comparative clinical trial. *J Euro Coll Neuropsychopharmacol* 2000;**10** Suppl 3:S236.

340. Boas J, Dam M, Friis ML, Kristense O, Pedersen B, Gallagher J. Controlled trial of lamotrigine (Lamictal registered trade mark) for treatment-resistant partial seizures. *Acta Neurol Scand* 1996;**94**:247–52.

341. Boati E, Defanti CA, Franza A, Scaturro M. Vigabatrin versus carbamazepine in patients with newly diagnosed partial epilepsy. *Boll Lega Ital Epilessia* 1998;**102–103**:123–7.

342. Brodie, M-J, McKee, P-J-W, Blacklaw J, Forrest G, Gillham RA, Walker S, *et al*. Double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, valproate, and phenytoin in epileptic patients. *Epilepsia* 1993;**34** Suppl 6:68–9.

343. Brodie MJ, Biton V, Montouris GD, Shu CW. Topiramate therapy in patients with generalized tonic–clonic seizures without focal onset: long-term outcome. *Epilepsia* 1998;**39** Suppl 2:2.

344. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsy Res* 1999;**37**:81–7.

345. Brodie MJ. Erratum: double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy (*The Lancet* (February 25) (476)). *Lancet* 1995;**345**:662.

346. Brodie MJ, The-Topiramate YTC E Study Group. Topiramate as long-term therapy in generalised tonic–clonic seizures of non-focal origin. *Epilepsia* 1997;**38** Suppl 3:60.

347. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, *et al*. A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989;**27** Suppl 1:95S–100S.

109

348. Browne TR, Mattson RH, Napoliello MJ, Penry JK, Smith DB, Treiman DM, *et al*. Multicenter single-blind study of gamma-vinyl-GABA for refractory partial seizures. *Epilepsia* 1983;**24**:521.

349. Browne TR, Smith DB, Mattson RH, Penry JK, Sherry KM, Treiman DM, *et al*. Multicenter single-blind study of vigabatrin for refractory complex partial seizures – long term follow-up. *Epilepsia* 1986;**27**:641.

350. Browne TR, Mattson RH, Penry JK. Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. *Neurology* 1987;**37**:184–9.

351. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, *et al*. Multicenter long-term safety and efficacy study of vigabatrin for refractory complex partial seizures: an update. *Neurology* 1991;**41**:363–4.

352. Brozmanova M, Tkacova J, Szabova I. Add-on trial with lamotrigine in refractory epilepsies in childhood – two and half years follow-up study. *Epilepsia* 1995;**36**:S111.

353. Bruni J, Guberman A, Vachon L, Desforges C. Vigabatrin as add-on therapy for adult complex partial seizures: a double-blind, placebo-controlled multicentre study. *Seizure Euro J Epilepsy* 2000; **9**:224–32.

354. Bruni J. Outcome evaluation of gabapentin as add-on therapy for partial seizures. "NEON" Study Investigators Group. Neurontin Evaluation of Outcomes in Neurological Practice. *Can J Neurol Sci* 1998;**25**:134–40.

355. Bruni J. Gabapentin as adjunctive therapy for partial seizures. *Epilepsia* 1999;**40** Suppl 6:S27–28.

356. Buchanan N. The efficacy of lamotrigine on seizure control in 34 children, adolescents and young adults with intellectual and physical disability. In *Lamotrigine: A Brighter Future – International Congress and Symposium*. 1996; Series **214**:89–102.

357. Buchholt J, Uldall P. Oxcarbazepine in childhood epilepsy. *Epilepsia* 1995;**36**:S118–19.

358. Canger R, Avanzini G, Tartara A, Durisotti C, Guidolin L, Binelli S, *et al*. Topiramate efficacy and tolerability as add-on therapy: interim analysis of an open multicenter study. *Boll Lega Ital Epilessia* 1996;**95–96**:251–3.

359. Carrazana EJ, Wheeler SD. Exacerbation of juvenile myoclonic epilepsy with lamotrigine. *Neurology* 2001;**56**:1424.

360. Chadwick D, Anhut H, Murray G, Greiner M, Alexander J. Gabapentin (GBP; Neurontin) monotherapy in patients with newly-diagnosed epilepsy: results of a double-blind fixed-doses study comparing three dosages of gabapentin and open-label carbamazepine. *Epilepsia* 1997; **38** Suppl 3:34.

361. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, *et al*. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet* 2000; **356**:1638–42.

362. Clark P, Glauser TA, Hamant E, McGee K, Khoury P. Topiramate's effect on height and weight in children with partial-onset seizures. *Epilepsia* 1999;**40**:115.

363. Cocito L, Maffini M, Perfumo P, Roncallo F, Loeb C. Vigabatrin in complex partial seizures: a long-term study. *Epilepsy Res* 1989;**3**:160–6.

364. Cocito L, Maffini M, Loeb C. Vigabatrin in chronic epilepsy: a 7-year follow-up study of responder patients. *Seizure* 1993;**2**:301–7.

365. Collins TL, Petroff OAC, Mattson RH. A comparison of four new antiepileptic medications. *Seizure Euro J Epilepsy* 2000;**9**:291–3.

366. Coppola G, Bove RM, Nazzaro A, Pascotto A. Lamotrigine in children with refractory epilepsy-an open trial. *Epilepsia* 1995;**36**:S111–12.

367. Coppola G, Caliendo G, Terracciano MM, Buono S, Pellegrino L, Pascotto A. Topiramate in refractory partial-onset seizures in children, adolescents and young adults: a multicentric open trial. *Epilepsy Res* 2001;**43**:255–60.

368. Coppola G, Capovilla G, Montagnini A, Romeo A, Spano M, Tortorella G, *et al*. Topiramate as add-on drug in severe myoclonic epilepsy in infancy: an Italian multicenter open trial. *Epilepsy Res* 2002; **49**:45–8.

369. Cramer JA. Oxcarbazepine in a monotherapy trial for partial seizures – placebo-controlled studies in neurology: where do they stop? *Neurology* 1999; **53**:2212–13.

370. Crawford P, Meinardi H, Brown S, Rentmeester TW, Pedersen B, Pedersen PC, *et al*. Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001;**42**:531–8.

371. Crawford P, Ghadiali E, Lane R, Blumhardt L, Chadwick D. Gabapentin as an antiepileptic drug in man. *J Neurol Neurosurg Psychiatry* 1987; **50**:682–6.

372. Curatolo P. Vigabatrin for refractory partial seizures in children with tuberous sclerosis. *Neuropediatrics* 1994;**25**:55.

373. Czapinski P, Terczynski A, Czapinska E. Open randomised comparative study of vigabatrin (VGB) and lamotrigine (LTG) efficacy in monotherapy of patients with drug-resistant epilepsy with partial complex seizures resistant to carbamazepine. *Epilepsia* 1997;**38**(Suppl 3)35.

374. Dalla BB, Fontana E, Vigevano F, Fusco L, Torelli D, Galeone D, *et al*. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995;**36**:687–91.

375. Davies G, Sweet R, Mullens EL, Messenheimer J. Clinical trial experience with lamotrigine (Lamictal) in the management of adults with epilepsy. *J Neurol Sci* 1997;**150** (Suppl):S163.

