The Epilepsies

The diagnosis and management of the epilepsies in adults and children in primary and secondary care

Clinical guideline
Methods, evidence and recommendations
July 2010  Draft for Consultation

Commissioned by the National Institute for Health and Clinical Excellence
Foreword (2004)

Dr Mayur Lakhani
Chairman-Elect, Royal College of General Practitioners
Founding Chairman of the National Collaborating Centre for Primary Care (2001-2004)

It gives me great pleasure to see the publication of the first major clinical practice guideline from the National Collaborating Centre for Primary Care, hosted by the Royal College of General Practitioners.

As a practising GP, I am well aware of the challenges faced when dealing with patients with epilepsy. It is well recognised that the care of patients with epilepsy is sub-optimal and more needs to be done to improve clinical standards. GPs are faced with a complex set of issues on a regular basis including giving advice to patients about epilepsy and driving, planning a pregnancy and the thorny issue of withdrawal of anti-epileptic medication. In these and other areas, practical recommendations are essential: It is therefore welcome to have this clear guidance which will support GPs to implement the Quality and Outcomes Framework of the new General Medical Services contract. In addition the guideline contains important recommendations about service for patients with epilepsy and the organisation of care.

The Royal College of General Practitioners exists to promote the highest possible standards of general medical care and it is committed to increasing support for GPs to enable them to do so. I commend these guidelines to the health community as a whole and urge commissioners to support its implementation. I would like to acknowledge the excellent work of the staff of National Collaborating Centre for Primary Care and colleagues at the University of Leicester in producing this guideline.

Dr Richard Roberts
Consultant Neurologist, Ninewells Hospital, Dundee
Chairman, SIGN 70 Diagnosis and management of epilepsy in adults (2003)

The inadequacies that have existed in the services, care and treatment for people with epilepsy are well recognised. Important issues include misdiagnosis, inappropriate or inadequate treatment, sudden unexpected death that might have been prevented, advice about pregnancy and contraception and management of status epilepticus. Service provision for people with epilepsy has been patchy and sometimes poor both in primary and secondary care. This is now changing. The new GMS contract includes targets for epilepsy. The number of specialists with expertise in epilepsy is increasing. There has been a great increase in the number of epilepsy specialist nurses, and structured services for epilepsy across primary and secondary care are emerging. At the same time a number of new antiepileptic drugs have been licensed.

This guideline is published, therefore, at a time when it is likely to have a major impact. The recommendations on service provision, such as waiting times to see specialists and for investigations, will be challenging for the service providers, as they have been in Scotland following similar recommendations (SIGN Guideline 70). The guidance on the use of the newer antiepileptic drugs confirms their important role in the treatment of epilepsy. Clear guidance is given in various specific areas such as pregnancy and contraception, learning disability, young people, repeated seizures in the community and status epilepticus. The importance of the provision of information for people with epilepsy and their carers is stressed. If there is successful implementation of the recommendations, there will be a great improvement in the care of people with epilepsy.
Update 2011

This document is a partial update of the original guideline published in 2004. The sections that have been updated are:

- Introduction
- Methodology
- Pharmacological management of the epilepsies
- Ketogenic diet
- Appendices

The content of other sections has not been amended and we have integrated these new sections into the old publication. This has inevitably led to inconsistencies in style of write up for reviews and where new recommendations (without any gradings) have been added to, or replaced, existing recommendations which do have gradings.

New or amended sections of the guideline are highlighted by a bar in the right hand margin.
Acknowledgements

2004

The Guideline Development Group would like to thank Nancy Turnbull and Charmaine Larment of the National Collaborating Centre for Primary Care, Royal College of General Practitioners for all their hard work in arranging GDG meetings and supporting the guideline development process.

The Project Team would like to thank Ms Vicki Cluley, University of Leicester, for secretarial support and Dr Ali Al-Ghorr and Dr Moray Nairn, Scottish Intercollegiate Guidelines Network, Edinburgh for their help in sharing relevant searches and evidence reviews on the epilepsies in adults and children. The team would also like to thank Dr Allan Wailloo, University of Sheffield for his initial health economic input and Ms Nicola Costin for her help with the second draft.

2011

The Guideline Development Group and project team would like to thank Dr Lee-Yee Chong, Mrs Fulvia Ronchi, Ms Abigail Jones, Mr David Wonderling, and Dr Norma O‘Flynn for all their help and support throughout the guideline development process. The project team would also like to thank Professor Tony Marson for providing further data for the evidence analyses.
Stakeholder list

2004

- Acute Care Collaborating Centre
- Ambulance Service Association
- Anglesey Local Health Board
- Ashfield and Mansfield District PCTs
- Association of British Neurologists
- Association of Clinical Biochemists, The
- Association of Paediatric Emergency Medicine
- Association of the British Pharmaceuticals Industry (ABPI)
- Aventis Pharma
- Barts and the London NHS Trust
- Bradford South & West Primary Care Trust
- Bradford Teaching Hospitals Trust
- Britannia Pharmaceuticals Ltd
- British Association for Accident and Emergency Medicine
- British Association of Art Therapists
- British Epilepsy Association (BEA)
- British Geriatrics Society
- British Maternal and Fetal Medicine Society
- British National Formulary (BNF)
- British Paediatric Neurology Association
- British Psychological Society, The
- British Society for Clinical Neurophysiology
- British Society of Neuroradiologists
- CEMACH
- Cephalon UK Ltd
- Chartered Society of Physiotherapy
- Chronic Conditions Collaborating Centre
- CLIMB - Children Living with Inherited Metabolic Disorders
- Cochrane Epilepsy Group
- College of Occupational Therapists
- Community Psychiatric Nurses' Association
- Cornwall Partnership NHS Trust
CRISIS
Croydon Primary Care Trust
Cyberonics S.A./N.V.
Cymdeithas Tai Hafan
David Lewis Centre, The
Denbighshire Local Health Board
Department of Health
Devon Partnership NHS Trust
Dudley Beacon & Castle Primary Care Trust
Eisai Limited
Eli Lilly and Company Ltd
Epilepsy Bereaved
Epilepsy Specialist Nurses Association
Faculty of Public Health
First Person Plural
General Medical Council
GlaxoSmithKline UK
Gloucestershire Partnership NHS Trust
Hampshire Partnership NHS Trust
Healthcare Commission
Hertfordshire Partnership NHS Trust
Institute of Sport and Recreation Management
International League Against Epilepsy (ILAE)
Janssen-Cilag Ltd
Joint Epilepsy Council (JEC)
Kingston Primary Care Trust
L'Arche UK
Leeds Teaching Hospitals NHS Trust
Long Term Medical Conditions Alliance
Luton and Dunstable Hospital NHS Trust
Medeus Pharma Ltd
Medicines and Healthcare Products Regulatory Agency (MHRA)
Medtronic Limited
Medway NHS Trust
Mental Health Collaborating Centre
## Abbreviations and glossary of terms

### Abbreviations

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<td>Anti-Epileptic Drug</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>EBQ</td>
<td>Evidence-Based Question</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>FBC</td>
<td>Full Blood Count</td>
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<td>GDG</td>
<td>Guideline Development Group</td>
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<tr>
<td>GP</td>
<td>General (medical) Practitioner</td>
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<td>GPP</td>
<td>Good Practice Point</td>
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<td>GRP</td>
<td>Guidelines Review Panel</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>KCQ</td>
<td>Key Clinical Question</td>
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<td>MCG</td>
<td>Microgram</td>
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<td>MG</td>
<td>Milligram</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NCC-PC</td>
<td>National Collaborating Centre for Primary Care</td>
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<td>NCGC</td>
<td>National Clinical Guideline Centre</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NSF</td>
<td>National Service Framework</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>RR</td>
<td>Relative Risk (or Risk Ratio)</td>
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<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<td>SUDEP</td>
<td>Sudden Unexpected Death in Epilepsy</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>VNS</td>
<td>Vagus (or Vagal) Nerve Stimulation</td>
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</tbody>
</table>
1 Glossary of terms

Absence Seizure  A seizure characterised by behavioural arrest associated with generalised spike wave activity on EEG.

Absolute risk reduction (Risk difference)  The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.

Abstract  Summary of a study, which may be published alone or as an introduction to a full scientific paper.

Adherence  The extent to which the patient’s behaviour matches the prescriber’s recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor’s recommendation.¹

Adjustment  A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.

Aetiology  The cause or origin of a disease or disorder as determined by medical diagnosis.

Algorithm (in guidelines)  A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.

Allocation concealment  The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.

Anti-epileptic drug (AED)  Medication taken daily to prevent the recurrence of epileptic seizures. Refer to Appendix K concerning the choice of drug, side effects and suitability to syndrome.

Applicability  The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.

Appraisal of Guidelines Research and Evaluation (AGREE)  An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org/). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.

Arm (of a clinical study)  Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.

Association  Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.

Atonic Seizures  A generalised seizure characterised by sudden onset of loss of muscle tone causing a fall.

Attack  An episode in the course of an illness.
| **Audit** | See ‘Clinical audit’. |
| **Baseline** | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| **Benign epilepsy syndrome** | A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. |
| **BECTS** | Benign epilepsy with centrottemporal spikes. An epilepsy syndrome of childhood (5-14 years) characterised by focal motor seizures in the majority from sleep, in an otherwise normal individual and centrottemporal spikes on EEG. |
| **BEOP** | Benign epilepsy with occipital paroxysms. An epilepsy syndrome associated with occipital spikes seen on EEG, more specifically paroxysms of occipital spikes with loss of fixation. Two forms are described; an early form (Panayiotopoulos) characterised by seizures with loss of awareness and prominent autonomic features eg flushing, retching, vomiting in which seizures may be infrequent, and an older form (Gastaut type) mean age of onset 8 years characterised by visual seizures and commonly postictal headache. |
| **Bias** | Systematic (as opposed to random) deviation of the results of a study from the ‘true’ results that is caused by the way the study is designed or conducted. |
| **Blinding (masking)** | Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study. |
| **Capital costs** | Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time. |
| **Carer (caregiver)** | Someone other than a health professional who is involved in caring for a person with a medical condition. |
| **Case-control study** | Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause. |
| **Case series** | Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients. |
| **Childhood Absence Epilepsy** | An epilepsy syndrome, of peak onset 4-10 years, characterised by frequent absence seizures associated with 3Hz spike wave activity on EEG. |
| **Clinical audit** | A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. |
**Clinical efficacy**  
The extent to which an intervention is active when studied under controlled research conditions.

**Clinical effectiveness**  
The extent to which an intervention produces an overall health benefit in routine clinical practice.

**Clinical impact**  
The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.

**Clinical presentation**  
Refer to Appendix A for principal differential diagnoses for each presenting clinical scenario and their diagnostic features.

**Clinical question**  
In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.

**Clinician**  
A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.

**Cluster**  
A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.

**Cochrane Library**  
A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.

**Cochrane Review**  
A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

**Cohort study**  
A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

**Co-morbidity**  
Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.

**Comparability**  
Similarity of the groups in characteristics likely to affect the study results (such as health status or age).

**Compliance**  
The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as ‘adherence’ or ‘concordance’.¹

**Concordance**  
This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.¹
Conference proceedings

Compilation of papers presented at a conference.

Confidence interval (CI)

A range of values for an unknown population parameter with a stated ‘confidence’ (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The ‘confidence’ value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.

Confounding

In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the ‘confounding variable’) that can influence the outcome independently of the intervention under study.

Consensus methods

Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.

Containment products

Materials or devices which are used to collect urine in patients suffering from incontinence i.e. external collection devices, pads, indwelling catheters.

Control group

A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)

A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.

Convulsive Status Epilepticus

When a seizure continues for a prolonged period (longer than 30 minutes), or when seizures occur one after the other with no recovery between. Status epilepticus is an emergency and requires immediate medical attention.

Cost benefit analysis

A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)
A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis (CEA)
An economic study design in which consequences of different interventions are measured using a single outcome, usually in ‘natural’ units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-utility analysis (CUA)
A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Credible interval
The Bayesian equivalent of a confidence interval.

Cross-over trial
A trial in which each of the study groups will receive each of the treatments, but in a randomised order: that is, they will start off in one arm of the trial, but will deliberately ‘cross over’ to the other arm(s) in turn (HTA).

Cryptogenic
A disease of unknown cause.

CSWS
Continuous spike wave of slow sleep; an epilepsy syndrome of onset in children characterised by plateau and regression of cognitive abilities associated with dramatic increase in spike wave activity in slow sleep (>85% of slow sleep). There may be few seizures at presentation.

Decision analysis
An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.

Decision problem
A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.

Diplopia
Double vision.

Discounting
Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Dominance</td>
<td>An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.</td>
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<tr>
<td>Dosage</td>
<td>The prescribed amount of a drug to be taken, including the size and timing of the doses.</td>
</tr>
<tr>
<td>Double blind/masked study</td>
<td>A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.</td>
</tr>
<tr>
<td>Drop-out</td>
<td>A participant who withdraws from a clinical trial before the end.</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.</td>
</tr>
<tr>
<td>Effect (as in effect measure, treatment effect, estimate of effect)</td>
<td>The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.</td>
</tr>
<tr>
<td>Effect size</td>
<td>This term is usually used in meta-analysis to denote treatment effect, or estimate of effect.</td>
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<tr>
<td>Effect size</td>
<td>It also refers to standardised mean difference (SMD), obtained by dividing the mean difference with the pooled standard deviation. This is the meaning usually referred to in GRADE.</td>
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<tr>
<td>Effectiveness</td>
<td>See ‘Clinical effectiveness’.</td>
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<tr>
<td>Efficacy</td>
<td>See ‘Clinical efficacy’.</td>
</tr>
<tr>
<td>Electroencephalography (EEG)</td>
<td>The process of recording brain wave activity. Electrodes are attached to various areas of the individual’s head with collodion. Refer to 8.2 for the role of EEG in diagnosis of epilepsy and epilepsy syndromes.</td>
</tr>
<tr>
<td>Epidemiological study</td>
<td>The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Recurrent epileptic seizures of primary cerebral origin.</td>
</tr>
<tr>
<td>Epileptic seizure*</td>
<td>A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. An ictal event believed to represent a unique pathophysiological mechanism and anatomical substrate. This is a diagnostic entity with aetiological, therapeutic, and prognostic implications.</td>
</tr>
<tr>
<td>Epilepsy syndrome*</td>
<td>A complex of signs and symptoms that define a unique epilepsy condition. However, not all epilepsy syndromes are easily covered by a single definition. An epilepsy syndrome must involve more than just the seizure type: thus frontal lobe seizures <em>per se</em>, for instance, do not constitute a syndrome. For example,</td>
</tr>
</tbody>
</table>
Lennox-Gastaut syndrome has three main characteristics:

- presence of different seizure types, EEG abnormalities, onset between 1 and 5 years of age, and a slowing and plateauing of cognitive development.