376. De Romanis F, Sopranzi N. Lamotrigine: first Italian trials. *Clin Ter* 1995;**146**:203–9.

377. Dean C, Mosier M, Penry K. Dose–response study of vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures. *Epilepsia* 1999;**40**:74–82.

378. Dodrill CB, Arnett JL, Hayes AG, Garofalo EA, Greeley CA, Mann ME, *et al*. Evaluation of quality of life during a double-blind multicenter study of gabapentin (GBP Neurontin®) monotherapy in patients with medically refractory partial seizures. *Epilepsia* 1995;**36**:G1.

379. Dodrill CB, Arnett J, Deaton R, Lenz GT, Sommerville KW. Adjunctive tiagabine, phenytoin, and carbamazepine, and neuropsychological tests in a multicenter trial for partial seizures. *Epilepsia* 1998;**39** Suppl 6:147.

380. Dodrill CB, Arnett JL, Hayes AG, Garofalo EA, Greeley CA, Greiner MJ, *et al*. Cognitive abilities and adjustment with gabapentin: results of a multisite study. *Epilepsy Res* 1999;**35**:109–21.

381. Dollar L, French J, Krauss G, Ruckh S. The safety of long-term add-on therapy with Sabril (vigabatrin) in patients with uncontrolled complex partial seizures. *Epilepsia* 1998;**39** Suppl 6:190.

382. Drory VE, Korczyn AD. Apparent placebo effect in epilepsy. *New Trends Clin Neuropharmacol* 1991; **5**:49–56.

383. Dulac O, D'Souza J, Motte J. Multicenter study of oxcarbazepine pharmacokinetics and tolerability in children with refractory epilepsy. *Ann Neurol* 2001;**50**:S104.

384. Dulac O. Efficacy and safety of lamotrigine in children. In *Lamotrigine: A Brighter Future – International Congress and Symposium*. 1996;Series 214:69–73.

385. Duric B, Marjanovic B, Zamurovic D, Jovic N, Rajcic N. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, double blind placebo-controlled study and open-label extension of a double-blind study. *Epilepsia* 1999;**40**:156.

386. Edwards K, Kalogjera SD, Sackellares C, Vuong A, Hammer AE, Barrett PS. Lamotrigine monotherapy improves mood in epilepsy: a randomized, double-blind comparison with valproate. *Epilepsia* 2000;**41** Suppl 7:104.

387. Eriksson AS, Nergardh A, Boreus L, Knutsson E. Double-blind cross-over study of lamotrigine in children with Lennox–Gastaut syndrome and other types of generalized intractable epilepsy. *Epilepsia* 1995;**36**:S110–1.

388. Ericksson AS, Knutsson E, Nergardh A. The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. *Epilepsia* 2001;**42**:230–6.

389. Farrell K, Connolly M, Munn R, Peng SM, Berg M. Open study of lamotrigine in children with intractable generalized epilepsy. *Ann Neurol* 1995;**38**:506.

390. Faught E, Wilder BJ, Ramsay RE, Reife RA, Kramer LD, Pledger GW, *et al*. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996;**46**:1684–90.

391. Faught E. Efficacy of topiramate as adjunctive therapy in refractory partial seizures: United States trial experience. *Epilepsia* 1997;**38** Suppl 1:S24–7.

392. Fichtner K, Appleton R, Murray G, Maton S, Alexander J. Gabapentin as add-on therapy in children with refractory partial seizures: a 24-week, open-label extension study. *Epilepsia* 1999;**40**:156.

393. Franzoni E, Marchiani V, Pignotti M, Moscano FC, Migliore MR. Gabapentin (GBP) as add-on treatment in children and adolescents with refractory epilepsy. *Epilepsia* 1999;**40**:239.

394. French JA, Mosier M, Walker S, Sommerville K, Sussman N, Barry E, *et al*. A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996;**46**:54–61.

395. Froscher W, Bulau P, Burr W, Penin H, Rao ML, De Beukelaar F. Double-blind placebo-controlled trial with flunarizine in therapy-resistant epileptic patients. *Clin Neuropharmacol* 1988;**11**:232–40.

396. Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, *et al*. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000;**20**:607–14.

397. Galas-Zgorzalewicz B, Steinborn B, Zgorzalewicz M. Vigabatrin in the treatment of drug resistant childhood and adolescence epilepsies: a three-year study prospective. *Epilepsia* 1999;**40**:273.

398. Garofalo E, Hayes A, Greeley C, Hes MK, Mann M, Greiner M, *et al*. Gabapentin (Neurontin) monotherapy in patients with medically refractory partial seizures – an open-label extension study. *Epilepsia* 1995;**36**:S119-S120.

399. Garofalo E, Hayes A, Hes M, Mann M, Greeley C, Pierce M. Quality-of-life assessments during open-label multicenter study evaluating gabapentin

111

(Neurontin) monotherapy in medically refractory patients with partial seizures. *Epilepsia* 1995; **36**:S187.

400. Gherpelli JLD, Guerreiro MM, da Costa JC, Rotta NT, Manreza MLG, Reed UC, *et al*. Vigabatrin in refractory childhood epilepsy. The Brazilian multicenter study. *Epilepsy Res* 1997; **29**:1–6.

401. Glauser TA, Elterman R, Wyllie E, Topiramate YP Study Team. Open-label topiramate in paediatric partial epilepsy. *Epilepsia* 1997;**38** Suppl 3:94.

402. Glauser TA, Levisohn PM, Ritter F, Sachdeo RC, Crumrine P, Ferreira J, *et al*. Topiramate in Lennox–Gastaut syndrome: open-label treatment of patients completing a randomized controlled trial. *Epilepsia* 2000;**41** Suppl 4:S86–90.

403. Glauser TA, Sachdeo RC, Ritter FJ, Reife R, Lim P, Topiramate YL Study Group. A double-blind trial of topiramate in Lennox–Gastaut syndrome (LGS). *Epilepsia* 1997;**38** Suppl 3:131.

404. Glauser TA, Wyllie E, Elterman R, Wu SC. Topiramate initiated as add-on therapy in children with partial-onset seizures: long-term findings. *Epilepsia* 1998;**39** Suppl 2:2.

405. Glauser TA, Elterman R, Wyllie E, Wu SC. Long-term topiramate therapy in children with partial-onset seizures. *Neurology* 1998;**50**(4):A99.

406. Gobbi G, Bertani G, Pini A, Guerrini R, Tiberti A, Valseriati D, *et al*. 1st line vigabatrin monotherapy in childhood partial epilepsy. *Epilepsia* 1995; **36**:S102.

407. Gram L, Lyon BB, Dam M. Gamma-vinyl-GABA: a single-blind trial in patients with epilepsy. *Acta Neurol Scand* 1983;**68**:34–9.

408. Gross-Tsur V, Shalev RS, Shahar E, Lahat E. Ophthalmological abnormalities in children with epilepsy treated with vigabatrin. *Ann Neurol* 1999;**46**:524–5.

409. Gross-Tsur V, Banin E, Shahar E, Shalev RS, Lahat E. Visual impairment in children with epilepsy treated with vigabatrin. *Ann Neurol* 2000;**48**:60–4.

410. Guberman A, Bruni J. Long-term open multicentre, add-on trial of vigabatrin in adult resistant partial epilepsy. *Seizure Euro J Epilepsy* 2000;**9**:112–18.

411. Hamilton MJ, Cohen AF, Yuen AW, Harkin N, Land G, Weatherley BC, *et al*. Carbamazepine and lamotrigine in healthy volunteers: relevance to early tolerance and clinical trial dosage. *Epilepsia* 1993;**34**:166–73.

412. Handforth A, Treiman DM. Efficacy and tolerance of long-term, high-dose gabapentin: additional observations. *Epilepsia* 1994;**35**:1032–7.

413. Hanefeld F. Effectivity and tolerability of vigabatrin in childhood and adolescent. *Aktuelle Neurol* 1992;**19** Suppl 1:S17–20.

414. Hanny A, Litzinger MJ. Tiagabine add-on treatment improves neurobehavioral and epilepsy-related symptoms in pediatric seizure patients. *Epilepsia* 1999;**40**:132.

415. Harding GFA, Robertson KA, Edson AS, Barnes P, Wild J. Visual electrophysiological effect of a GABA transaminase blocker. *Doc Ophthalmol* 1998;**97**:179–88.

416. Hayes A, Garofalo E, Mann M, Hes MK, Greeley C, Greiner M, *et al*. Gabapentin (Neurontin) monotherapy – a double-blind study in patients with medically refractory partial seizures. *Epilepsia* 1995;**36**:S119.

417. Hayes A, Garofalo E, Mann M, Hes MK, Greeley C, Pierce M. Quality-of-life assessments during a double-blind-study of gabapentin (Neurontin) in patients with medically refractory partial seizures. *Epilepsia* 1995;**36**:S187.

418. Hayes AG, Garofalo EA, Greeley CA, Mann ME, Hes MS, Greiner MJ, *et al*. A double-blind multicenter study of gabapentin (GBP Neurontin®) monotherapy in patients with medically refractory partial seizures. *Epilepsia* 1995;**36**:G3.

419. Hogan RE, Lenz GT, Deaton R, Sommerville KW. Weight changes with adjunctive therapy of phenytoin, carbamazepine, or tiagabine in a multicenter trial of partial seizures. *Epilepsia* 1998; **39** Suppl 6:125.

420. Hogan RE, Bertrand ME, Deaton RL, Sommerville KW. Total percentage body weight changes during add-on therapy with tiagabine, carbamazepine and phenytoin. *Epilepsy Res* 2000; **41**:23–8.

421. Hosain S, Solomon G, Joshi C, Chutorian A. Efficacy of topiramate in infants and children with symptomatic generalized epilepsies. *Ann Neurol* 1999;**46**:532.

422. Houtkooper M, Vanoorschot C, Hoppener RJ. Oxcarbamazepine (GP-47680) versus carbazepine – double blind crossover study in patients with epilepsy. *Acta Neurol Scand* 1984; **70**:221–2.

423. Ignatowicz R, Chmielik J, Michalowicz R, Ignatowicz L, Jozwiak S, Karkowska B. Sabril (vigabatrin) efficacy in therapy in epilepsy in children. *Epilepsia* 1995;**36**:S103.

424. Isojarvi JIT, Tapanainen J, Rattya J, Knip M, Pakarinen AJ, Tekay A, *et al*. Changes in body-weight, fasting serum-insulin and testosterone levels and ovarian structure in women with epilepsy after substituting lamotrigine for valproate. *Epilepsia* 1995;**36**:290.

425. Isojarvi JIT, Tapanainen J, Rattya J, Pakarinen AJ, Knip M, Tekay A, *et al*. Body-weight, serum testosterone levels, and ovarian structure in women with epilepsy after replacement of valproate with lamotrigine. *Epilepsia* 1995;**36**:S117.

426. Jawad S, Richens A, Goodwin G, Yuen WC. Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* 1989; **30**:356–63.

427. Kalviainen R, Brodie MJ, Duncan J, Chadwick D, Edwards D, Lyby K. A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. *Epilepsy Res* 1998;**30**:31–40.

428. Kalviainen R, Nousiainen I, Nikoskelainen E, Partanen J, Partanen K, Mantyjarvi M, *et al*. Visual field defects associated with initial vigabatrin monotherapy as compared with initial carbamazepine monotherapy. *Epilepsia* 1998; **39** Suppl 2:5.

429. Kalviainen R, Aikia M, Mervaala E, Saukkonen AM, Pitkanen A, Riekkinen PJ Sr. Long-term cognitive and EEG effects of tiagabine in drug-resistant partial epilepsy. *Epilepsy Res* 1996;**25**:291–7.

430. Kluger G, Berz K, Holthausen H. The long-term use of vigabatrin and lamotrigine in patients with severe childhood onset epilepsy. *Eur J Paediatr Neurol* 2001;**5**:37–40.

431. Kohrman MH. Use of gabapentin adjunctive therapy for nocturnal partial seizures with secondary generalization during adolescence. *Ann Neurol* 1998;**44**:B14.

432. Koul RL, Aithala GR, Joshi RM, Elbualy MS. Vigabatrin as add-on therapy in severely intractable seizures in children in Oman. *Epilepsia* 1995;**36**:S103–4.

433. Kraemer G, Canger R, Deisenhammer E, Moore A, Sterm Y. Double-blind, multicenter, noncomparative assessment of the retention rate of b.i.d. administration of oxcarbazepine as monotherapy for epilepsy in adults. *Epilepsia* 1998;**39** Suppl 6:132.

434. Lee S-K, Chang I. Comparative add-on trial of vigabatrin and valproic acid on intractable partial seizures with carbamazepine monotherapy. *Epilepsia* 1997;**38** Suppl 3:70.

435. Leiderman DB. Gabapentin as add-on therapy for refractory partial epilepsy: results of five placebo-controlled trials. *Epilepsia* 1994;**35** Suppl 5:S74–6.

436. Leoni S, Guerra A, Galli V, Rozzi N, Cavazzuti GB. Evaluation of the efficacy and tolerance to gabapentin in pharmacoresistant partial epilepsy in children. *Epilepsia* 1999;**40**:171–2.

437. Levisohn PM. Safety and tolerability of topiramate in children. *J Child Neurol* 2000;**15** Suppl 1:S22–6.

438. Lindberger M. A Nordic multicenter, randomized, double-blind, comparative study of gabapentin and vigabatrin. *Epilepsia* 1999;**40** Suppl 7:98–9.

439. Livingston JH, Beaumont D, Arzimanoglou A, Aicardi J. Vigabatrin in the treatment of epilepsy in children. *Br J Clin Pharmacol* 1989;**27**:S109–12.

440. Loiseau P, Yuen AW, Duche B, Menager T, Arne-Bes MC. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures. *Epilepsy Res* 1990;**7**:136–45.

441. Luna D, Dulac O, Pajot N, Beaumont D. Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. *Epilepsia* 1989;**30**:430–7.

442. Mandelbaum DE, Kugler SL, Wenger EC, Wollack JB, Venkat A. Clinical experience with Levetiracetam and Zonisamide in children with intractable epilepsy. *Neurology* 2001;**56**:A46.

443. Marescauz C. Lamotrigine and generalized paediatric epilepsy syndromes. In *Lamotrigine: A Brighter Future – International Congress and Symposium*. 1996;Series 214:75–80.

444. Martin R, Meador K, Turrentine L, Faught E, Sinclair K, Kuzniecky R, *et al*. Comparative cognitive effects of carbamazepine and gabapentin in healthy senior adults. *Epilepsia* 2001;**42**:764–71.

445. Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, Sinclair K, *et al*. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 1999;**52**:321–7.

446. Martinez W, Kaminow L, Nanry KP, Hammer AE, Barrett PS. Evaluation of lamotrigine versus carbamazepine, phenytoin, or divalproex sodium as monotherapy for epilepsy patients who failed or could not tolerate previous antiepileptic drug therapy. *Epilepsia* 2000;**41** Suppl 7:100.

447. Martinez Bermejo A, Lopez Martin V, Arcas J, Roche C, Tendero A, Castroviejo I. Vigabatrin in resistant childhood epilepsy. *Epilepsia* 1995; **36**:S104.

448. Martinezlage J, Ben-Menachem E, Shorvon SD, Weber M. Double-blind, placebo-controlled trial of 400 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1995;**36**:S149–50.

449. Martinovic Z. Gabapentin in the treatment of children and adolescents with partial epilepsy. *Epilepsia* 1999;**40**:224.

450. Matsuo F, Gay P, Madsen J, Tolman KG, Rollins DE, Risner ME, *et al*. Lamotrigine high-dose tolerability and safety in patients with epilepsy: a double-blind, placebo-controlled, eleven-week study. *Epilepsia* 1996;**37**:857–62.

451. Matsuo F, Bergen D, Faught E, Messenheimer JA, Dren AT, Rudd GD, *et al*. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. *Neurology* 1993;**43**:2284–91.

452. Mattson RH, Kamin M, Siu C. Seizure freedom with topiramate: results from an open-label follow-on to a double-blind titration study. *Epilepsia* 1998;**39** Suppl 6:55.

453. McKee PJW, Blacklaw J, Forrest G, Gillham RA, Walker SM, Connelly D, *et al*. A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 1994;**37**:27–32.

454. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Nichols ME, *et al*. Differential cognitive effects of carbamazepine and gabapentin. *Epilepsia* 1999;**40**:1279–85.

455. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Perrine KR, *et al*. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. *Neurology* 2001;**56**:1177–82.

456. Mecarelli O, Rinalduzzi S, Accornero N. Changes in color vision after a single dose of vigabatrin or carbamazepine in healthy volunteers. *Clin Neuropharmacol* 2001;**24**:23–6.

457. Mervaala E, Partanen J, Nousianinen U, Sivenius J, Riekkinen P. Electrophysiologic effects of gamma-vinyl GABA and carbamazepine. *Epilepsia* 1989;**30**:189–93.

458. Messenheimer J, Ramsay RE, Willmore LJ, Leroy RF, Zielinski JJ, Mattson R, *et al*. Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. *Epilepsia* 1994;**35**:113–21.

459. Messenheimer JA, Haynie CJ, Risner ME. Long-term tolerability of Lamictal in pediatric patients. *Epilepsia* 1998;**39** Suppl 6:51–2.

460. Michelucci R, Passarelli D, Di Fazio M, Tassinari CA. Topiramate in the treatment of drug-resistant epilepsy: a long-term follow-up study. *Boll Lega Ital Epilessia* 1996;**95–96**: 255–6.

461. Michelucci R, Passarelli D, Tassinari CA. Topiramate in the treatment of refractory partial epilepsy – a double-blind-study with long-term follow-up. *Epilepsia* 1995;**36**:S150.

462. Michelucci R, Passarelli D, Riguzzi P, Volpi L, Tassinari CA. Long-term follow-up of TPM [topiramate] in refractory partial seizures. *Epilepsia* 1998;**39** Suppl 2:67.

463. Michelucci R, Cavaciocchi P, Riguzzi P, Passarelli D, Parmeggiani L, Santangelo M, *et al*. Single-blind, placebo-controlled dose-modification study of vigabatrin in refractory epileptic patients. *J Epilepsy* 1992;**5**:248–52.

464. Michelucci R, Veri L, Passarelli D, Zamagni M, Strumia S, Buzzi AM, *et al*. Long-term follow-up study of vigabatrin in the treatment of refractory epilepsy. *J Epilepsy* 1994;**7**:88–93.

465. Micheu C, Foisoreanu V. Study on efficacy of lamotrigine in child epilepsies. *Epilepsia* 1999; **40**:229.

466. Mikati M, Khurana D, Riviello J, Holmes G, Helmers S, Anderson J. Efficacy of gabapentin in children with refractory partial seizures. *Neurology* 1995;**45**:A201–2.

467. Mims J, Penovich P, Ritter F, Frost MD. Treatment with high doses of lamotrigine in children and adolescents with refractory seizures. *J Child Neurol* 1997;**12**:64–7.

468. Montouris GD, Biton V, Rosenfeld WE. Nonfocal generalized tonic–clonic seizures: response during long-term topiramate treatment. Topiramate YTC/YTCE Study Group. *Epilepsia* 2000;**41** Suppl 1:S77–81.

469. Morita DA, Glauser TA, Hamant E, Guo SS. Effect of topiramate on linear growth in children with refractory complex partial seizures. *Neurology* 2000;**54**:A193.

470. Mortimore C, Trimble M, Emmers E. Effects of gabapentin on cognition and quality of life in patients with epilepsy. *Seizure* 1998;**7**:359–64.

471. Muscas GC, Chiroli S, Luceri F, Mastio MD, Balestrieri F, Arnetoli G. Conversion from thrice daily to twice daily administration of gabapentin (GBP) in partial epilepsy: analysis of clinical efficacy and plasma levels. *Seizure* 2000; **9**:47–50.

472. Muszkat M, Rizzutti S, Decampos CJR. Lamotrigine in refractory childhood epilepsy. *Epilepsia* 1995;**36**:S111.

473. Noachtar S, von Maydell B, Fuhry L, Buttner U. Gabapentin and carbamazepine affect eye movements and posture control differently: a placebo-controlled investigation of acute CNS side effects in healthy volunteers. *Epilepsy Res* 1998; **31**:47–57.

474. O'Donoghue MF, Sander JWAS, Eeg-Olofsson O, Reynolds EH, Brodie MJ, Richens A, *et al*. Lamotrigine versus carbamazepine in epilepsy [2]. *Lancet* 1995;**345**:1300–2.

475. Oommen K, Penry J, Riela A, Rowan A, Rosenbaum D, Schear M, *et al*. The long-term safety and efficacy of gabapentin (Neurontin™) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994;**18**:67–73.

476. Penry KJ, Wilder BJ, Sachdeo RC, Vaughan LU, Ahlbrandt RA. Multicenter dose–response study of vigabatrin in adults with focal (partial) epilepsy. *Epilepsia* 1993;**34** Suppl 6:67.

477. Pledger G, Reife R, Lim P, Karim R. Overview of topiramate efficacy from adjunctive therapy trials. *Boll Lega Ital Epilessia* 1996;**95–96**:247–50.

478. Privitera M, Fincham R, Penry J, Reife R, Kramer L, Pledger G, *et al*. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. Topiramate YE Study Group. *Neurology* 1996;**46**:1678–83.

479. Ramsay RE, Pellock JM, Garnett WR, Sanchez RM, Valakas AM, Wargin WA, *et al*. Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with epilepsy. *Epilepsy Res* 1991;**10**:191–200.

480. Ramsey ER, Veloso F, Bomhof M, Pledger G, Wu SC. Patient factors affecting response to early AED monotherapy in partial-onset seizures: observations from a randomized controlled trial with topiramate (TPM). *Epilepsia* 1999;**40** Suppl 7:111.