**Epileptic disease***

A pathologic condition with a single specific, well-defined etiology. Thus progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundborg is a disease.

**Epileptic encephalopathy***

A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function.

**Equity**

Fair distribution of resources or benefits.

**Evidence**

Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).

**Evidence table**

A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

**Exclusion criteria**

Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.

**Exclusion criteria**

Criteria that define who is not eligible to participate in a clinical study.

**Expert consensus**

See ‘Consensus methods’.

**Exposed**

Children of mothers with epilepsy who were exposed to AED(s) in utero.

**Extrapolation**

In data analysis, predicting the value of a parameter outside the range of observed values.

**Focal Seizures**

Seizure in which the abnormal electrical activity begins in one part of the brain. Which part of the brain is involved will determine what actually happens during the seizure. (HTA)

**Focal seizures and syndromes***

Replaces the terms partial seizures and localization-related syndromes.

**Follow up**

Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.

**Ictal phenomenology**

Description or history of ictal events (seizures).

**Idiopathic**

Without known cause.

**General population**

Children of mothers without epilepsy.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Generalisability</td>
<td>The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.</td>
</tr>
<tr>
<td>Generalised Seizure</td>
<td>Generalised seizures are those in which the abnormal electrical activity begins in both hemispheres (sides) of the brain at the same time (HTA).</td>
</tr>
<tr>
<td>Gold standard</td>
<td>See ‘Reference standard’.</td>
</tr>
<tr>
<td>Goodness-of-fit</td>
<td>How well a statistical model or distribution compares with the observed data.</td>
</tr>
<tr>
<td>Grading of Recommendations</td>
<td>A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.</td>
</tr>
<tr>
<td>Assessment, Development and Evaluation (GRADE)</td>
<td>Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.</td>
</tr>
<tr>
<td>Grey literature</td>
<td>Adverse effects of an intervention.</td>
</tr>
<tr>
<td>Health economics</td>
<td>The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>A combination of an individual’s physical, mental and social well-being; not merely the absence of disease.</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>A supposition made as a starting point for further investigation.</td>
</tr>
<tr>
<td>Ictal phenomenology</td>
<td>Description or history of ictal events (seizures).</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Without known cause.</td>
</tr>
</tbody>
</table>

The epilepsies: full guideline DRAFT (July 2010)
Idiopathic epilepsy syndrome
A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurologic signs or symptoms. These are presumed to be genetic and are usually age-dependent.

Idiopathic Generalised Epilepsy (IGE)
A well defined group of disorders characterised by typical absences, myoclonic jerks and generalised tonic clonic seizures, alone or in varying combinations in otherwise normal individuals. The EEG is also characteristic demonstrating a distinct pattern of generalised polyspike wave discharges and/or generalised spike wave on EEG.

Idiosyncratic
Physical or behavioural characteristic that is personal to that individual.

ILAE
International League Against Epilepsy; The ILAE is a global professional non-profit international organisation and a non-governmental organisation in official relations with the WHO. The ILAE’s objectives are: to advance and disseminate knowledge about epilepsy (and have developed guidelines for the classification of epilepsy and the design of investigative trials); to promote research, education and training; and to improve (HTA).

Imprecision
Imprecision is one of the quality elements considered under the GRADE system. Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.

Inclusion criteria (literature review)
Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental analysis
The analysis of additional costs and additional clinical outcomes with different interventions.

Incremental cost
The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost effectiveness ratio (ICER)
The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.

ICER=(Cost_\text{A} – Cost_\text{B}) / (Effectiveness_\text{A} – Effectiveness_\text{B}).

Inconsistency
Inconsistency is one of the elements of quality considered under the GRADE system. Inconsistency refers to the unexplained heterogeneity in the results observed.

Index
In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.

Indirectness
Indirectness is one of the elements of quality considered under the GRADE system. Indirectness of evidence refers to the difference in study population, intervention, comparator and outcomes between the available evidenced and the clinical...
question or population addressed in the guideline recommendations.

**Indication (specific)**
The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

**Infantile Spasms**
A specific seizure type presenting in the first year of life, most commonly between 3 and 7 months of age. Spasms are brief axial movements lasting 0.2-2 seconds, most commonly flexor in nature, involving flexion of the trunk with extension of the upper and lower limbs.

**Intention-to-treat analysis (ITT analysis)**
An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

**Intermediate outcomes**
Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study. The reduction of prostate volume which in turn is related to the reduced risk of acute urinary retention.

**Internal validity**
The degree to which the results of a study are likely to approximate the ‘truth’ for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study’s findings. See ‘External validity’.

**Intervention**
Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.

**Juvenile Absence Epilepsy**
An epilepsy syndrome onset 9-13 year characterised by absence seizures (with generalised tonic clonics seizures in 80%) associated with 3-4Hz spike wave on EEG.

**Juvenile Myoclonic Epilepsy**
An epilepsy syndrome with onset 5-16 years, characterised by absence and generalised tonic clonic seizures, and more specifically myoclonic seizures on wakening from sleep. EEG demonstrates 3-6Hz generalised polyspike and wave activity, with photosensitivity in >30%.

**Ketogenic diet**
A specific diet which is high in fats and low in carbohydrates and protein.

**Landau-Kleffner Syndrome**
An epilepsy syndrome with onset 3-6 years characterised by loss of language (after a period of normal language development) associated with an epilepsy of centrotemporal origin, more specifically bitemporal spikes on EEG with enhancement in sleep or CSWS.

**Length of stay**
The total number of days a participant stays in hospital.

**Lennox-Gastaut Syndrome**
An epilepsy syndrome (age of onset 3-10 years) characterised by multiple seizure types (including atonic, tonic, tonic clonic and atypical absence seizures), cognitive impairment and specific
EEG features of diffuse slow spike and wave (<2.5Hz))

**Licence**

See ‘Product licence’.

**Life-years gained**

Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.

**Likelihood ratio (LR)**

The ratio of the probability that a person with a condition has a specified test result to the probability that a person without the condition has the same specified test result. For positive test results, this is referred to as “Likelihood ratio positive”, LR+. For negative test result, this is known as “Likelihood ration negative”, LR-.

**Literature review**

An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.

**MAE**

Myoclonic-astatic epilepsy or Doose syndrome. An epilepsy syndrome age of onset 18-60m, characterised by different seizure types with myoclonic and myoclonic-astatic seizures seen in all, causing children to fall.

**Marketing authorisation**

An authorisation that covers all the main activities associated with the marketing of a medicinal product. Medicines that meet the standards of safety, quality and efficacy set by the Medicines and Healthcare products Regulatory Agency (MHRA) are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold.

**Markov model**

A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).

**Medicines and Healthcare Products Regulatory Agency (MHRA)**

The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

**Meta-analysis**

A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

**Minimal important difference (MID)**

This is the smallest change which can be recognised by a patient as being clinically significant

**Monotherapy**

Children of mothers with epilepsy taking only one AED

**Multivariate model**

A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome
Myoclonic Seizures
Generalised seizure involving brief jerks of part of or the whole body. Recovery is rapid (HTA).

Narrative summary
Summary of findings given as a written description.

Negative likelihood ratio (LR-)
The ratio of the probability that a person with a condition has a negative test result to the probability that a person without the condition has negative test result.
Likelihood ratio negative, \( LR^- = \frac{1-\text{sensitivity}}{\text{specificity}} \)
See “likelihood ratio” and “positive likelihood ratio”.

Negative predictive value (NPV)
Proportion of patients with a negative test result who do not have the disease = \( \frac{TN}{FP+TN} \)

Neurological deficit
A deficiency or impairment of the nervous system.

Non-epileptic attack disorder (NEAD)
A disorder characterised by seizures which are not due to epilepsy. Movements are varied, and the attacks can be difficult to differentiate from epileptic seizures. Refer to Appendix A for differentiations of epileptic attacks and NEADs.

Non-convulsive Status Epilepticus
A change in mental status or behaviour from baseline, associated with continuous seizure activity on EEG.

Not exposed
children of mothers with epilepsy who were not exposed to AED(s) in utero

Nystagmus
Involuntary rapid movement (horizontal, vertical, rotatory, or mixed) of the Eyeball. (HTA)

Number needed to treat (NNT)
The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.

Observational study
Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case-control studies.

Odds ratio
A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The ‘odds’ is the ratio of events to non-events.

Off-label
A drug or device used treat a condition or disease for which it is not specifically licensed.

Older people
People over the age of 65 years.

Operating costs
Ongoing costs of carrying out an intervention, excluding capital costs.

Opportunity cost
The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome

Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See ‘Intermediate outcome’.

P value

The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be ‘statistically significant’.

Parasomnia

Any dysfunction associated with sleep. For example, headbanging/confusional arousal/REM sleep disorder – night terrors.

Patient reported outcomes (PRO) or Patient Reported Outcomes Measures (PROMS)

These terms covers a whole range of potential types of measurements (e.g. symptoms severity or bother, health related quality of life, satisfaction with treatment) but is used specifically to refer to questionnaires designed to obtain the perspective of the patient rather than the perspective of clinicians or carers. PRO data may be collected via self-administered questionnaires completed by the patient themselves or via interviewer-administered questionnaires. These questionnaires should be developed and validated before use.

Pharmacokinetic interaction

The way, in which a drug is processed by the body, influencing absorption, metabolism, distribution and excretion.

Peer review

A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.

Placebo

An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.

Placebo effect

A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.

Polytherapy

children of mothers with epilepsy taking more than one AED

Primary care

Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.

Primary Generalised Tonic-Clonic Seizure

A seizure of sudden onset involving generalised stiffening and subsequent rhythmic jerking of the limbs, the result of rapid widespread engagement of bilateral cortical and subcortical networks in the brain.

Primary research

Study generating original data rather than analysing data from existing studies (which is called secondary research).

Probably symptomatic epilepsy syndrome*

Synonymous with, but preferred to, the term cryptogenic; used to define syndromes that are believed to be symptomatic, but no aetiology has been identified.

Product licence

An authorisation from the MHRA to market a medicinal product. A drug may be “licensed” for several conditions. When a drug is
referred to as “unlicensed” for a particular indication, that means that the may have a marketing authorisation for other conditions, but not for the condition discussed. This is also known as “off label” use.

Prognosis

A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.

Proportion of children with borderline intelligence

defined as both scores for WIPPSI and LIPS <85, and at least one <70

Proportion of children with specific cognitive dysfunction

defined as performing below the 5th centile for one or more of
1. ‘visuoconstructive’ score of WIPPSI
2. auditory phonemic score of ITPA
3. comprehension score of NEPS

Prospective study

A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.

Provocation

Methods used to provoke seizures such as hyperventilation, photic stimulation, sleep deprivation and withdrawal of medication.

Psychogenic non-epileptic seizure (PNES)

Paroxysmal alterations in movement, sensation, or experience that resemble epileptic seizures. They are not caused by abnormal electrical discharges, but arise from purely psychological causes.

Puerperium

The time after childbirth, lasting approximately 6 weeks, during which the anatomic and physiologic changes brought about by pregnancy resolve and a woman adjusts to the new or expanded responsibilities of motherhood and non-pregnant life.

Qualitative research

Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.

Quality of life

See ‘Health-related quality of life’.

Quality-adjusted life year (QALY)

An index of survival that is adjusted to account for the patient’s quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.

Quantitative research

Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
**Quick Reference Guide**

An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.

**Randomisation**

Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.

**Randomised controlled trial (RCT)**

A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

**RCT**

See ‘Randomised controlled trial’.

**Reflex epilepsy syndromes**

A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that also are associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures also can occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures.

**Refractory status epilepticus**

Continued status epilepticus despite treatment with two anticonvulsants in appropriate doses.

**Relative risk (RR)**

The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).

**Remit**

The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.

**Resource implication**

The likely impact in terms of finance, workforce or other NHS resources.

**Retrospective study**

A retrospective study deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.

**Review of the literature**

An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.

**Secondary Generalisation Seizure**

Now referred to as a ‘focal seizure evolving to a bilateral convulsive seizure’.

**Selection bias (also allocation bias)**

A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
### Selection criteria
Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

### Sensitivity analysis (SA)
A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

- **One-way simple sensitivity analysis (univariate analysis):** each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.
- **Multi-way simple sensitivity analysis (scenario analysis):** two or more parameters are varied at the same time and the overall effect on the results is evaluated.
- **Threshold sensitivity analysis:** the critical value of parameters above or below which the conclusions of the study will change are identified.
- **Probabilistic sensitivity analysis:** probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

### SMEI
Severe myoclonic epilepsy of infancy (Dravet's syndrome). An epilepsy syndrome with onset in early childhood (<12m) characterised by initial prolonged lateralised, often febrile seizures with later development of multiple seizure types including myoclonic jerks, absence, focal and generalised tonic clonic seizures and subsequent developmental slowing.

### Simple and complex partial epileptic seizures*
These terms are no longer recommended, nor will they be replaced in the proposed 2001 classification system. Ictal impairment of consciousness should be described when appropriate for individual seizures, but not to classify specific seizure types.

### Spasm
An involuntary contraction of sudden onset. A convulsion or seizure.

### Specialist (as used in this guideline)
For adults: a medical practitioner with training and expertise in epilepsy.
For children: a paediatrician with training and expertise in epilepsy.

### Stakeholder
Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

### Statistical power
The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.

### Status epilepticus
A generalised convulsion lasting 30 minutes or longer or
repeated tonic-clonic convulsions occurring over a 30 minute period without recovery of consciousness between each convulsion. This definition is specific to convulsive status epilepticus, but there are other types, for example non-convulsive status epilepticus. Refer to Appendix C for treatment guidelines for children and adults.

**Sudden unexpected death in epilepsy (SUDEP)**

Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in individuals with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomic cause for death.


**Symptomatic seizure**

The consequence of a known or suspected disorder of the central nervous system.

**Symptomatic epilepsy syndrome***

A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain.

**Syncope (vasovagal syncopal attack)**

A brief lapse in consciousness caused by transient cerebral hypoxia. May be caused by many different factors, including emotional stress, vagal stimulation, vascular pooling in the legs, diaphoresis, or sudden change in environmental temperature or body position.

**Synthesis of evidence**

A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.

**Systematic review**

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

**Teratogenic**

An event or process which interferes with normal prenatal development, causing the development of one or more developmental abnormalities in the fetus.

**Tertiary centre**

Specialist care delivery unit. Centre for access to secondary care.

**Time horizon**

The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.

**Tonic Seizures**

Generalised seizure in which the person's body becomes stiff and they may fall backwards. The seizure usually lasts less than a minute and recovery is rapid (HTA).