481. Regesta G, Tanganelli P. Vigabatrin vs carbamazepin monotherapy in newly diagnosed focal epileptics. A randomized response conditional cross-over study [Abstract]. *J Neurol Sci* 1997;(Sept):S167.

482. Regesta G, Tanganelli P. Vigbatrin monotherapy in newly diagnosed focal epilepsy. *Boll Lega Ital Epilessia* 1997;**99**(Suppl 1):27–32.

483. Regesta G, Tanganelli P. Vigabatrin versus carbamazepine monotherapy in newly diagnosed focal epileptics: a randomised response condition cross-over study. *Epilepsia* 1997;**38** Suppl 3:58.

484. Reinikainen K, Keranen T, Hallikainen E, Riekkinen PJ. Substitution of diphenylhydantoin by oxcarbazepine or carbamazepine: double-blind study. *Acta Neurol Scand* 1984;**69** Suppl 98:89–90.

485. Reinikainen KJ, Keranen T, Halonen T, Komulainen H, Riekkinen PJ. Comparison of oxcarbazepine and carbamazepine: a double-blind study. *Epilepsy Res* 1987;**1**:284–9.

486. Richens A, Chadwick DW, Duncan JS, Dam M, Gram L, Mikkelsen M, *et al*. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. *Epilepsy Res* 1995;**21**:37–42.

487. Richens A, Mawer G, Crawford P, Harrison B. A placebo-controlled, double-blind cross-over trial of adjunctive one month remacemide hydrochloride treatment in patients with refractory epilepsy. *Seizure* 2000;**9**:537–43.

488. Richens A. Lamotrigine versus carbamazephine double-blind comparative trial. In *Lamotrigine: A Brighter Future – International Congress and Symposium*. 1996;Series 214:9–14.

489. Ritter F, Glauser TA, Elterman RD, Wyllie E. Effectiveness, tolerability, and safety of topiramate in children with partial-onset seizures. Topiramate YP Study Group. *Epilepsia* 2000;**41** Suppl 1:S82–5.

490. Ritter FJ, Glauser TA, Sachdeo RC, Shu-Chen W. Long-term experience with topiramate in Lennox–Gastaut syndrome. *Epilepsia* 1998; **39**;Suppl 2:2–3.

491. Rosenfeld WE, Abou-Khalil BW, Reife R, Hegadus R, Pledger G, Johnson RW. Placebo-controlled trial of topiramate as adjunctive therapy to carbamazepine or phenytoin for partial-onset epilepsy. *Epilepsia* 1996;**37** Suppl 1:153.

492. Rosenfeld WE. Topiramate, a broad-spectrum agent, in patients with juvenile myoclonic epilepsy. *Epilepsia* 1999;**40**:226.

493. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998;**280**:1837–42.

494. Sachdeo R, Leroy R, Krauss G, Green P, Drake M, Leppik I, *et al*. Safety and efficacy of bid and qid dosing with tiagabine HCL versus placebo as adjunctive treatment for partial seizures. *Neurology* 1995;**45**:A202.

495. Sachdeo RC, Narang-Sachdeo S. Placebo controlled trial of oxcarbazepine in recent onset partial seizures. *Epilepsia* 1997;**38** Suppl 3:80.

496. Sander JWAS, Patsalos PN, Oxley JR, Hamilton MJ, Yuen WC. A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. *Epilepsy Res* 1990;**6**:221–6.

497. Sanmarti F, Pires M, Pineda M, Conill J, Vernet A, Campistol J, *et al*. Lamotrigine in 68 children with refractory epilepsy. *Epilepsia* 1995;**36**:S111.

498. Schachter S, Biton V, Boellner S, Edwards K, Cybulski K, Shu V, *et al*. Safety and efficacy of tiagabine HCl monotherapy in the treatment of partial seizures – high dose versus low dose. *Epilepsia* 1995;**36**:S148.

499. Schachter SC, Leppik IE, Matsuo F, Messenheimer JA, Faught E, Moore EL, *et al*. Lamotrigine: A six-month, placebo-controlled, safety and tolerance study. *J Epilepsy* 1995;**8**:201–9.

500. Schachter SC. Tiagabine monotherapy in the treatment of partial epilepsy. *Epilepsia* 1995; **36** Suppl 6:S2–6.

501. Schacter SC, Vasquez B, Fisher R, Bennett D. Placebo-controlled inpatient monotherapy trial of oxcarbazepine. *Epilepsia* 1997;**38** Suppl 3:30.

502. Schapel G, Beran R, Berkovic SF, Mashford ML, Dunagan FM. Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures. *Aust N Z J Med* 1991;**21**:620.

503. Schlumberger E, Chavez F, Palacios L, Rey E, Pajot N, Dulac O. Lamotrigine in treatment of 120 children with epilepsy. *Epilepsia* 1994;**35**: 359–67.

115

504. Schmidt D, Reid S, Rapp P. Add-on treatment with lamotrigine for intractable partial epilepsy: a placebo-controlled cross-over trial. *Epilepsia* 1993;**34** Suppl. 2:66.

505. Schmitz-Moormann W, Kruse R. Vigabatrin long-term therapy in symptomatic epilepsies with complex focal seizures in pediatrics. *Aktuelle Neurol* 1992;**19** Suppl 1:S23–5.

506. Schwabe MJ, Wheless JW. Clinical experience with topiramate (Topamax) dosing and serum levels in children 12 years or younger with epilepsy. *Ann Neurol* 2000;**48**:17.

507. Sharief M, Viteri C, Ben Menachem E, Weber M, Reife R, Pledger G, *et al*. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. *Epilepsy Res* 1996;**25**:217–24.

508. Siemes H. Lamotrigine as add-on therapy an difficult-to-treat epilepsies in children and adolescents. *Epilepsia* 1999;**40**:68.

509. Sillanpaa M, Pihlaja T. Oxcarbazepine (GP 47 680) in the treatment of intractable seizures. *Acta Paediatr Hung* 1988;**29**:359–64.

510. Sinclair KR, Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, *et al*. Comparative cognitive effects of topiramate, gabapentin, and lamotrigine: an acute and steady-state dosing study in healthy young adults. *Epilepsia* 1998;**39** Suppl 6:250–1.

511. Siskova D, Dolansky J, Hadac J. Efficacy of Sabril in treatment of epilepsy in children. *Epilepsia* 1995;**36**:S104.

512. Sivenius J, Ylinen A, Matilainen R, Reinikainen K, Riekkinen P. Double-blind dose reduction study in complex partial epilepsy with vigabatrin – an interim report. *Epilepsia* 1985;**26**:537.

513. Sivenius J, Ylinen A, Matilainen R, Murros K, Riekkinen PJ. Double-blind dose reduction study in complex partial epilepsy with gamma-vinyl-gaba. *Uppsala J Med Sci* 1986;Suppl 43:46.

514. Sivenius J. Long-term therapy with vigabatrin in patients with complex partial epilepsy. *Acta Neurol Scand* 1988;**77**:139.

515. Smith D, Chadwick D, Baker G, Davis G, Dewey M. Seizure severity and the quality of life. *Epilepsia* 1993;**34** Suppl 5:S31–5.