**Tonic-Clonic Seizure**

This is a generalised seizure. The person becomes stiff and may fall. This is followed by rhythmical jerking of the limbs, usually lasting a few minutes. The person may bite their tongue and may be incontinent. They may feel confused or sleepy afterwards,
and take a while to recover fully (HTA)

**Treatment allocation**  Assigning a participant to a particular arm of the trial.

**Treatment options**  The choices of intervention available.

**Utility**  A measure of the strength of an individual’s preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or ‘perfect’ health). Health states can be considered worse than death and thus have a negative value.

**Wash-out period (for cross-over studies)**  A stage in a crossover trial after the first treatment is withdrawn, but before the second treatment is started. The washout period allows time for any active effects of the first treatment to wear off before the next phase begins.

**West Syndrome**  An epilepsy syndrome with onset in the first year of life characterised by infantile spasms, an EEG pattern described as hypsarrhythmia and developmental plateau.

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1 Unless otherwise stated, taken from Mosby’s Medical, Nursing and Allied Health Dictionary 5th edition and supplemented by the text of the full guideline (2004 Guideline).

2 Definitions from ILAE Task Force on Classification 2
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1 Introduction

1.1 Definition of epilepsy

An epilepsy is defined as a neurological condition characterised by recurrent epileptic seizures unprovoked by any immediately identifiable cause. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. Epilepsy should be viewed as a symptom of an underlying neurological disorder and not as a single disease entity. The term 'epilepsies' is used in the title of the guideline to reflect this.

1.2 Clinical aspects

The clinical presentation depends on a number of factors, chiefly: the parts of the brain affected, the pattern of spread of epileptic discharges through the brain, the cause of the epilepsy and the age of the individual. The classification of the epilepsies is controversial and has tended to focus on both the clinical presentation (type of epileptic seizure) and on the underlying neurological disorder (epilepsies and epilepsy syndromes).

Epilepsy is primarily a clinical diagnosis based on a detailed description of the events before, during and after a seizure given by the person and/or witness. Electroencephalogram (EEG), magnetic resonance imaging (MRI) and computed tomography (CT) are used to investigate individuals with known and suspected epilepsy. The diagnosis of epilepsy requires that seizure type, epilepsy syndrome and any underlying cause are determined. It can be difficult to make a diagnosis of epilepsy and misdiagnosis is common.

The UK National General Practice Study of Epilepsy found that 60% of people have convulsive seizures, of which two thirds have focal epilepsies and secondarily generalised seizures and the other third will have generalised tonic-clonic seizures. About one-third of cases have less than one seizure a year, one-third have between one and 12 seizures per year and the remainder have more than one seizure per month.

In adults and children with epilepsy, most (70%) will enter remission (being seizure free for five years on or off treatment) but 30% develop chronic epilepsy. The number of seizures in the 6 months after first presentation is an important predictive factor for both early and long-term remission of seizures.

The UK National General Practice Study of Epilepsy found that the majority (60%) of people with newly diagnosed or suspected epileptic seizures had epilepsy with no identifiable aetiology. Vascular disease was the aetiology in 15% and tumour in 6%.
Among older subjects the proportion with an identifiable cause was much higher: 49% were due to vascular disease and 11% to tumours.7

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) taken daily to prevent the recurrence of epileptic seizures. Since the development of MRI there has been an increase in the number of people identified with epilepsy who could benefit from surgery. There is also a need to ensure provision of appropriate information to people with epilepsy and their carers. In the UK the voluntary sector has an important role in helping people with epilepsy.12

Since 2004, discussion with regard to the classification of the epilepsies has continued. With advances in technology, particularly imaging and genetics, some of the older terminology eg idiopathic/symptomatic/cryptogenic, has become redundant in general use. Furthermore, although seizures may be focal or generalised in onset, such terminology cannot be applied to syndromes. The terms partial, complex and simple are also replaced simply by focal. Ensuring an accurate diagnosis is important for planning management. Although the primary aim is to diagnose a recognisable electroclinical syndrome, it is recognised this may not be possible in a not insignificant number of individuals. Moreover, in some aetiology may be of equal importance. A more descriptive approach has been recommended, retaining the electroclinical syndromes where possible but where underlying aetiology is taken into account.13 This in increasing situations has implications for treatment.

1.3 Epidemiology

Epilepsy is the most common chronic disabling neurological condition in the UK. It affects between 260,000 and 416,000 people in England and Wales (Appendix G).14

The incidence of epilepsy is about 50 per 100,000 per annum.15 The incidence is high in childhood, decreases in adulthood and rises again in older people.7 The usual prevalence figure given for active epilepsy in the UK is 5-10 cases per 1,000.12

Epidemiological studies consistently report a standardised mortality rate (SMR) of 2-4 for epilepsy.16,17 In newly diagnosed epilepsy, death is largely attributable to the underlying disease (for example, vascular disease, tumour). In chronic epilepsy, however, the main cause of excess mortality is death during a seizure: sudden unexpected death in epilepsy (SUDEP).18 SUDEP is estimated to account for 500 deaths a year in the UK and has been the subject of a recent National Sentinel Clinical Audit.19

Epilepsy is not always associated with significant morbidity. Many people with epilepsy continue to have highly productive and fruitful lives, in which the epilepsy does not interfere to a great extent. However, there is an associated morbidity which may be significant in some individuals, and may be due to the effects of seizures, their underlying cause and/or treatment. Epilepsy may sometimes result in significant disability, social exclusion and stigmatisation. People with epilepsy commonly encounter problems in the following areas: education; employment; driving; personal development; psychiatric and psychological aspects and social and personal relationships.12 In addition, it is important to recognise that people with epilepsy may
have co-morbidities. For example, children with epilepsy may have attentional
difficulties or learning difficulties.20

The rate of learning disability in the epilepsy population remains high; in particular
children with early onset epilepsy are highly unlikely to achieve an IQ in the normal
range 21. Even in those with later onset, numbers with any degree of learning disability
are thought to be underestimated. The prevalence of behaviour disorder in children
with epilepsy also remains high; the British child and adolescent mental Health survey,
questioning 10,438 children in the UK age 5-15 years found a prevalence of
behaviour disorder in children with ‘pure’ epilepsy to be up to three times that of
another chronic disorder (diabetes, 10.2%) or the general population (9.3%) and in
‘epilepsy plus’ almost six times (56%) 22. Both may be compounded by medication and
must therefore be taken into consideration when discussing medication to use. An
increasing population is the elderly, where the incidence of new onset epilepsy is
increasing, although the possibility of misdiagnosis also remains high23. Special
consideration needs to be given when prescribing any medication within this
population, not least because of drug interaction and pharmacokinetic issues, and this
similarly applies to antiepileptic medication. Increasing information is also being
gathered on the effect of antiepileptic drugs on the unborn child; further data have to
be accumulated to ensure accurate information on treatment and its possible effects
are given to a woman so she is able to make choices 24.

1.4 Cost of epilepsy

2004

The medical cost to the NHS in 1992/1993 of newly diagnosed epilepsy in the first
year of diagnosis was calculated as £18 million and the total annual cost of
established epilepsy estimated at £2 billion (direct and indirect costs), over 69% of
which was due to indirect costs (unemployment and excess mortality).25

The costs of treating epilepsy are likely to increase given the new trends in prescribing
patterns towards newer and more expensive AEDs. One of the latest studies in the
literature26 estimated that the costs of prescribing costs in the community has risen
three-fold in the last 10 years, from £26 million to £86 million, a yearly increase five
times the rate of inflation. The author concluded that this was largely explained by a
rapid increase in the prescribing of newer AEDs. Over the period 1991 to 1999, the
number of AED prescription items in England rose by 33%, and 42% of this increase
was accounted for by increased prescribing of new AEDs. The volume of older AEDs
prescribed increased from 4.8 million prescription items in 1991 to 5.7 million in 1999,
compared with more than a hundred-fold increase in prescribing of new AEDs from
5,400 to 721,000 over the same period.26

2011

Since 2004, a further six AEDs have become licensed for use in the UK for the
treatment of epilepsy. A more recent cost analysis estimated the total cost of epilepsy
in Europe in 2004 was 15.5 billion Euros; the cost of antiepileptic drug use being
£400,000 27. Economic cost however is only one aspect to be considered when
discussing the cost of epilepsy to the individual. Lost employment, hospital visits and
overall life disruption/quality of life need to be carefully considered. Studies
reviewing quality of life of individuals with epilepsy highlight important determinants
to be seizure freedom and medication side effects amongst others. This should be
strived for in each individual who presents with epilepsy, although not at the expense
of excess side effects. Choices of anti-epileptic medication therefore have to measured
and tailored to the individual, informed by data available from the existing evidence
base.

1.5 Health Services for people with epilepsy

Since 1953 six major reports have made recommendations to improve
services for people with epilepsy in the UK, but these services remain patchy and
fragmented. The Department of Health has recently published an action plan to
improve services for people with epilepsy in response to the National Sentinel Clinical
Audit (SUDEP report).

A key aim of the audit was to establish whether deficiencies in the standard of clinical
management or overall package of healthcare could have contributed to deaths. The
issues raised by the SUDEP report as they relate to primary and secondary care are
summarised here.

Since 2004, guidelines have provided a framework by which epilepsy services can be
improved. However services remain patchy; a further report in 2008 by the All Party
Parliamentary Group on epilepsy (wasted money, wasted lives) recognised that much
of the guidelines as published in 2004 had not been implemented, and that an early
review was required as to the progress of implementation of the NICE guidelines in
England & Wales. Furthermore, the wider need for training was also recognised.

1.5.1 Primary care

General practitioners (GPs) have a central role in the provision of medical care to
adults with epilepsy. The new GP contract includes quality markers, and hence
financial incentive, for the management of epilepsy in primary care. They also have
an important, although more limited, role in the management of epilepsy in children. A
GP who has a list of 2,000 people can expect to care for between 10 to 20 people
with epilepsy who are on treatment and to see one to two new cases per year.

The SUDEP report found that the main problems in primary care for people with
epilepsy were: lack of timely access to skilled specialists; sparse evidence of structured
management plans; triggers for referral were sometimes missed, and there were
failures of communication between primary and secondary care.

Who takes primary responsibility for individuals with epilepsy may depend on local
networks of care. In children, care remains primarily within secondary care. Training
has been standardised with courses through the British Paediatric Neurology
Association and others. Transition of care into adulthood may prove problematic, as
differing groups of individuals may fall within the remit of differing professional
groups and teams eg adults with learning disability, and the elderly. Some Primary
Care Trusts have developed the role of the GP with a special interest in the epilepsies (GPSIES) who are responsible for individuals with epilepsy. Defined care pathways for individuals presenting with seizures are recommended, from initial diagnosis to complex care (NICE 2004).

1.5.2 Secondary care

2004

The majority of people with epilepsy receive most of their initial care in secondary care and those whose seizures are not well controlled continue to receive ongoing care in secondary care. The SUDEP report identified deficiencies in care provided to both adults and children in secondary care.19

A majority of adults (54%, 84/158) had inadequate care, which led to the conclusion that 39% of adult deaths were considered potentially or probably avoidable. The main deficiencies identified were (in descending order of frequency): inadequate access to specialist care, inadequate drug management, lack of appropriate investigations, no evidence of a package of care, inadequate recording of histories, adults with learning difficulties 'lost' in transfer from child to adult services, and one or more major clinical management errors.

A majority of children (77%, 17/22) had inadequate care, which led to the conclusion that 59% of deaths in children were considered potentially or probably avoidable. The main deficiencies identified were (in descending order of frequency): inadequate drug management, inadequate access to specialist care, and inadequate investigations.

There was concern that documentation was poor in both primary and secondary care; only 1% of hospital records for adults showed that SUDEP had been discussed.2011

Criteria by which individuals should be referred into tertiary care were included in the 2004 guideline. Care of individuals with epilepsy will be optimised where these guidelines are followed and care pathways are in place. Audit of care is yet to be undertaken however; HQIP in collaboration with British Paediatric Neurology Association and the Royal College of Paediatrics and Child Health have initiated an audit of 12 outcomes from the NICE guideline to be conducted throughout the UK in children (Epilepsy 12) to be complete by 2014.

1.6 Guideline aims

Clinical guidelines are defined as ‘systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances’.34

This guideline is a partial update of the 2004 guideline and offers best practice advice on the treatment and management of the epilepsies in children and adults.

1.7 Principles underlying the guideline development

The key principles behind the development of this guideline were that it should:
consider all the issues that are important in the diagnosis, treatment and management of epilepsy in children and adults

base the recommendations on the published evidence that supports them, with explicit links to the evidence

be useful and usable by all healthcare professionals dealing with people with epilepsy

take full account of the perspective of the person with epilepsy and their family and/or carers

Indicate areas of uncertainty requiring further research.

1.8 Who should use this guideline

The guideline is intended for use by individual healthcare professionals, people with epilepsy and their carers and healthcare commissioning organisations and provider organisations.

Separate short form documents for people with epilepsy and healthcare professionals are available without details of the supporting evidence. These are available from the Institute’s website (www.nice.org.uk).

1.9 Structure of guideline documentation

The guideline is divided into sections which cover in detail specific topics relating to the diagnosis, investigation and management of people with epilepsy. For each topic the lay out is similar.

The background to the topic is provided in one or two paragraphs that set the recommendations in context.

The recommendations are presented in both the executive summary and each section. These are graded to indicate the strength of the evidence behind the recommendation.

The evidence statements are presented that summarise the evidence. These evidence statements provide the basis on which the guideline development group made their recommendations. The evidence statements are graded according to the strength of the available evidence. An evidence statement based on the available health economic evidence is provided where appropriate.

A narrative review of the secondary and primary evidence, and health economic evidence where appropriate, that was used to produce the evidence statements follows. Important general methodological issues are flagged up as appropriate. Where appropriate, full details of the papers reviewed are presented in the evidence tables (see Appendix F).
The guideline is divided into sections which cover in detail specific topics relating to the treatment and management of people with epilepsy. For each topic the lay out is similar.

The introduction of the topic is given at the beginning of the section that puts the recommendations in context.

A matrix of evidence presents the comparisons of treatments for which evidence was identified. When the box is left empty, then no evidence was found. In this case, no section on this comparison of treatment is included in the chapter. All the comparisons are presented individually and, when applicable, the comparisons are listed separately for adults and children. The clinical evidence is summarised in Grade profile tables (Please see Appendix N). For each comparison, the first set of tables presents a summary of clinical study characteristics and the second set of tables presents a summary of clinical findings (Appendix N). Further explanations on quality assessment decisions are given in footnotes.

The evidence statements presented summarise the evidence. These evidence statements are grouped in five main sections; the first four sections follow the main four categories of outcome measures (efficacy, adverse events, quality of life and cognitive outcomes) and the fifth section presents any economic considerations. All evidence statements are graded according to the strength of available evidence. The last section of evidence statements refers to outcomes for which no evidence was retrieved. These evidence statements provide the basis on which the guideline development group made their recommendations.