516. Steiner TJ, Findley LJ. Safety data from a placebo-controlled trial of lamotrigine. In *Lamotrigine: A Brighter Future – International Congress and Symposium* 1996;Series 214:31–5.

517. Steinhoff BJ, Freudenthaler N, Paulus W. The influence of established and new antiepileptic drugs on visual perception. 1. A placebo-controlled, double-blind, single-dose study in healthy volunteers. *Epilepsy Res* 1997;**29**:35–47.

518. Stolarek I, Blacklaw J, Forrest G, Brodie MJ. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994;**57**:921–4.

519. Tanganelli P, Regesta G. Vigabatrin versus carbamazepine in newly-diagnosed epileptic patients – a randomized-response conditional cross-over study. *Epilepsia* 1995;**36**:S104.

520. Tanganelli P, Regesta G. Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study. *Epilepsy Res* 1996;**25**:257–62.

521. Tartara A, Manni R, Galimberti CA, Morini R, Mumford JP, Iudice A, *et al*. Six-year follow-up study on the efficacy and safety of vigabatrin in patients with epilepsy. *Acta Neurol Scand* 1992;**86**:247–51.

522. Tassinari C, Chauvel P, Chodkiewicz J, Shorvon SD, Henriksen O, Dam M, *et al*. Double-blind, placebo-controlled trial of 600 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1995;**36**:S150.

523. Tassinari CA, Michelucci R, Chauvel P, Chodkiewicz J, Shorvon S, Henriksen O, *et al*. Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. *Epilepsia* 1996;**37**:763–8.

524. The Italian Study Group on Vigabatrin. Single-blind, placebo-controlled multicenter trial of vigabatrin in the treatment of epilepsy. The Italian Study Group on Vigabatrin. *Italian J Neurol Sci* 1992;**13**:741–7.

525. Thomas L, Trimble M. The effects of vigabatrin on attention, concentration and mood: an investigation in healthy volunteers. *Seizure* 1996;**5**:205–8.

526. Trudeau VL, Dimond KR, Smith FB, Wilensky AJ, Chmelir T, Ricker B, *et al*. Gabapentin (GBP neurontin®) monotherapy compared with carbamazepine (CBZ) monotherapy and combination GBP plus CBZ (GBP/CBZ) therapy in patients with medically refractory partial seizures – a 3-way cross-over trial (94536). *Epilepsia* 1995;**36**:343.

527. Uldall P, Bulteau C, Pedersen SA, Dulac O, Meinild H, Lassen LC. Single-blind study of safety, tolerability, and preliminary efficacy of tiagabine as adjunctive treatment of children with epilepsy. *Epilepsia* 1995;**36**:S147–8.

528. Uldall P, Bulteau C, Pedersen SA, Dulac O, Lyby K. Tiagabine adjunctive therapy in children with refractory epilepsy: a single-blind dose escalating study. *Epilepsy Res* 2000;**42**:159–68.

529. Uthman B, Rowan AJ, Ahmann P, Wannamaker B, Schachter S, Rask C. Safety and efficacy of 3 dose levels of tiagabine HCL versus placebo as

adjunctive treatment for complex partial seizures. *Ann Neurol* 1993;**34**:272.

530. Wheless JW. Use of topiramate in childhood generalized seizure disorders. *J Child Neurol* 2000;**15** Suppl 1:S7–13.

531. Wieser HG, Truog B, Vogt H, Honneger UE. The Swiss lamotrigine study – results of an open, multicenter, add-on treatment with lamotrigine in drug-resistant epileptic patients. *Epilepsia* 1995; **36**:S114–15.

532. Wieser HG. The Swiss Lamotrigine (Lamictal™) Study. Results of an open, multicenter add-on-treatment in therapy resistant epilepsy. *Ars Med* 1995;**85**:449–53.

533. Yen DJ, Yu HY, Guo YC, Chen C, Yiu CH, Su MS. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. *Epilepsia* 2000;**41**:1162–6.

534. Yuen AW, Chapman A. Interim report on an open multicentre lamotrigine (Lamictal) versus carbamazepine monotherapy trial in patients with epilepsy. *Can J Neurol Sci* 1993;**20** Suppl. 4: S150.

535. Zahner B, Stefan H, Blankenhorn V, Kramer G, Richens A, Thumler R. Double-blind cross-over study comparing once-daily versus twice-daily vigabatrin add-on therapy in patients with previously refractory epilepsy. *Epilepsia* 1995; **36**:S106.

536. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997;**73**:223–30.

537. Aikia M, Sivenius JK. Oxcarbazepine vs phenytoin in monotherapy for newly diagnosed epilepsy with a special reference to memory function. In *18th International Epilepsy Congress*.1989. p. 91.

538. Loiseau P, Bes AM. Double-blind placebo controlled crossover study of lamotrigine (Lamictal) as add-on therapy in patients with refractory partial seizures. In *18th International Epilepsy Congress*. 1989. p. 144.

539. Sivenius J, Kalviainen RY. A double-blind study of gabapentin in the treatment of partial seizures. In *18th International Epilepsy Congress*. 1989. p. 91.

540. Yu H-Y, Yen D-J, Yiu C-H, Su M-S. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1999;**40**:97.

541. Kharlamov DA, Prityko AG, Ayvazian SO, Yavorskaya MM. Lamotrigine in the treatment of drug-resistant epilepsies in children. *Epilepsia* 1999;**40**:175.

542. Kivity S, Shorer Z, Unit S. Lamotrigine add-on therapy in children with drug-resistant epilepsy: low incidence of rash associated with low initial and titration doses. *Epilepsia* 1999;**40**:172.

543. Mirza W, Biton V, Barrett P, Vuong A, Hammer A. Weight gain associated with valproate monotherapy in patients with epilepsy: an interim analysis of a randomized, double-blinded comparative clinical trial with lamotrigine. *Epilepsia* 1999;**40**:282.

544. Mojs E, Galas-Zgorzalewicz B. The long term prognosis of cognitive functioning in epileptic children and adolescents in bitherapy with vigabatrin. *Epilepsia* 1999;**40**:275.

545. Rintahaka PJ, Gaily E, Liukkonen E, Paetau R, Grandstrom ML. Topiramate in the treatment of intractable pediatric epilepsy. *Epilepsia* 1999;**40**:135.

546. Slapal R, Zaplatilova L. Quality of life with lamotrigine in epileptic children – our five-year experience. *Epilepsia* 1999;**40**:180–1.

547. Sokic DV, Pavlovic Z, Jankovic SM, Levic Z. Lamotrigine for the treatment of juvenile myoclonic epilepsy. *Epilepsia* 1999;**40**:38.

548. Uran N, Calkavur SS, Kalkan S. Vigabatrin in the therapy-resistant childhood epilepsies. *Epilepsia* 1999;**40**:255.

549. Uran N, Serdarodlu G, Calkavur T, Serdarodlu E. Lamotrigine treatment in childhood drug resistant epilepsy. *Epilepsia* 1999;**40**:176.

550. Uysal S, Deda G, Karagol U. Lamotrigine monotherapy in childhood epilepsy and the comparative evaluation of the effects of other antiepileptic drugs on evoked potentials. *Epilepsia* 1999;**40**:251–2.

551. Biraben A, Beaussart M, Josien E, Pestre M, Schaff JL, Sevestre M. Tiagabine as adjunctive treatment of partial seizures in patients with epilepsy: A comparison of two dose regimens. *Epilepsia* 2000;**41** Suppl Florence:96.

552. Brodie MJ, Anhut H, Murray G, Maton S. Gabapentin versus lamotrigine monotherapy: a double-blind comparison. *Epilepsia* 2000; **41** Suppl Florence:138.

553. Carpay JA, Veendrick-Meekes MJBM, Beun AM, Arends LR, Schlosser A. Carer assessment of quality of life related to seizure severity and side effects of lamotrigine in mentally retarded epilepsy patients. *Epilepsia* 2000;**41** Suppl Florence:114.

554. Gil KB, Nagel N, Verger K, Sol JM, Morralla C, Hernandez G. Safety of gabapentin vs. valproic acid as add-on therapy to carbamazepine. *Epilepsia* 2000;**41** Suppl Florence:105.

555. Kazibutowska Z, Stelmach-Wawrzyczek A. Efficacy of therapy with new antiepileptic drugs (tiagabine, gabapentin, topiramate) in drug-resistant epilepsy. *Epilepsia* 2000;**41** Suppl Florence:38.

556. Kwan SY, Yiu CH, Su MS. A double blind study of gabapentin in partial seizures. *Epilepsia* 2000; **41** Suppl Florence:69.

557. Meador KJ, Loring DW, Ray PG, Perrine KR, Vasquez BR, Kalbosa T. Cognitive side effects of carbamazepine and lamotrigine compared to non-drug state. *Epilepsia* 2000;**41** Suppl Florence:113.

558. Neto W, Gassmann-Mayer C. Efficacy and tolerability of 200 mg/day topiramate in a placebo-controlled comparison of titration rates. *Epilepsia* 2000;**41** Suppl Florence:35.

559. Privitera MD, Brodie MJ, Neto W, Wang S. Monotherapy in newly diagnosed epilepsy: topiramate vs. investigator choice of carbamazepine or valproate. *Epilepsia* 2000; **41** Suppl Florence:138.

560. Veendrick-Meekes MJBM, Beun AM, Carpay JA, Arends LR, Schlosser A. Use of lamotrigine as adjunctive therapy in patients with mental retardation and epilepsy: an interim analysis of a double blind study with evaluation of behavioural effects. *Epilepsia* 2000;**41** Suppl Florence:97.

561. Abou KB. Long-term seizure freedom with levetiracetam. *J Neurol Sci* 2001;**187:**(Suppl 1).

562. Cramer JA. Short-term treatment with levetiracetam enhances health-related quality of life in patients with refractory epilepsy. *J Neurol Sci* 2001;**187:**(Suppl 1).

563. Kerr M, Moorat A, Curtis P. Lamotrigine compared to valproate: a randomised open label switch to monotherapy study in patients with uncontrolled epilepsy. *J Neurol Sci* 2001; **187:**(Suppl 1).

564. Michelucci R, Tassinari CA, Forti A, Ambrosetto G, Rubboli G, Iudice A, *et al*. Vigabatrin in the treatment of drug-resistant epilepsy: short-term results of 2 placebo-controlled trials. *Boll Lega Ital Epilessia* 1988;**64**:167–9.

565. Angeleri F, Scarpino O, Avanzini G, Binelli D, Baruzzi A, Procaccianti G, *et al*. A multicenter study of Vigabatrin in refractory epilepsy. *Boll Lega Ital Epilessia* 1990;**70–71**:121–3.

566. Dulac O, Chiron C, Luna D, Cusmai R, Pajot N, Beaumont D, *et al*. Vigabatrin in childhood epilepsy. *J Child Neurol* 1991;**6** Suppl 2: 2S30–2S37.

567. Kalviainen R, Aikia M, Partanen J, Sivenius J, Mumford J, Saksa M, *et al*. Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: an interim report. *J Child Neurol* 1991; Suppl 2:S60–S69.

568. Espe-Lillo J, Ritter FJ, Frost MD, Spiegel RE, Reife R. Topiramate in childhood epilepsy – titration, adverse events, and efficacy in multiple seizure types. *Epilepsia* 1995;**36** Suppl 4:287.

569. Mumford JP, Dam M. Meta-analysis of European placebo controlled studies of vigabatrin in drug resistant epilepsy. *Br J Clin Pharmacol* 1989;**27**(Suppl 1):101S–7S.

570. Richens A, Yuen AW. Overview of the clinical efficacy of lamotrigine. *Epilepsia* 1991;**32**(Suppl 2): S13–16.

571. Leach JP, Marson AG, Hutton JL. Remacemide for drug-resistant localization related epilepsy. *Cochrane Database Syst Rev* 2002(4):CD001900.

572. Selai CE, Smith K, Trimble MR. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of two AEDs. *Seizure* 1999;**8**(1):8–13.

573. Jacoby A, Buck D, Baker G, McNamee P, Graham-Jones S, Chadwick D. Uptake and costs of care for epilepsy: findings from a U.K. regional study. *Epilepsia* 1998;**39**(7):776–86.

574. Elterman R, Glauser TA, Ritter FJ, Sell SF, Wyllie E, Reife R, *et al*. A double-blind trial of topiramate in partial seizures in children. *Epilepsia* 1997;**38**(Suppl 3):131.

575. Elterman R, Glauser TA, Ritter FJ, Reife R, Wu SC. Topiramate as adjunctive therapy in children with partial-onset seizures. *Annals of Neurology* 1997;**42**(3):12.

576. Elterman P, Glauser T, Ritter FJ, Reife R, Wu SC. Efficacy and safety of topiramate in partial seizures in children. *Neurology* 1997;**48**(6):4.

This version of HTA monograph volume 10, number 7 does not include the 360 pages of appendices. This is to save download time from the HTA website.

The printed version of this monograph also excludes the appendices.

[View/download the appendices](#) (1300 kbytes).

Health Technology Assessment Programme

Director,
Professor Tom Walley,
Director, NHS HTA Programme,
Department of Pharmacology &
Therapeutics,
University of Liverpool

Deputy Director,
Professor Jon Nicholl,
Director, Medical Care Research
Unit, University of Sheffield,
School of Health and Related
Research

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme,
Department of Pharmacology &
Therapeutics,
University of Liverpool

Professor Bruce Campbell,
Consultant Vascular & General
Surgeon, Royal Devon & Exeter
Hospital

Dr Edmund Jessop, Medical
Advisor, National Specialist,
Commissioning Advisory Group
(NSCAG), Department of
Health, London

Professor Jon Nicholl, Director,
Medical Care Research Unit,
University of Sheffield, School
of Health and Related Research

Dr John Reynolds, Clinical
Director, Acute General
Medicine SDU, Radcliffe
Hospital, Oxford

Dr Ron Zimmern, Director,
Public Health Genetics Unit,
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme,
Department of Pharmacology &
Therapeutics,
University of Liverpool

Chair,
Professor Jon Nicholl,
Director, Medical Care Research
Unit, University of Sheffield,
School of Health and Related
Research

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care
Psychology, Academic Unit of
Psychiatry and Behavioural
Sciences, University of Leeds
School of Medicine

Dr Jeffrey Aronson
Reader in Clinical
Pharmacology, Department of
Clinical Pharmacology,
Radcliffe Infirmary, Oxford

Professor Deborah Ashby,
Professor of Medical Statistics,
Department of Environmental
and Preventative Medicine,
Queen Mary University of
London