The recommendations are presented in both the executive summary and in the last section in each evidence review. For the purposes of the update guideline, the [2004] recommendations will be in a blue shaded box at the start of a new section, whilst the new recommendations [2011] and [New 2011] will be at the end of each section with the relevant evidence to recommendations.

For each recommendation, the following points are taken into consideration; relative value placed on the outcomes considered, trade off between clinical benefits and harms, economic considerations, quality of evidence for which this recommendation was based and any other consideration made under that recommendation.

Labelling of recommendations

- New recommendations are defined as either an additional area for the guideline or changed because of an updated evidence review. New recommendations are labelled by adding [NEW 2011] to the end of the recommendation.
- Unchanged recommendations where the evidence has been reviewed for the 2010 updated are labelled as [2010]. These recommendations can be reworded to match new-style recommendations but the developers need to check with the GDG that rewording hasn’t changed the meaning.
- Unchanged recommendations from 2004, where the evidence has not been formally reviewed for the 2010 update, are labelled as [2004].
Where evidence has not been reviewed, but there have been minor changes in 2010 to the wording of a 2004 recommendation that do not affect the meaning, for specific reasons such as in terminology or availability of drugs, these are labelled as [2004].

1.10 Guideline limitations

The guideline documentation and recommendations are subject to various limitations. The National Institute for Clinical Excellence (NICE), the commissioner of this work, is primarily concerned with the National Health Service in England and Wales and is not able to make recommendations for practice outside the NHS. It is important to stress that social services, educational services and the voluntary sector have an important role to play in the care of people with epilepsy and this guideline is highly relevant to these agencies. The methodological limitations of the guideline are discussed in chapter 2.

1.11 Plans for updating the guideline

The process of reviewing the evidence is expected to begin 4 years after the date of issue of this guideline. Reviewing may begin earlier than 4 years if significant evidence that affects the guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

This guideline is a partial update of ‘The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care’ (NICE clinical guideline 20, 2004). It updates the pharmacological management sections of the 2004 guideline and also includes the use of the ketogenic diet.

Three years after publication of the clinical guideline, the NCGC will determine whether an update is warranted.
2 Methods

2.1 Introduction
This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the National Institute for Clinical Excellence (the Institute) in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at: http://www.nice.org.uk).

2.2 The developers

2.2.1 The National Collaborating Centre for Primary Care
The National Collaborating Centre for Primary Care (NCC-PC) is based at the Royal College of General Practitioners (RCGP), and involves the following partners: Royal College of General Practitioners, Royal Pharmaceutical Society of Great Britain, Community Practitioners and Health Visitors Association, and the Clinical Governance Research and Development Unit (CGRDU), Division of General Practice and Primary Healthcare, Department of Health Sciences, University of Leicester. The Collaborating Centre was set up in 2000, to undertake commissions from the National Institute for Clinical Excellence to develop clinical guidelines for the National Health Service in England and Wales.

The 2004 guideline was developed by the Clinical Governance Research and Development Unit (CGRDU), Division of General Practice and Primary Healthcare, Department of Health Sciences, University of Leicester.

2.2.2 The National Clinical Guidelines Centre
The 2011 guideline was commissioned by NICE to the National Collaborating Centre for Primary Care (NCC-PC). On 1st April 2009 the NCC-PC merged with 3 other collaborating centres to form the National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGC). The development of this guideline was therefore started at the NCC-PC and completed at the NCGC. The centre is one of four centres funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work.

2.2.3 The methodology team
2004

The methodology team was led by the Deputy Director of the NCC-PC Leicester, a Senior Lecturer in General Practice (the project lead). Other members of the team were a systematic reviewer, an information librarian, a health economist, and the Director of the NCC-PC Leicester. Where appropriate, the advice and opinion of the
2.2.4 The Guideline Development Group

Nominations for group members were invited from various stakeholder organisations who were selected to ensure an appropriate mix of healthcare professionals and delegates of patient groups. In view of the number of organisations who needed to contribute to the guideline it was decided that there should be two groups: members of the Guideline Development Group and co-optees. Each nominee was expected to serve as an individual expert in their own right and not as a representative of their parent organisation, although they were encouraged to keep their nominating organisation informed of the process. Co-optees contributed to aspects of the guideline development but did not sit on the guideline development group and were not involved in the final wording of the recommendations. Group membership and co-optee details can be found in the preface to the guideline.

The GDG met at six weekly intervals for 16 months to review the evidence identified by the methodology team, to comment on its quality and completeness and to develop recommendations for clinical practice based on the available evidence. In order to generate separate recommendations for adults and children the GDG was divided into adult and child sub-groups. Each subgroup met to discuss the evidence reviews and to make preliminary recommendations. The final recommendations were agreed by the full GDG.

All GDG members made a formal ‘Declaration of Interests’ at the start of the guideline development and provided updates throughout the development process.

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

The GDG consisted of a diverse multidisciplinary group with an interest and/or expertise in the pharmacological management of the epilepsies.

The professional representatives on the group were chosen according to a set process. The NCCPC project team decided on the necessary professional representation required for the GDG, based on the scope of the guideline. Professional registered stakeholder organisations were written to notify them of the advertisement and recruitment process. Once all of the applications were received, the NCC-PC Clinical Director, chairman and the project lead selected the individual members, on the basis

Chief Executive of the NCC-PC, the appointed Chair of the Guidelines Development Group (GDG, see below) and members and co-optees of the GDG was sought.

Editorial responsibility for the guideline rested solely with the methodology team.

The methodology team was led by the Operations Director of the National Clinical Guidelines Centre (NCGC), and comprised: a senior research fellow which acted also as project manager, two systematic reviewers, one health economist and two information scientists. Advice and guidance was also sought from the clinical advisor (Professor Helen Cross), the appointed Chair of the Guidelines Development Group (Dr Nick Kosky), and members and co-optees of the GDG.
of their CV’s, supporting statements, and against a selection criteria adapted from the person specification and job description.

For the patient members, the PPIP at NICE submitted the received applications, from which the NCC-PC Clinical Director, chairman and the project lead chose two as patient members based on the aim (as with the professional healthcare applicants) of including as wide a range as possible of expertise, experience, and professional and geographic representation from across England and Wales. Applicants who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

In accordance with guidance from NICE, all GDG members’ and chairman declared in writing interests that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry and these were made available in the public domain. Details of these can be seen in Appendix R. Declaration of interests were updated at the start of each GDG meeting. A record of updated declarations of interest was recorded in the NCGC’s database and the minutes of each meeting were produced. The minutes of the GDG meetings were published on the NICE website within 10 weeks of being agreed by the GDG. The names of GDG members appear listed in section

2.3 Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope (see appendix B) into a series of key clinical questions (KCQs) which reflected the clinical care pathway for adults and children with epilepsy. These KCQs formed the starting point for the subsequent systematic review and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG, with input as appropriate from co-optees and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

A total of 72 KCQs were identified, of which 52 had separate child and adult stems (see Appendix E). The methodology team and the GDG agreed that a full literature search and critical appraisal could not be undertaken for all of these KCQs due to the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Reasons for this included awareness that the evidence was conflicting or that there was a particular need for evidence-based guidance in that area.

A total of 24 KCQs were identified;
- 17 key clinical questions focused on the effectiveness and cost-effectiveness of AEDs and had common stems for children and adults;
three key clinical questions specifically addressed children; two key clinical questions addressed the effectiveness and cost effectiveness of AEDs in treating children with childhood absence epilepsy and children with infantile spasms. The third key clinical question assessed the clinical effectiveness and cost-effectiveness of treating children with the ketogenic diet;

one key clinical question focused on the clinical effectiveness, cost effectiveness of AEDs and the safety of their use in pregnant women and women currently breastfeeding;

one key clinical question addressed which AEDs are the most tolerable for older people, which was defined as those aged 65 years and over.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified clinical questions, with the exception of one subgroup for the clinical question: “Which AEDs are clinically effective, cost effective and safest for use in pregnancy?”. The subgroup addressed women who were currently breastfeeding.

2.4 Identifying the evidence

2.4.1 Literature search strategies

The aim of the literature review was to seek to identify all available, relevant published evidence in relation to the key clinical questions generated by the GDG. The prioritised KCQs were turned into EBQs by the project lead and systematic reviewer. Literature searches were conducted using generic search filters and modified filters, designed to best address the specific question being investigated. Searches included both medical subject headings (MeSH terms) and free-text terms. Details of all literature searches are available from the NCC-PC, University of Leicester.

The information librarian developed a search strategy for each question with the assistance of the systematic reviewer and the project lead. Searches were re-run at the end of the guideline development process, thus including evidence published up to the end of December 2003.

Depending on the clinical area, some or all of the following databases were searched: Cochrane Library (up to Issue 3, 2003) was searched to identify any relevant systematic reviews, and for reports of randomised controlled trials, MEDLINE (for the period January 1966 to November 2003, on the OVID interface), EMBASE (for the period January 1980 to November 2003, on the OVID interface), the Cumulative Index of Nursing and Allied Health Literature (for the period January 1982 to November 2003, on the Dialog DataStar interface), PsycINFO (for the period 1887 to September 2003, on the OVID and the Dialog DataStar interfaces), the Health Management Information Consortium database (HMIC), the British Nursing Index (BNI), and the Allied and Complementary Medicine Database (AMED). Searches for non-systematic reviews of the literature were limited to 1997 – November 2003. This was a pragmatic decision that draws on the search strategies used by the North Of England Evidence Based Guideline Development Project. No systematic attempt was
made to search ‘grey literature’ (such as conference proceedings, abstracts, unpublished reports or trials, etc.).

Existing systematic reviews and meta-analyses relating to epilepsy were identified. Recent (last 6 years) high quality reviews of the epilepsy literature were also identified. New searches, including identification of relevant randomised controlled trials (RCTs), were conducted in areas of importance to the guideline development process, for which existing systematic reviews were unable to provide valid or up to date answers. The search strategy was dictated by the exact evidence based question (EBQ) the GDG wished to answer. Expert knowledge of group members was also drawn upon to corroborate the search strategy.

The National Research Register (NRR), National Guidelines Clearinghouse (NGC), New Zealand Guidelines Group (NZGG) and the Guidelines International Network (GIN) were searched to identify any existing relevant guidelines produced by other organisations. The reference lists in these guidelines were checked against the methodology team’s search results to identify any missing evidence.

The titles and abstracts of records retrieved by the searches were scanned for relevance to the GDG’s clinical questions. Any potentially relevant publications were obtained in full text. These were assessed against the inclusion criteria and the reference lists were scanned for any articles not previously identified. Further references were also suggested by the GDG. Evidence submitted by stakeholder organisations that was relevant to the GDG’s KCQs, and was of at least the same level of evidence as that identified by the literature searches, was also included.

The aim of the literature search was to find update the evidence from the 2004 guideline and to identify new ‘evidence within the published literature,’ to answer the clinical review questions as per The NICE Guidelines Manual (2009) 37. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Non-English studies were not reviewed and were therefore excluded from searches. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, Medline, Embase, Cinahl and The Cochrane Library. Initial searches for each section were performed when the literature was needed for the review. Each search was updated 3 months (23/04/10) and 6 weeks (03/06/10) before the end of guideline development period. No papers indexed in the databases after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The search strategies along with the databases searched and the years covered can be found in Appendix J.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not systematically undertaken. All references were sent by stakeholders were considered.
2.4.2 Health economics

A separate systematic literature review was conducted to assess the state of the economic evidence, given that in the main searches this evidence was limited. The systematic reviewer and the health economist carried out these searches for health economics evidence. Economic search filters were used -including the one developed by the Centre for Reviews and Dissemination- in the following bibliographic electronic databases MEDLINE, PreMEDLINE, EMBASE, PsycINFO, CINAHL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Review of Effectiveness (DARE), the Cochrane Controlled Trials Register (CCTR) and the NHS R&D Health Technology Assessment Programme and special health economic databases Office of Health Economics – OHE - Health Economic Evaluations Database (HEED) and NHS Economic Evaluation Database (NHS EED) were searched. The details of the electronic search (interfaces, dates) will be reported in the guideline.

Given the limited economic evidence in the area it was decided to perform a broad search for evidence that was designed to identify information about the costs or resources used in providing a service or intervention and/or the benefits that could be attributed to it. No criteria for study design were imposed a priori. In this way the searches were not constrained to RCTs or formal economic evaluations. Papers included were limited to papers written in English and health economic information that could be generalized to UK studies on epilepsy published after 1990.

Literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix J. All searches were updated on 3rd June 2010. No papers published indexed in the databases after this date were considered.
2.5 Reviewing and grading the evidence

2.5.1 Methods for 2004 Guideline

The studies identified following the literature search were reviewed to identify the most appropriate evidence to help answer the KCQs and to ensure that the recommendations were based on the best available evidence. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results and grading of the evidence.

The searches were first sifted by the information librarian and systematic reviewer to exclude papers that did not relate to the scope of the guideline. The abstracts of the remaining papers were scrutinised for relevance to the EBQ under consideration. Initially both the systematic reviewer and project lead reviewed the abstracts independently. This proved impractical as the guideline progressed and the task was delegated to the systematic reviewer. The project lead was asked to review the abstracts in cases of uncertainty.

The papers chosen for inclusion were obtained and assessed for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differed according to study type and were based on the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). Critical appraisal was carried out by the systematic reviewer. To minimise bias in the assessment a sample of papers was independently appraised by the project lead. Further appraisal was provided by the GDG members at the relevant GDG meeting.

The data were extracted to a standard template on an evidence table. The findings were summarised by the systematic reviewer into a series of evidence statements and an accompanying narrative review. The project lead independently assessed the accuracy of the derived evidence statements. None of the EBQs required the preparation of a quantitative synthesis (meta-analysis) by the project team.

The evidence statements were graded by the systematic reviewer according to the established hierarchy of evidence table presented in section 11 of this chapter. This system reflects the susceptibility to bias inherence in particular study designs. The project lead independently assessed the accuracy of the grading.

The type of EBQ dictates the highest level of evidence that may be sought. For questions relating to therapy/treatment the highest possible level of evidence is a systematic review or meta-analysis of RCTs (evidence level Ia) or an individual RCT (evidence level Ib). For questions relating to prognosis, the highest possible level of evidence is a cohort study (evidence level IIb). For diagnostic tests, the highest possible level of evidence is a test evaluation study using a quasi-experimental design that uses a blind comparison of the test with a validated reference standard applied to a sample of individuals who are representative of the population to whom the test would apply (evidence level IIb). For questions relating to information needs and support, the highest possible level of evidence is a descriptive study using either questionnaire survey or qualitative methods (III).