Professor Ann Bowling,
Professor of Health Services
Research, Primary Care and
Population Studies,
University College London

Dr Andrew Briggs, Public
Health Career Scientist, Health
Economics Research Centre,
University of Oxford

Professor John Cairns, Professor
of Health Economics, Public
Health Policy, London School of
Hygiene and Tropical Medicine,
London

Professor Nicky Cullum,
Director of Centre for Evidence
Based Nursing, Department of
Health Sciences, University of
York

Mr Jonathan Deeks,
Senior Medical Statistician,
Centre for Statistics in
Medicine, University of Oxford

Dr Andrew Farmer, Senior
Lecturer in General Practice,
Department of Primary
Health Care,
University of Oxford

Professor Fiona J Gilbert,
Professor of Radiology,
Department of Radiology,
University of Aberdeen

Professor Adrian Grant,
Director, Health Services
Research Unit, University of
Aberdeen

Professor F D Richard Hobbs,
Professor of Primary Care &
General Practice, Department of
Primary Care & General
Practice, University of
Birmingham

Professor Peter Jones, Head of
Department, University
Department of Psychiatry,
University of Cambridge

Professor Sallie Lamb,
Professor of Rehabilitation,
Centre for Primary Health Care,
University of Warwick

Professor Stuart Logan,
Director of Health & Social
Care Research, The
Peninsula Medical School,
Universities of Exeter &
Plymouth

Dr Linda Patterson,
Consultant Physician,
Department of Medicine,
Burnley General Hospital

Professor Ian Roberts, Professor
of Epidemiology & Public
Health, Intervention Research
Unit, London School of
Hygiene and Tropical Medicine

Professor Mark Sculpher,
Professor of Health Economics,
Centre for Health Economics,
Institute for Research in the
Social Services, University of York

Dr Jonathan Shapiro, Senior
Fellow, Health Services
Management Centre,
Birmingham

Ms Kate Thomas,
Deputy Director,
Medical Care Research Unit,
University of Sheffield

Ms Sue Ziebland,
Research Director, DIPEx,
Department of Primary Health
Care, University of Oxford,
Institute of Health Sciences

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

283

Diagnostic Technologies & Screening Panel

Members

**Chair,
Dr Ron Zimmern,** Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Lay Member, Bolton

Professor Max Bachmann Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant Paediatrician/ Hon. Senior Lecturer, Population Health Unit, Great Ormond St. Hospital, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Professor William Rosenberg, Professor of Hepatology, Liver Research Group, University of Southampton

Dr Susan Schonfield, Consultant in Public Health, Specialised Services Commissioning North West London, Hillingdon Primary Care Trust

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr Margaret Somerville, PMS Public Health Lead, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Associate Dean for Education, Head of Department of Obstetrics and Gynaecology, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

**Chair,
Dr John Reynolds,** Chair Division A, The John Radcliffe Hospital, Oxford Radcliffe Hospitals NHS Trust

Professor Tony Avery, Head of Division of Primary Care, School of Community Health Services, Division of General Practice, University of Nottingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Consultant in Pharmaceutical Public Health, National Public Health Service for Wales, Cardiff

Mrs Sharon Hart, Head of DTB Publications, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, South Gloucestershire Primary Care Trust

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, The Royal Marsden Hospital, Sutton

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer
Research UK Med Stat Gp,
Centre for Statistics in
Medicine, University of Oxford,
Institute of Health Sciences,
Headington, Oxford

Professor John Bond,
Director, Centre for Health
Services Research, University of
Newcastle upon Tyne, School of
Population & Health Sciences,
Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the
Chief Executive. Trust
Headquarters, Altnagelvin
Hospitals Health & Social
Services Trust, Altnagelvin Area
Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World
Confederation for Physical
Therapy, London

Professor Iain T Cameron,
Professor of Obstetrics and
Gynaecology and Head of the
School of Medicine,
University of Southampton

Dr Christine Clark,
Medical Writer & Consultant
Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing & Head of
Research, School of Health
Sciences, University of
Birmingham, Edgbaston,
Birmingham

Professor Barry Cookson,
Director, Laboratory of
Healthcare Associated Infection,
Health Protection Agency,
London

Professor Howard Cuckle,
Professor of Reproductive
Epidemiology, Department of
Paediatrics, Obstetrics &
Gynaecology, University of
Leeds

Dr Katherine Darton,
Information Unit, MIND –
The Mental Health Charity,
London

Professor Carol Dezateux,
Professor of Paediatric
Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic
Surgeon, Cardiothoracic
Surgical Unit, Papworth
Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon,
Gloucestershire Royal Hospital,
Gloucester

Professor Martin Eccles,
Professor of Clinical
Effectiveness, Centre for Health
Services Research, University of
Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community
Rehabilitation, Institute of
General Practice and Primary
Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle
upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine,
Child Health, The Leicester
Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and
President, National Childbirth
Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine,
Department of Medicine,
University of Birmingham,
Queen Elizabeth Hospital,
Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive,
Director for Nursing, Midwifery
& Clinical Support Services,
West Middlesex University
Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist,
Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics,
Department of Public Health,
University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of
Medical Oncology, Christie CRC
Research Centre, Christie
Hospital NHS Trust, Manchester

Professor Allen Hutchinson,
Director of Public Health &
Deputy Dean of ScHARR,
Department of Public Health,
University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch
& Ptnrs), The Health Centre,
Thame

Dr Donna Lamping,
Research Degrees Programme
Director & Reader in Psychology,
Health Services Research Unit,
London School of Hygiene and
Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor
Neurone Disease Association,
Northampton

Professor James Lindesay,
Professor of Psychiatry for the
Elderly, University of Leicester,
Leicester General Hospital

Professor Julian Little,
Professor of Human Genome
Epidemiology, Department of
Epidemiology & Community
Medicine, University of Ottawa

Professor Rajan Madhok,
Medical Director & Director of
Public Health, Directorate of
Clinical Strategy & Public
Health, North & East Yorkshire
& Northern Lincolnshire Health
Authority, York

Professor David Mant,
Professor of General Practice,
Department of Primary Care,
University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Chris McCall,
General Practitioner, The
Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics,
London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Sue Moss, Associate Director,
Cancer Screening Evaluation
Unit, Institute of Cancer
Research, Sutton

Mrs Julietta Patnick,
Director, NHS Cancer Screening
Programmes, Sheffield

Professor Tim Peters,
Professor of Primary Care
Health Services Research,
Academic Unit of Primary
Health Care, University of
Bristol

Professor Chris Price,
Visiting Chair – Oxford, Clinical
Research, Bayer Diagnostics
Europe, Cirencester

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Dr Eamonn Sheridan,
Consultant in Clinical Genetics,
Genetics Department,
St James's University Hospital,
Leeds

Dr Ken Stein,
Senior Clinical Lecturer in
Public Health, Director,
Peninsula Technology
Assessment Group,
University of Exeter

Professor Sarah Stewart-Brown,
Professor of Public Health,
University of Warwick,
Division of Health in the
Community Warwick Medical
School, LWMS, Coventry

Professor Ala Szczepura,
Professor of Health Service
Research, Centre for Health
Services Studies, University of
Warwick

Dr Ross Taylor,
Senior Lecturer, Department of
General Practice and Primary
Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA –
Expert Advisory Network

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.