For each clinical question, the highest level of evidence was selected. If a systematic review, meta-analysis or RCT existed in relation to an EBQ, studies of a weaker design were ignored.
Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables (Appendix F).

A number of KCQs could not appropriately be answered using a systematic review, for example, where the evidence base was very limited. These questions were addressed by the identification of ‘published expert’ narrative reviews by the project team and/or GDG which formed the basis of discussion papers written either by the project lead or a member of the GDG.

2.5.2 Methods for 2011 Guideline

2.5.2.1 Quality assessment for intervention studies

For each clinical question the highest level of evidence was sought. We included only randomised controlled trials as they are considered the most robust type of a study design that could produce an unbiased estimate of the intervention effects. Where an appropriate randomised (double blinded) controlled trial was identified, we did not search for studies of a weaker design. Therefore, we did not include unblinded trials for the comparisons for which blinded trials were available unless the sample size of an unblinded study was as large as over 1,000 participants.

The quality assessment criteria as listed in the NICE Guidelines Manual 2009 were used to assess systematic reviews, meta-analysis, and randomised controlled trials.

For randomised controlled trials, the main criteria considered were:

- An appropriate and clearly focused question was addressed
- Appropriate randomisation allocation and concealment methods were used
- Subjects, investigators and outcomes assessors were masked about treatment allocation
- The intervention and control groups are similar at baseline
- The only difference between group is the type of intervention received
- All outcomes are measured in a standard and reliable method
- Drop out rates reported and are acceptable, and all participants are analysed in the groups to which they were randomly allocated the treatment
- For multi-centred trials, results are comparable between sites

Only studies which fulfilled some to all of the criteria included were considered in the evidence review.
2.5.2.2 GRADE (Grading of Recommendations Assessment, Development and Evaluation)

The evidence for outcomes from studies which passed the quality assessment were evaluated and presented using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess pooled outcome data using individual study quality assessments and results from meta-analysis.

The summary of findings was presented as two separate tables in this guideline. The “Clinical Study Characteristics” table includes details of the quality assessment while the “Clinical Summary of Findings” table includes pooled outcome data, an absolute measure of intervention effect calculated and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate pooled sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N) are shown with percentages. Reporting or publication bias was considered in the quality assessment but not included in the Clinical Study Characteristics table because this was a rare reason for downgrading an outcome in this guideline.

Each outcome was examined separately for the quality elements listed and each graded using the quality levels listed in Section 2.9. The main criteria considered in the rating of these elements are discussed in the literature reviewing process (see section 2.9 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems.

The GRADE toolbox is currently designed only for randomised controlled trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

2.6 Methods of combining studies (2011)

Where possible, meta-analyses were conducted to combine the results of studies for each clinical question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes and the continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. Statistical heterogeneity was assessed by considering the chi-squared test for significance at p<0.05 or an I-squared inconsistency statistic of ≥ 50% to indicate significant heterogeneity.

Sensitivity analysis based on the quality of studies was carried out if there were differences (e.g. open label vs. masked studies). Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

2.7 Methods for combining direct and indirect evidence (2011)

The results of conventional meta-analyses of direct evidence alone make it difficult to determine which intervention is most effective in the treatment of epilepsy. Two reasons for this include:
In isolation, each pair-wise comparison does not inform the choice among all the different AEDs, and in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, adjuncive sodium valproate versus placebo for an adult population with refractory focal seizures).

There are frequently multiple overlapping comparisons (for example, adjunctive lamotrigine versus placebo, gabapentin versus placebo and gabapentin versus lamotrigine for an adult population with focal seizures), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy. The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk. The NMA was conducted following the review of direct evidence and the results were interpreted within the context of the direct evidence. The GDG broadly considered whether estimates of effect from the NMA trended in the same direction as estimates from the direct evidence or whether there was contradiction between results. The GDG accounted for uncertainty in the results by looking at the confidence intervals and credible intervals from the conventional meta-analysis and network meta-analysis, respectively.

The treatment effect estimates from the NMA provide a useful clinical summary of the results and were used in conjunction with the estimates from the direct evidence to form recommendations based on all the best available evidence. Furthermore, these estimates were used as measure of treatment effectiveness of first line interventions in the de novo cost-effectiveness modelling presented in appendix P.

An overview of the rationale and methods for the NMA along with a summary of results is presented in sections 10.2.5 and 10.3.7. A full report on the methods, assumptions, results and limitations is included in Appendix O.

2.8 Protocol for guideline evidence reviews for the partial update
A partial update of the guideline published in 2004 has been conducted. This includes an update of the pharmacological management (also applicable to people with learning disabilities, older people and pregnant women) and ketogenic diet. The evidence reviews conducted as part of the guideline development followed the agreed reviewing protocol outlined below:

Types of studies
Randomised controlled trials (RCTs) and cross-over trials were included in the evidence reviews conducted for the partial update (2011). Cross-over trials that did not report the placebo arm data were excluded.

---

a Credible intervals are the Bayesian equivalent of confidence intervals and are based on the percentiles of the posterior distribution of the parameter of interest.
We included only randomised controlled trials as they are considered the most robust type of a study design that could produce an unbiased estimate of the intervention effects. By including only randomized trials, we aimed to eliminate the methodological diversity arising from non randomized studies in relation to variation in their selection bias and variation in the way in which confounding is considered in the analysis.

We included studies comparing one drug versus another drug or a drug versus placebo and did not include trials which did not report a second arm. Dose-response trials without a comparative drug or placebo arm were therefore excluded. We did not include response-selected trials whereby only participants who responded to a drug were included in the trial. The results of these studies would have been biased towards the drug as the participant had already responded to it.

We did not include unblinded trials for the comparisons for which blinded trials were available unless the sample size of an unblinded study was over 1,000 participants. This methodological decision was based on the concern about performance bias due to lack of blinding and its impact on the precision of effect estimates. We assumed that an unblinded study as large as of 1,000 participants would produce more precise estimate effects compared to an unblinded study of a smaller sample size. The choice of a sample size of 1,000 participants was based on arbitrary criteria and no predefined formula was used for this calculation. Furthermore, we assumed that the results of a large unblinded study could be pooled together with that of a double blinded study in a meta-analysis without compromising the validity of the synthesis of the evidence.

We included blinded or unblinded studies with cognitive and/or quality of life outcomes even where we had blinded studies for a comparison. This is because many trials report the cognitive and/or quality of life outcomes in a separate paper. We only included these outcomes in comparisons that already had efficacy or tolerability data. A blinded cognitive or quality of life study would not supersede an unblinded study with efficacy or tolerability data.

For the comparisons for which blinded trials were not available, the GDG downgraded the level of quality due to the higher risk of bias.

Crossover studies were included and were meta-analysed with parallel studies as long as any differences they had were explored and no significant heterogeneity were present.

**Types of participants**

Adults and children were included in the evidence reviews. They were analyzed and presented in separate evidence reviews unless the data were not organized separately in the trials. In this case the evidence from this mixed populations was downgraded for indirectness, and noted in the explanatory GRADE footnotes.

The GDG asserted that structuring the guideline according to epilepsy seizure type or syndrome would be the most useful to practicing clinicians, and most clinically meaningful. However, many studies do not specify a particular epilepsy seizure type or syndrome in their inclusion criteria nor stratify their results according to these seizure types and syndromes. This “contamination” of the seizure type of interest meant that many of the populations were unable to be categorised. This was particularly common in newly diagnosed conditions as the seizure type may not have been established. Consequently, the GDG decided to use a “contamination” cut-off point for the minimum
proportion of trial participants with the relevant seizure type that would be allowed within a given study. This cut off point was set by the GDG to be a minimum of 80% for focal seizures and a minimum of 60% for generalised seizures (both primary generalised tonic-clonic seizures and Idiopathic Generalised Epilepsy). Studies were excluded where both partial and primary generalised seizures were combined and the number of patients with the seizure type of interest was less than the cut off point.

Types of interventions

We included studies that compared pharmacological interventions (as listed under our clinical questions) either as monotherapy or adjunctive treatment for the epilepsy syndromes and seizure types listed under our clinical questions. Placebo controlled trials and trials comparing drugs were included. Non comparative trials were not included.

The scope of the partial update of the epilepsies guideline included only pharmacological interventions because new evidence had emerged in this area since the previous published epilepsies guideline. As listed in our clinical questions the GDG included all AEDs that were considered to be still clinically relevant. This included all AEDs included in the previous guideline and Health Technology Appraisals and further new drugs as listed in the scope of the update guideline (appendix I).

Duration of studies

We specified no particular time duration for our inclusion criteria.

Posology

The doses given within the studies were checked according to the usual doses ranges specified in the British National Formulary, and the maximum and minimum doses specified in the summary of product characteristics (SPC). Any dose outside these ranges was not included in the meta-analysis. If a study assessed different doses within the usual therapeutic range, then these were amalgamated for the purposes of the meta-analysis.

The GDG thought it important to look for AEDs and the doses which were appropriate in a clinical setting rather than just in a trial setting. If a study assessed different doses within the usual therapeutic range, as we were not assessing the difference in results for different doses, we amalgamated their results for the purposes of the meta-analysis.

Types of outcome measures

We extracted data on the following outcomes from the trials:

- The proportion of seizure-free participants,
- proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders),
- the proportion of participants having treatment withdrawn,
- time to exit/withdrawal of allocated treatment (retention time),
- incidence of adverse events (10% or above),
- any outcomes relating to cognitive effects,
and any outcomes relating to quality of life.

When the proportion of participants who withdrew due to adverse events was reported for the whole sample and not per seizure type, explanatory footnotes were added in the tables. We analysed only validated measures of cognitive effect and quality of life in this review.

The outcomes we chose were the same as the HTAs and the previous guideline and these were similar to many of the outcomes within various epilepsy Cochrane reviews. Most studies gave incidence of adverse events, so in order to contain the list of adverse events the GDG suggested the use of only those with 10% or more incidence. This was thought to be the cut-off used in many studies.

**Type of analysis**

Estimates of effect from individual trials are based on Intention to Treat (ITT) data, that is, all participants included in the randomization process are considered in the final analysis based on the treatment groups to which they were originally assigned. In some cases, these data were not reported in the studies and where ITT data were presented, a true ITT population was sometimes not reported. In order to allow for the inclusion of all of the studies, regardless of the type of the data they presented and to be considered in an equivalent manner, all data considered in this review were based on true ITT populations. Thus in several cases, we needed to recalculate the data reported in the studies. Similarly the HTA used ITT analysis and where a true ITT was not reported they assumed missing data had a negative outcome. Further explanations were given as footnotes in the tables.

**Use of unpublished data in the guideline**

A large multicentre trial (SANAD) was published since the publication of the 2004 guideline and the newer AED health technology appraisals, which evaluated the treatment for focal and generalised seizures (Marson 2007). Arm B of the published SANAD document did not specify certain types of seizures or syndromes as their inclusion criteria and therefore the data did not follow the same stratification that was used in the guideline evidence reviews. We contacted the lead author to determine whether further subgroup analyses according to the syndromes, seizure types, and outcomes of interest to the guideline evidence reviews had been conducted. Unpublished data on the following subgroups was provided: juvenile myoclonic epilepsy, absence seizures and generalized tonic-clonic seizures only. The outcomes included time to treatment failure, time to first seizure and incidence of adverse events. When unpublished SANAD data has been used within the analyses, this has been referenced as “work in progress” in the relevant GRADE profile tables.

**2.9 Grading of quality of evidence for outcomes (2011)**

After results were pooled, the overall quality of evidence for each outcome was considered using the GRADE system. The following is the procedure adopted when using GRADE

1. The evidence for all outcomes start with a HIGH quality rating as only RCTs were considered.

2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below.
3. The downgrade marks are then summed. Each quality element being considered as having "serious" or "very serious" risk of bias were rated down -1 or -2 points respectively. All studies started as HIGH and the quality became MODERATE, LOW or VERY LOW when 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes whenever possible.

The details of criteria used for each of the main quality element are discussed below:

**Inconsistency**

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.05$ or I$^2$ $>50\%$), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. On top of the I$^2$ and Chi square values the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. In this situation, the quality of evidence would not be downgraded.

**Indirectness**

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. It was also looked at carefully in surgical intervention procedures where the specific technique used and local protocol may affect the outcomes (e.g. blood transfusions). This rating was reevaluated when recommendations had been made, for example, an outcome based on studies limited to patients with large prostates were downgraded during review but no longer downgraded when recommendation specific to patients with large prostates were made.

**Imprecision**

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered. Where the minimal important difference (MID) of an outcome is known, the optimal information size (OIS), i.e. the sample size required to detect the difference with 80% power and $p\leq0.05$ was calculated and used as the criteria. The criteria applied for imprecision are based on the confidence intervals for pooled outcomes as illustrated in Figure 2.1 and outlined in Table 2.
Figure 2.1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot.

Appreciable harms

MID

MID

Precise

Imprecise

no difference

Table 2-1: Criteria applied to determine precision

Criteria for downgrading an outcome for imprecision

The GDG decided the difference that is likely to be considered clinically important within epilepsy is 0.95 to 1.05.

2.9.1.1 NICE Economic Profile

Since GRADE was not originally designed for economic evidence, the NICE economic profile was developed to present cost and cost-effectiveness estimates from published studies or analyses conducted for the guideline. As for the clinical evidence, the economic evidence has separate tables for the quality assessment and for the summary of results. The quality assessment is based on two criteria – limitations and applicability (table 2-1 and each criterion is graded using the levels in table 2-2 and table 2-3).

Table 2-2: Description of quality elements for economic evidence in NICE economic profile

<table>
<thead>
<tr>
<th>Quality element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>This criterion relates to the methodological quality of cost, cost-effectiveness or net benefit estimates.</td>
</tr>
<tr>
<td>Applicability</td>
<td>This criterion relates to the relevance of the study to the specific guideline question and NICE Reference Case.</td>
</tr>
</tbody>
</table>
### Table 2-3: Levels for limitations for economic evidence in NICE economic profile

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor limitations</td>
<td>The study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.</td>
</tr>
<tr>
<td>Serious limitations</td>
<td>The study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness.</td>
</tr>
<tr>
<td>Very serious limitations</td>
<td>The study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.</td>
</tr>
</tbody>
</table>

### Table 2-4: Levels for applicability for economic evidence in NICE economic profile

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly applicable</td>
<td>The applicability criteria are met, or one or more criteria are not met but this is not likely to change the cost-effectiveness conclusions.</td>
</tr>
<tr>
<td>Partially applicable</td>
<td>One or more of the applicability criteria are not met, and this might possibly change the cost-effectiveness conclusions.</td>
</tr>
<tr>
<td>Not applicable</td>
<td>One or more of the applicability criteria are not met, and this is likely to change the cost-effectiveness conclusions.</td>
</tr>
</tbody>
</table>

An overall score of the evidence is not given as it is not clear how the quality elements could be summarised into a single quality rating.

A limited number of published economic evaluations were identified for inclusion, and most simultaneously compared multiple drug options. Instead of disaggregating the complete incremental analysis from each study to present all possible pair wise comparisons along with the direct evidence, study results were presented as a whole at the end of a given evidence review. A health economic evidence section and evidence statement accompanies each pair wise comparison and directs readers to the complete economic results at the end of the review. There, a table summarising the study characteristics of all included studies is presented and followed by incremental analysis results tables for each study with a summary of analysis uncertainty. Finally, each study is followed by a series of summary evidence statements.

#### 2.9.2 Health economics methods

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraisal by the health economist using a standard validated checklist. A general descriptive overview of the studies, their qualities, and conclusions was presented and summarized in the form of a short narrative review. The economic evidence was not summarized in the form of meta-analyses given the limited evidence found.
The GDG identified the issue of the costs of misdiagnosis in epilepsy as an important area for further economic analysis. This choice was made on the grounds that the misdiagnosis of epilepsy is common and is likely to lead to significant direct costs to the NHS, and to society as a whole. At present the costs of misdiagnosis to the NHS are uncertain. The results of this analysis are presented in Appendix G.

2011

It is important to investigate whether health services are cost-effective (that is, value for money). If a particular treatment strategy were found to yield little health gain relative to the resources used, then it would be advantageous to re-deploy resources to other activities that yield greater health gain.

In accordance with the NICE social value judgements the primary criteria applied for an intervention to be considered cost effective were either:

a) The intervention dominated other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies),
b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

The full economic evaluation of any strategy has to be in comparison with another strategy. Hence we refer to:

- incremental cost: the mean cost of one strategy minus the mean cost of a comparator study
- QALYs gained: the mean QALYs associated one strategy minus the mean QALYs of a comparator study
- incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained
- incremental net benefit (INB): the (monetary) value of a strategy compared with an alternative strategy for a given cost-effectiveness threshold (For example: £20,000 per QALY gained).

In our own cost-effectiveness analysis, we use the following formula to estimate the INB of each strategy:

\[ \text{INB} = (\text{QALYs gained compared with a baseline drug} \times £20,000) \text{ minus the incremental cost compared with a baseline drug.} \]

This indicates that we will invest up to £20,000 to gain one additional QALY. The strategy that has the highest INB is the optimal (that is, most cost-effective) strategy. Strategies that have a negative INB are not cost-effective even compared with the baseline drug.

### 2.9.2.1 Literature review for health economics

A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.
Papers were excluded from the review and evidence tables if:

- The study was reviewed previously as part of TA76 or TA79.
- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper).
- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios).
- Cost analyses were excluded if the results were not presented in a way that would allow the incremental cost per patient to be extracted or derived.

Included papers were critically appraised by a health economist using the quality and applicability checklist outlined in the NICE guidelines manual 2009. If a paper was included, costs, outcomes and a description of its quality and applicability were presented in the economic evidence table with a brief description. Economic evidence tables for included studies are presented in Appendix M.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost–utility analysis (that is, cost–effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We did not find any cost benefit analyses (studies that put a monetary value on health gain).

Models are analogous to systematic reviews as they are pooling evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in our economics evidence tables and write-up may not necessarily imply statistical significance.

We state that cost-effectiveness is “indeterminable” in cases where outcomes are expressed only in terms of seizures avoided or percent of successfully treated patients rather than overall health outcomes and where one intervention is both more costly and more effective.

### 2.9.2.2 Cost-effectiveness modelling

Five economic models were developed as part of the guideline development, one for each of the following clinical areas:

- a) Monotherapy for adults with newly diagnosed focal epilepsy
- b) Adjunctive therapy for adults with refractory focal epilepsy
- c) Monotherapy for children with newly diagnosed focal epilepsy
- d) Adjunctive therapy for children with refractory focal epilepsy
- e) Adjunctive therapy for adults with refractory generalised tonic-clonic seizures

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- The model was based on the systematic review of clinical evidence.
- Model assumptions were reported fully and transparently.
- The results were subject to thorough sensitivity analysis and limitations discussed.
Costs were calculated from a health services perspective.

Effects were measured in terms of quality-adjusted life years.

The details of the methods, assumptions, results and limitations of each economic model are described in Appendix P.

2.10 Developing recommendations

For each key clinical question (KCQ), the recommendations were derived from the evidence statements presented to the GDG. The link between the evidence statement and recommendation was made explicit. The GDG were able to reach their agreed recommendations through a process of informal consensus.

Each recommendation was graded according to the level of evidence upon which it was based using the established grading of recommendations table presented in section 12 of this chapter. For questions relating to therapy/treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For questions relating to prognosis and diagnostic tests, the best possible level of evidence (a cohort study) would equate to a grade B recommendation. For questions relating to information needs and support, the best possible level of evidence (descriptive study) would equate to a grade C recommendation. It is important that the grading in such areas is not treated as inferior to those of therapy as it represents the highest level of relevant evidence.

Four main areas were taken place in the GDG discussions of interpreting evidence to make recommendations; relative value placed on the outcomes considered important for decision making, balancing the clinical benefits and harms of an intervention, including cost effectiveness (economic considerations) and assessing the quality of evidence (potential bias and uncertainty in the clinical and economic evidence). Lastly, the GDG has the opportunity to include other considerations in relation to their responsibilities under equalities legislation and NICE’s equality scheme (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

Over the course of the guideline development process, the GDG was presented with the following:

- Evidence tables of the clinical and economic evidence reviewed. All evidence tables are in appendix L.

- Summary of clinical evidence and quality (as presented in evidence review section in appendix N).

- A description of the methods and results of the cost-effectiveness analysis (appendix P)
Recommendations were drafted on the basis of this evidence whenever it was available. When clinical and economic evidence was poor or absent, the GDG drafted recommendations based on their clinical expertise. The GDG added supporting recommendations whenever it was necessary in order to improve clinical practice. The supporting recommendations were not derived from clinical questions and were based on GDG expert opinion.

The development of the recommendations required several steps:

- Whenever possible, a preliminary draft recommendation was presented by NCGC staff after each summary of evidence presentation during GDG meetings. This draft was discussed and modified by the group to form the first draft recommendation.

- Where necessary, NCGC staff suggested modifications to the draft recommendations as a result of the discussion and in the light of NICE guidance on writing recommendations.

- Towards the end of the guideline development process, a list of all the draft recommendations was sent to the GDG members. The GDG members independently completed a consensus exercise to feedback comments and level of agreement on each recommendation. This procedure allowed the NCGC to verify the level of agreement between the GDG members.

- All GDG feedback was collated and circulated again to the GDG. The recommendations which did not have unanimous agreement were discussed again during a GDG meeting before being finalised.

- During the writing up phase of the guideline, the GDG could further refine each recommendation working in subgroups on each chapter.

- NCGC staff verified the consistency of all recommendations across the guideline.

2.11 Research Recommendations

2.11.1 Newly diagnosed seizures (focal and generalised) - monotherapy

How do the newer AEDs compare in efficacy to the standard AEDs in the treatment of newly diagnosed epilepsy?

- Focal seizures: carbamazepine, eslicarbazepine, lamotrigine, lacosamide, levetiracetam, pregabalin and zonisamide.
- Generalised seizures: lamotrigine, levetiracetam, sodium valproate and zonisamide.

Why is this important

Levetiracetam and other AEDs licensed for the treatment of focal and generalised seizures since publication of the original guideline in 2004 have not been evaluated as first-line monotherapy.

Research should include:
• A prospective randomised controlled trial.
• All ages.
• Primary outcome of seizure freedom.
• Secondary outcomes should include seizure-reduction, quality of life and cognitive outcome.
• An attempt to obtain some data on pharmaco-resistance.

2.11.2 Epilepsy syndromes

What is the initial and add-on AEDs of choice in the treatment of the epilepsy syndromes with onset in childhood, for example, myoclonic-astatic epilepsy and SMEI?

Why is this important

Despite the need to diagnose individual epilepsy syndromes, there is little evidence base for the most appropriate initial or add-on AEDs in the treatment of the rarer epilepsies.

Research should include:

• Multicentre randomised controlled comparative trials with centralised national data collection.
• The ketogenic diet as one of the randomised treatments.
• Primary outcome of seizure freedom.
• Secondary outcome measures including seizure-reduction, quality of life and cognitive outcome.
• An attempt to obtain some data on pharmaco-resistance
• The possibility to include all children with specific epilepsy syndromes to be considered in the trial.

2.11.3 Infantile spasms

Does treatment response relate to cause in infantile spasms? Does early treatment success in seizure control and resolution of the hypsarrhythmic EEG influence the long-term developmental and cognitive outcome more than the underlying cause of the spasms?

Why is this important

The UK Infantile Spasms Study (UKISS)b study demonstrated 14-day outcome efficacy of steroids over vigabatrin although this excluded children with tuberous sclerosis. This study provided no specific sub-group analysis based on the cause of the spasms. There was no analysis on the effect of treatment lag on the study findings. Further data are available on behavioural outcome at 14 months and 5 years with regard to different treatments but with no analysis based on cause or treatment lag. Further

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Developmental and cognitive outcomes would be useful, including response by specific cause and by treatment lag (delay).

Research should include:
- Prospective randomised design; this should include sub-group analyses based on both cause and treatment lag (delay); this will necessitate large numbers of patients and will need to be multicentre, possibly involving Western Europe.
- EEG outcomes.
- Developmental status at presentation, and at follow-up.
- Attempt to obtain some data on pharmaco-resistance.

2.11.4 Treatment of refractory status epilepticus

What is the most effective and safest anticonvulsant to treat refractory convulsive status epilepticus (RCSE)?

Why is this important
Convulsive status epilepticus that is refractory or resistant to first-line drug treatment is rare and often complicated by irreversible neurological and intellectual sequelae, including death. Reasons for these complications include the underlying cause of RCSE and its duration but also its management. The majority, if not all patients with RCSE will be managed on an intensive care unit (ICU). There are no agreed drugs or treatment protocols for treating RCSE. The three most commonly used anticonvulsants are thiopentone, midazolam and propofol (although this latter drug is rarely used in children). There are very limited and all anecdotal data on the treatment and outcome of RCSE in adults and children. A two-year audit of all children with RCSE treated on a paediatric intensive care unit in England, Wales and Scotland has recently been completed. This will provide unique epidemiological data on paediatric RCSE and its current management. These data will facilitate the design of a randomised controlled trial of specific drug treatments and protocols.

Research should include:
- A multi-centre, randomised comparative trial on intensive care units – this could involve adult and paediatric care units (it will not be able to be a blinded study, and randomisation may have to exclude propofol for children).
- Primary outcome should be cessation of the RCSE.
- Secondary outcomes should include a recurrence with a designated period (12 hours), mortality and morbidity.
- Cost data should include treatment costs and days on intensive care.

2.11.5 AEDs and pregnancy

What is the malformation rate and longer-term neurodevelopmental outcome of children born to mothers who have taken the AEDs in pregnancy?

Why is this important
Pregnancy registers are increasing the data that are available on established AEDs; however, these registers may give malformation rates but do not provide controlled long-term data on neurodevelopmental outcome.
Research should include:

- Measures of maternal outcome, including seizure frequency and quality of life.
- Major and minor rates of congenital malformations.
- Prospective neurodevelopmental (including cognitive) and behavioural outcomes in children born to women with epilepsy; these should be undertaken on a long-term basis and ideally using a cohort study, followed from birth and until adult life.

2.12 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would do at least one of the following actions:

- have a high impact on outcomes that are important to patients
- have a high impact on reducing variation in care and outcomes
- lead to a more efficient use of NHS resources
- promote patient choice
- promote equalities

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- relates to an intervention that is not part of routine care
- requires changes in service delivery
- requires retraining staff or the development of new skills and competencies
- highlights the need for practice to change
- affects and needs to be implemented across various agencies or settings (complex interactions)
- may be viewed as potential contentious, or difficult to implement for other reasons.
2.13 The relationship between the guideline and the Technology Appraisals for the newer antiepileptic drugs (AEDs)

2004

The guideline was developed in parallel with two technology appraisals whose remit was to establish the clinical and cost effectiveness of newer drugs for adults and children with epilepsy and to provide guidance to the NHS in England and Wales (www.nice.org.uk).

The project lead of the guideline worked with the technical lead on the technology appraisals to ensure that the release of the final appraisal determination coincided with the completion of the first draft of the guideline and that there was appropriate exchange of information during the development process. In particular, it was important to ensure that there was no conflict between the recommendations of the guideline and the technology appraisals.

The appraisal recommendations, as they relate to the technology under review, have been reproduced unchanged in the most appropriate section within the guideline, as required by the Institute. They have been graded ‘A (NICE)’ as this reflects the comprehensive evidence base and rigorous evaluation on which the Institute’s appraisal recommendations were based. The evidence statements taken from the relevant appraisal have also been presented in the relevant chapter.

Where the appraisals made additional recommendations in areas that were covered in detail by the scope of the guideline, the project lead negotiated with the Institute that the GDG’s recommendations, and not those of the technology appraisal, appeared in the published guideline.

2011

The 2011 guideline partially updated the 2004 guideline and the two technology appraisals listed above. This update has reviewed additional published evidence on the AEDS included in the 2004 guideline technology appraisals. Therefore, the 2011 recommendations will supersede those contained in the appraisals published in 2003. Further newer AEDs were also included in the 2011 guideline.

2.14 The relationship between the guideline and National Service Frameworks

2004

This guideline was developed at the same time as two relevant National Service Frameworks (NSFs): those for long-term conditions (focusing on neurological conditions) and children. NSFs have a different remit than clinical guidelines. A clinical guideline aims to ‘assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances’, whereas an NSF is primarily concerned about service delivery. Thus, NSFs set national standards and identify key interventions for a defined service or care group; put in place strategies to support implementation; establish ways to ensure progress within an agreed time-scale and form one of a range of measures to raise quality and decrease variations in service.
It is therefore outside the scope of this guideline to consider issues of service delivery and the emphasis is on providing a process of care necessary for the individual with epilepsy to achieve the best possible health outcomes.

2.15 The relationship between the guideline and the Scottish Intercollegiate Guidelines Network guidelines on epilepsy

The Institute received the remit to develop a clinical guideline on epilepsy for the NHS in England and Wales from the Department of Health and National Assembly for Wales in July 2001 as part of its 6th wave programme of work. Concurrently with this commission, the Scottish Intercollegiate Guidelines Network (SIGN) were in the process of updating clinical guidelines on the diagnosis and management of epilepsy in adults (published April 2003) and developing guidelines for the diagnosis and management of epilepsy in children and young people (publication date 2004).

As part of a policy of joint working between the Institute and SIGN, a working relationship was established between the project lead and his respective colleagues in SIGN. It was agreed that the NCC-PC and SIGN teams would share relevant searches and evidence reviews but would each make their own separate guideline recommendations as required by their respective guideline methodologies. It was hoped this process would minimise the risk of two national groups making conflicting recommendations for clinical practice in the same clinical area.

2.16 External review

The guideline has been developed in accordance with the Institute’s guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline, the first draft of the full and short form guideline and the final draft of the guideline. In addition, the first draft was reviewed by nominated individuals with an interest in epilepsy and an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented anonymously for consideration by the GDG. All comments were considered systematically by the GDG and the project team recorded the agreed responses.
### 2.17 Level of evidence table

#### Table 2.5 Level of evidence table

<table>
<thead>
<tr>
<th>Hierarchy of evidence</th>
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<tbody>
<tr>
<td>Ia  Systematic review or meta-analysis of randomised controlled trials</td>
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<tr>
<td>Ib  At least one randomised controlled trial</td>
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<tr>
<td>Ila At least one well-designed controlled study without randomisation</td>
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<tr>
<td>Ilb At least one well-designed quasi-experimental study, such as a cohort study</td>
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<tr>
<td>III Well-designed non-experimental descriptive studies, case-control studies, and case series</td>
</tr>
<tr>
<td>IV  Expert committee reports, opinions and/or clinical experience of respected authorities</td>
</tr>
<tr>
<td>NICE guidelines or Health Technology Appraisal programme</td>
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</table>
3 Key priorities for implementation

The following recommendations have been identified as key priorities for implementation.

Diagnosis
- All individuals with a recent onset suspected seizure should be seen urgently\(^c\) by a specialist\(^d\). This is to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

Management
- Healthcare professionals should adopt a consulting style that enables the individual with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs. [2004]
- All individuals with epilepsy should have a comprehensive care plan that is agreed between the individuals, their family and/or carers as appropriate, and primary and secondary care providers. [2004]
- The AED (anti-epileptic drug) treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the individual’s lifestyle, and the preferences of the individual, their family and/or carers as appropriate. [2004]

Prolonged or repeated seizures and convulsive status epilepticus
- Use buccal midazolam\(^*\) as first-line treatment in adults and children with prolonged or repeated seizures. Use rectal diazepam if buccal midazolam\(^*\) is not available. If intravenous access is already established and resuscitation facilities are available, offer intravenous lorazepam. [new 2011]
- Only prescribe rectal diazepam or buccal midazolam\(^*\) for adults and children who have had a previous episode of prolonged or repeated convulsive seizures. [new 2011]

Special considerations for women of childbearing potential
- Women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children, breastfeeding and menopause. [2004]

Review and referral
- All individuals with epilepsy should have a regular structured review. In children, this review should be carried out at least yearly (but may be between 3 and 12 months by arrangement) by a specialist. In adults, this review should be carried out at least

\(^{c}\) The Guideline Development Group considered that ‘urgently’ meant being seen within 2 weeks.
\(^{d}\) For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy. For children, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.
\(^{*}\) Please see appendix K for licensing details.
yearly by either a generalist or specialist, depending on how well the epilepsy is
controlled and/or the presence of specific lifestyle issues. [2004]

- At the review, individuals should have access to: written and visual information;
counselling services; information about voluntary organisations; epilepsy specialist
nurses; timely and appropriate investigations; referral to tertiary services, including
surgery if appropriate. [2004]

- If seizures are not controlled and/or there is diagnostic uncertainty or treatment
failure, individuals should be referred to tertiary services soon for further
assessment. [2004]

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The Guideline Development Group considered that ‘soon’ meant being seen within 4 weeks.
4 Guidance

The following guidance is based on the best available evidence.

Note: In this guideline, adults are defined as aged 18 years and older and children as aged 28 days to 17 years. Young people are defined as being 12 to 17 years of age. However, it is recognised that there is a variable age range (15–19 years) at which care is transferred between child and adult health services by local healthcare trusts and primary care organisations.

This guideline is a partial update of ‘The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care’ (NICE clinical guideline 20, 2004) and updates the pharmacological management sections of the guideline, including the use of ketogenic diet.

[2004] has been added to the end of recommendations where the evidence has not been formally reviewed for the 2011 update,

[2011] has been added to the end of unchanged recommendations where the evidence has been reviewed in the update but the actual meaning of the recommendation is unchanged,

[new 2011] to the end of new recommendations where there is either an additional area for the guideline or recommendations have changed because of an updated evidence review

Anti-epileptic drug will be referred to in this document as AEDs.
4.1 Principle of decision making

4.1.1 Healthcare professionals should adopt a consulting style that enables the individual with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs. [2004]

4.2 Coping with epilepsy

4.2.1 People with epilepsy and their families and/or carers should be empowered to manage their condition as well as possible. [2004]

4.2.2 Adults should receive appropriate information and education about all aspects of epilepsy. This may be best achieved and maintained through structured self-management plans. [2004]

4.2.3 In children, self-management of epilepsy may be best achieved through active child-centred training models and interventions. [2004]

4.2.4 Healthcare professionals should highlight the Expert Patients Programme (www.expertpatients.nhs.uk) to individuals with epilepsy who wish to manage their condition more effectively. [2004]

4.3 Information

4.3.1 Individuals with epilepsy and their families and/or carers should be given, and have access to sources of, information about (where appropriate):

- epilepsy in general
- diagnosis and treatment options
- medication and side effects
- seizure type(s), triggers and seizure control
- management and self-care
- risk management
- first aid, safety and injury prevention at home and at school or work
- psychological issues
- social security benefits and social services
- insurance issues
- education and healthcare at school
- employment and independent living for adults
- importance of disclosing epilepsy at work, if relevant (if further information or clarification is needed, voluntary organisations should be contacted)
- road safety and driving
- prognosis
- sudden death in epilepsy (SUDEP)
• status epilepticus
• lifestyle, leisure and social issues (including recreational drugs, alcohol, sexual activity and sleep deprivation)
• family planning and pregnancy
• voluntary organisations, such as support groups and charitable organisations, and how to contact them. [2004]

4.3.2 The time at which this information should be given will depend on the certainty of the diagnosis, and the need for confirmatory investigations. [2004]

4.3.3 Information should be provided in formats, languages and ways that are suited to the individual’s requirements. Consideration should be given to developmental age, gender, culture and stage of life of the individual. [2004]

4.3.4 If individuals and families and/or carers have not already found high-quality information from voluntary organisations and other sources, healthcare professionals should inform them of different sources (using the Internet, if appropriate: see, for example, the website of the Joint Epilepsy Council of the UK and Ireland, www.jointepilepsycouncil.org.uk). [2004]

4.3.5 Adequate time should be set aside in the consultation to provide information, which should be revisited on subsequent consultations. [2004]

4.3.6 Checklists should be used to remind both individuals and healthcare professionals about information that should be discussed during consultations. [2004]

4.3.7 Everyone providing care or treatment for individuals with epilepsy should be able to provide essential information. [2004]

4.3.8 The person with epilepsy and their family and/or carers as appropriate should know how to contact a named individual when information is needed. This named individual should be a member of the healthcare team and be responsible for ensuring that the information needs of the individual and/or their family and/or carers are met. [2004]

4.3.9 The possibility of having seizures should be discussed, and information on epilepsy should be provided before seizures occur, for people at high risk of developing seizures (such as after severe brain injury), people with a learning disability, or people who have a strong family history of epilepsy. [2004]

4.3.10 People with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). [2004]
Sudden death in epilepsy (SUDEP)

4.3.11 Information on SUDEP should be included in literature on epilepsy to show why preventing seizures is important. Tailored information on the individual's relative risk of SUDEP should be part of the counselling checklist for people with epilepsy and their families and/or carers. [2004]

4.3.12 The risk of SUDEP can be minimised by:

- optimising seizure control
- being aware of the potential consequences of nocturnal seizures. [2004]

4.3.13 Tailored information and discussion between the individual with epilepsy, their family and/or carers (as appropriate) and healthcare professionals should take account of the small but definite risk of SUDEP. [2004]

4.3.14 Where families and/or carers have been affected by SUDEP, healthcare professionals should contact families and/or carers to offer their condolences, invite them to discuss the death, and offer referral to bereavement counselling and a SUDEP support group. [2004]

4.4 Following a first seizure

4.4.1 Individuals presenting to an Accident and Emergency department following a suspected seizure should be screened initially. This should be done by an adult or paediatric physician with onward referral to a specialist when an epileptic seizure is suspected or there is diagnostic doubt. [2004]

4.4.2 Protocols should be in place that ensure proper assessment in the emergency setting for individuals presenting with an epileptic seizure (suspected or confirmed). [2004]

4.4.3 The information that should be obtained from the individual and/or family or carer after a suspected seizure is contained in Appendix A. [2004]

4.4.4 The information that should be obtained from the child and/or parent or carer after a suspected seizure is contained in Appendix A. [2004]

4.4.5 It is recommended that all people having a first seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

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[1] For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy. For children, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.
[2] The GDG considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.
4.4.6 It is recommended that all children who have had a first non-febrile seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

4.4.7 At the initial assessment for a recent onset seizure, the specialist should have access to appropriate investigations. [2004]

4.4.8 In an individual presenting with an attack, a physical examination should be carried out. This should address the individual's cardiac, neurological and mental status, and should include a developmental assessment where appropriate. [2004]

4.4.9 Essential information on how to recognise a seizure, first aid, and the importance of reporting further attacks should be provided to a person who has experienced a possible first seizure, and their family/carer/parent as appropriate. This information should be provided while the individual is awaiting a diagnosis and should also be provided to their family and/or carers. [2004]

4.5 Diagnosis

4.5.1 The diagnosis of epilepsy in adults should be established by a specialist medical practitioner with training and expertise in epilepsy. [2004]

4.5.2 The diagnosis of epilepsy in children should be established by a specialist paediatrician with training and expertise in epilepsy. [2004]

4.5.3 Individuals and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. [2004]

4.5.4 A detailed history should be taken from the individual and an eyewitness to the attack, where possible, to determine whether or not an epileptic seizure is likely to have occurred. [2004]

4.5.5 The clinical decision as to whether an epileptic seizure has occurred should then be based on the combination of the description of the attack and different symptoms. Diagnosis should not be based on the presence or absence of single features. [2004]

4.5.6 It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations (see Section 4.6) and/or referral to a tertiary centre (See Section 4.10.16.3) should be considered. Follow-up should always be arranged. [2004]

4.5.7 Where non-epileptic attack disorder is suspected, suitable referral should be made to psychological or psychiatric services for further investigation and treatment. [2004]
4.5.8 Prospective recording of events, including video recording and written
descriptions, can be very helpful in reaching a diagnosis. [2004]

4.6 Investigations

4.6.1 Information should be provided to individuals and families and/or carers
as appropriate on the reasons for tests, their results and meaning, the
requirements of specific investigations, and the logistics of obtaining
them. [2004]

4.6.2 All investigations for children should be performed in a child-centred
environment. [2004]

4.7 Electroencephalogram (EEG)

4.7.1 Individuals requiring an EEG should have the test performed soon after it
has been requested. [2004]

4.7.2 An EEG should be performed only to support a diagnosis of epilepsy in
adults in whom the clinical history suggests that the seizure is likely to be
epileptic in origin. [2004]

4.7.3 An EEG should be performed only to support a diagnosis of epilepsy in
children. If an EEG is considered necessary, it should be performed after
the second epileptic seizure but may, in certain circumstances, as
evaluated by the specialist, be considered after a first epileptic seizure.
[2004]

4.7.4 An EEG should not be performed in the case of probable syncope
because of the possibility of a false-positive result. [2004]

4.7.5 The EEG should not be used to exclude a diagnosis of epilepsy in an
individual in whom the clinical presentation supports a diagnosis of a
non-epileptic event. [2004]

4.7.6 The EEG should not be used in isolation to make a diagnosis of epilepsy.
[2004]

4.7.7 An EEG may be used to help determine seizure type and epilepsy
syndrome in individuals in whom epilepsy is suspected. This enables
individuals to be given the correct prognosis. [2004]

4.7.8 In individuals presenting with a first unprovoked seizure, unequivocal
epileptiform activity shown on EEG can be used to assess the risk of
seizure recurrence. [2004]

4.7.9 For individuals in whom epilepsy is suspected, but who present diagnostic
difficulties, specialist investigations should be available. [2004]

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h The Guideline Development Group considered that ‘soon’ meant being seen within 4 weeks.
4.7.10 Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful. [2004]

4.7.11 Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. [2004]

4.7.12 When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed. [2004]

4.7.13 In children, a sleep EEG is best achieved through sleep deprivation or the use of melatonin. [2004]

4.7.14 Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG. [2004]

4.7.15 Provocation by suggestion may be used in the evaluation of non-epileptic attack disorder. However, it has a limited role and may lead to false positive results in some individuals. [2004]

4.7.16 Photic stimulation and hyperventilation should remain part of standard EEG assessment. The individual and family and/or carer should be made aware that such activation procedures may induce a seizure and they have a right to refuse. [2004]

Neuroimaging

4.7.17 Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. [2004]

4.7.18 MRI should be the imaging investigation of choice in individuals with epilepsy. [2004]

4.7.19 MRI is particularly important in those:
- who develop epilepsy before the age of 2 years or in adulthood
- who have any suggestion of a focal onset on history, examination or EEG (unless clear evidence of benign focal epilepsy)
- in whom seizures continue in spite of first-line medication. [2004]

4.7.20 Individuals requiring MRI should have the test performed soon\(^1\). [2004]

4.7.21 Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made. [2004]

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\(^1\) The Guideline Development Group considered that ‘soon’ meant being seen within 4 weeks.
4.7.22 CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children in whom a general anaesthetic or sedation would be required for MRI but not CT. [2004]

4.7.23 In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness. [2004]

4.7.24 Other tests

4.7.25 Measurement of serum prolactin is not recommended for the diagnosis of epilepsy. [2004]

4.7.26 In adults, appropriate blood tests (for example, plasma electrolytes, glucose, calcium) to identify potential causes and/or to identify any significant co-morbidity should be considered. [2004]

4.7.27 In children, other investigations, including blood and urine biochemistry, should be undertaken at the discretion of the specialist to exclude other diagnoses, and to determine an underlying cause of the epilepsy. [2004]

4.7.28 A 12-lead ECG should be performed in adults with suspected epilepsy. [2004]

4.7.29 In children, a 12-lead ECG should be considered in cases of diagnostic uncertainty. [2004]

4.7.30 In cases of diagnostic uncertainty, a referral to a cardiologist should be considered. [2004]

Neuropsychological assessment

4.7.31 Neuropsychological assessment should be considered in individuals in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory. [2004]

4.7.32 Referral for a neuropsychological assessment is indicated:
- when an individual with epilepsy is having educational or occupational difficulties
- when an MRI has identified abnormalities in cognitively important brain regions
- when an individual complains of memory or other cognitive deficits and/or cognitive decline. [2004]

4.8 Classification

4.8.1 Epileptic seizures and epilepsy syndromes in individuals should be classified using a multi-axial diagnostic scheme. The axes that should be considered are: description of seizure (ictal phenomenology); seizure type; syndrome and aetiology. [2004]
4.8.2 The seizure type(s) and epilepsy syndrome, aetiology, and co-morbidity should be determined, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment and persistence of seizures. [2004]

4.8.3 Individuals with epilepsy should be given information about their seizure type(s) and epilepsy syndrome, and the likely prognosis. [2004]

4.9 Management

4.9.1 People with epilepsy should have an accessible point of contact with specialist services. [2004]

4.9.2 All people with epilepsy should have a comprehensive care plan that is agreed between the individual, family and/or carers where appropriate, and primary care and secondary care providers. This should include lifestyle issues as well as medical issues. [2004]

4.9.3 Epilepsy specialist nurses (ESNs) should be an integral part of the network of care of individuals with epilepsy. The key roles of the ESNs are to support both epilepsy specialists and generalists, to ensure access to community and multi-agency services and to provide information, training and support to the individual, families, carers and, in the case of children, others involved in the child's education, welfare and well-being. [2004]

4.9.4 Healthcare professionals have a responsibility to educate others about epilepsy so as to reduce the stigma associated with it. They should provide information about epilepsy to all people who come into contact with people with epilepsy, including school staff, social care professionals and others. [2004]

4.10 Pharmacological treatment

4.10.1 General information about pharmacological treatment

4.10.1.1 Information that is provided about anti-epileptic drugs (AEDs) needs to be in the context of that provided by the manufacturer, for example, indications, side effects and licence status. [2004]

4.10.1.2 The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the individual's lifestyle, and the preferences of the individual and their family and/or carers as appropriate (see Appendix K). [2004]

4.10.1.3 The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first-line AED. [2004]

4.10.1.4 Changing the formulation or brand of AED is not recommended because different preparations may vary in bioavailability or have different
pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects. [2004]

4.10.1.5 It is recommended that individuals should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period. [2004]

4.10.1.6 If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly. [2004]

4.10.1.7 If the second drug is unhelpful, either the first or second drug may be tapered, depending on relative efficacy, side effects and how well the drugs are tolerated before starting another drug. [2004]

4.10.1.8 It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the individual, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. [2004]

4.10.2 Initiation of pharmacological treatment

4.10.2.1 AED therapy should only be started once the diagnosis of epilepsy is confirmed, except in exceptional circumstances that require discussion and agreement between the prescriber, the specialist and the individual and their family and/or carers as appropriate. [2004]

4.10.2.2 AED therapy should be initiated in adults on the recommendation of a specialist. [2004]

4.10.2.3 AED therapy in children should be initiated by a specialist. [2004]

4.10.2.4 The decision to initiate AED therapy should be taken between the individual, their family and/or carers (as appropriate) and the specialist after a full discussion of the risks and benefits of treatment. This discussion should take into account details of the individual's epilepsy syndrome, prognosis and lifestyle. [2004]

4.10.2.5 Treatment with AED therapy is generally recommended after a second epileptic seizure. [2004]

4.10.2.6 AED therapy should be considered and discussed with individuals and their family and/or carers as appropriate after a first unprovoked seizure if:

- the individual has a neurological deficit
- the EEG shows unequivocal epileptic activity
• the individual and/or their family and/or carers consider the risk of
  having a further seizure unacceptable

• brain imaging shows a structural abnormality. [2004]

4.10.2.7 It should be recognised that some individuals (through their families and/or
  carers, in some instances) may choose not to take AED therapy following a full
discussion of the risks and benefits. [2004]

7 4.10.3 Pharmacological treatment of focal seizures

8 First-line treatment in adults and children with newly diagnosed focal
seizures

10 4.10.3.1 Offer carbamazepine, lamotrigine, oxcarbazepine or sodium valproate as
first-line treatment to adults and children with newly diagnosed focal seizures,
unless contraindicated. If the first AED is ineffective or not tolerated, offer an
alternative from these four AEDs. If the second well-tolerated AED is
ineffective, consider adjunctive treatment. [new 2011]

14 4.10.3.2 Only offer levetiracetam to adults and children with focal seizures if first-line
treatments (see recommendation 4.10.3.1) are contraindicated. [new 2011]

17 Adjunctive treatment in adults and children with refractory focal seizures

18 4.10.3.3 Offer clobazam*, gabapentin*, lamotrigine, oxcarbazepine, or topiramate
as adjunctive treatment to adults and children with focal seizures if first-line
treatments (see recommendation 4.10.3.1 and 4.10.3.2) are ineffective or not
tolerated. [new 2011]

20 4.10.3.4 Discuss management with, or offer referral to, a tertiary epilepsy specialist if
adjunctive treatment with AEDs listed in recommendation 4.10.3.3 is
ineffective or not tolerated in adults and children with focal seizures. Other
AEDs that may be considered are: eslicarbazepine*, lacosamide,
levetiracetam, phenobarbital, phenytoin, pregabalin*, tiagabine and
zonisamide*. [new 2011]

27 4.10.3.5 Only offer vigabatrin to adults and children who are receiving tertiary
epilepsy specialist care, because of the potential for serious adverse effects.
[new 2011]

31 4.10.4 Pharmacological treatment of idiopathic generalised epilepsy
(IGE)

33 First-line treatment in adults and children with IGE

34 4.10.4.1 Offer sodium valproate as first-line treatment to adults and children with
newly diagnosed IGE. Offer lamotrigine or topiramate if sodium valproate is
contraindicated or not tolerated. Be aware that lamotrigine can exacerbate
myoclonic seizures. [new 2011]

* Please see appendix K for licensing details.
Adjunctive treatment in adults and children with IGE

4.10.4.2 Offer levetiracetam as adjunctive treatment to adults and children with IGE if first-line treatments (see recommendation 4.10.4.1) are ineffective or not tolerated. [new 2011]

4.10.5 Pharmacological treatment of absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes)

First-line treatment in adults and children with absence seizures

4.10.5.1 Offer ethosuximide or sodium valproate as first-line treatment to adults and children with absence seizures, unless they have also experienced generalised tonic-clonic seizures when sodium valproate should be offered first. [new 2011]

4.10.5.2 Offer lamotrigine* to adults and children with absence seizures if ethosuximide and sodium valproate have been ineffective or not tolerated. [new 2011]

4.10.5.3 Do not offer carbamazepine, oxcarbazepine, phenytoin, tiagabine or vigabatrin in the treatment of adults and children with absence seizures. [new 2011]

4.10.6 Pharmacological treatment of juvenile myoclonic epilepsy (JME)

First-line treatment in adults and children with JME

4.10.6.1 Offer sodium valproate as first-line treatment to adults and children with newly diagnosed JME. Offer lamotrigine* or topiramate* if sodium valproate is contraindicated or not tolerated. Offer topiramate if sodium valproate is ineffective. Be aware that lamotrigine can exacerbate myoclonic seizures. [new 2011]

Adjunctive treatment in adults and children with JME

4.10.6.2 Offer levetiracetam as adjunctive treatment to adults and children with JME if first-line treatments (see recommendation 4.10.6.1) are ineffective or not tolerated. [new 2011]

4.10.7 Pharmacological treatment of myoclonic seizures

First-line treatment in adults and children with myoclonic seizures

4.10.7.1 Offer sodium valproate as first-line treatment to adults and children with newly diagnosed myoclonic seizures. Offer topiramate* if sodium valproate is contraindicated, not tolerated or ineffective. [new 2011]

Adjunctive treatment in adults and children with myoclonic seizures

* Please see appendix K for licensing details.
4.10.7.2 Offer levetiracetam as adjunctive treatment to adults and children with myoclonic seizures if first-line treatments (see recommendation 4.10.7.1) are ineffective or not tolerated. If treatment is ineffective or not tolerated discuss with, or refer to, a tertiary epilepsy specialist, and consider offering clobazam*, clonazepam, piracetam or zonisamide*.

[new 2011]

4.10.8 Pharmacological treatment of newly diagnosed primary generalised tonic-clonic (PGTC) seizures

First-line treatment in adults and children with newly diagnosed PGTC seizures

4.10.8.1 Offer carbamazepine, lamotrigine, oxcarbazepine* or sodium valproate as first-line treatment to adults and children with PGTC seizures, unless they have also had myoclonic and/or absence seizures, when sodium valproate should be offered first. [new 2011]

Adjunctive treatment in adults and children with newly diagnosed PGTC seizures

4.10.8.2 Offer clobazam*, lamotrigine, levetiracetam or topiramate as adjunctive treatment to adults and children with PGTC seizures if first-line treatments (see recommendation 4.10.8.1) are ineffective or not tolerated. [new 2011]

4.10.8.3 Do not offer tiagabine and vigabatrin to adults and children with PGTC seizures. [new 2011]

* Please see appendix K for licensing details.
4.10.9 Pharmacological treatment of infantile spasms

First-line treatment in children with infantile spasms

4.10.9.1 Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with infantile spasms. [new 2011]

4.10.9.2 Offer a steroid (prednisolone or tetracosatide*) or vigabatrin as first-line treatment to children with infantile spasms that are not due to tuberous sclerosis. [new 2011]

4.10.9.3 Offer vigabatrin as first-line treatment to children with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosatide). [new 2011]

4.10.10 Pharmacological treatment of Lennox-Gastaut syndrome

First-line treatment in children with Lennox-Gastaut syndrome

4.10.10.1 Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. [new 2011]

Adjunctive treatment in adults and children with Lennox-Gastaut syndrome

4.10.10.2 Offer lamotrigine as adjunctive treatment to adults and children with Lennox-Gastaut syndrome if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2011]

4.10.10.3 Discuss with a tertiary epilepsy specialist if adjunctive treatment in adults and children with Lennox-Gastaut syndrome is ineffective or not tolerated. Other AEDs that may be considered are rufinamide or topiramate. [new 2011]

4.10.10.4 Do not offer carbamazepine or oxcarbazepine to adults and children with Lennox-Gastaut syndrome. [new 2011]

4.10.10.5 Only offer felbamate* to adults and children with Lennox-Gastaut syndrome in centres providing tertiary epilepsy specialist care and when treatment with all of the AEDs listed in recommendations 4.10.10.2 and 4.10.10.3 have proved ineffective or not tolerated. [new 2011]

* Please see appendix K for licensing details.
4.10.11 Pharmacological treatment of severe myoclonic epilepsy of infancy (SMEI)

First-line treatment in children with SMEI

4.10.11.1 Consider sodium valproate or topiramate* as first-line treatment in children with SMEI. [new 2011]

Adjunctive treatment in children with SMEI

4.10.11.2 Refer children with SMEI in whom first-line treatment was ineffective or not tolerated to a tertiary paediatric epilepsy specialist for consideration of stiripentol as adjunctive treatment. [new 2011]

4.10.11.3 Do not offer carbamazepine, lamotrigine, oxcarbazepine, phenytoin or vigabatrin in the treatment of children with SMEI. [new 2011]

4.10.12 Other epilepsy syndromes

4.10.12.1 Refer to a tertiary paediatric epilepsy specialist all children with continuous spike and wave during slow sleep (CSWS), Landau–Kleffner syndrome (LKS) or a myoclonic-astatic epilepsy (MAE). [new 2011]

4.10.13 Pharmacological treatment of benign partial epilepsies of childhood (benign epilepsy with centrotemporal spikes [BECTS] or benign epilepsy with occipital paroxysms [BEOP])

First-line treatment in children with BECTs or BEOP

4.10.13.1 Discuss with the child and their family and/or carers whether AED treatment for BECTs or BEOP in the individual circumstance is indicated. [new 2011]

4.10.13.2 Offer carbamazepine*, lamotrigine*, oxcarbazepine* or sodium valproate as first-line treatment to children with BECTs or BEOP when treatment is indicated. Offer levetiracetam* if first-line treatments are contraindicated. [new 2011]

4.10.14 Continuation of pharmacological treatment

4.10.14.1 Continuing AED therapy should be planned by the specialist. It should be part of the individual's agreed treatment plan, which should include details of how specific drug choices were made, drug dosage, possible side effects, and action to take if seizures persist. [2004]

4.10.14.2 The needs of the individual and their family and/or carers as appropriate should be taken into account when healthcare professionals take on the responsibility of continuing prescribing. [2004]

* Please see appendix K for licensing details.
4.10.14.3 If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. [2004]

4.10.14.4 The prescriber must ensure that the individual and their family and/or carers as appropriate are fully informed about treatment including action to be taken after a missed dose or after a gastrointestinal upset. [2004]

4.10.14.5 Adherence to treatment can be optimised with the following:

- educating individuals and their families and/or carers in the understanding of their condition and the rationale of treatment
- reducing the stigma associated with the condition (see also Section 4.2)
- using simple medication regimens
- positive relationships between healthcare professionals, the individual with epilepsy and their family and/or carers. [2004]

4.10.14.6 Regular blood test monitoring in adults is not recommended as routine, and should be done only if clinically indicated. [2004]

4.10.14.7 Regular blood test monitoring in children is not recommended as routine, and should be done only if clinically indicated and recommended by the specialist. [2004]

4.10.14.8 Indications for monitoring of AED blood levels are:

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- management of pharmacokinetic interactions
- specific clinical conditions, for example, status epilepticus, organ failure and pregnancy. [2004]

4.10.14.9 Examples of blood tests for adults include:

- before surgery – clotting studies in those on valproate
- full blood count, electrolytes, liver enzymes, vitamin D levels, and other tests of bone metabolism (for example, serum calcium and alkaline phosphatase) every 2–5 years for adults taking enzyme-inducing drugs. [2004]

4.10.14.10 Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication. [2004]

4.10.15 Withdrawal of pharmacological treatment
4.10.15.1 The decision to continue or withdraw medication should be taken by the
individual, their family and/or carers as appropriate, and the specialist after
a full discussion of the risks and benefits of withdrawal. At the end of the
discussion individuals, and their family and/or carers as appropriate, should
understand the individual's risk of seizure recurrence on and off treatment.
This discussion should take into account details of the individual's epilepsy
syndrome, prognosis and lifestyle. [2004]

4.10.15.2 Withdrawal of AEDs must be managed by, or be under the guidance
of, the specialist. [2004]

4.10.15.3 The risks and benefits of continuing or withdrawing AED therapy should
be discussed with individuals, and their families and/or carers as
appropriate, who have been seizure free for at least 2 years (see Appendix
H) of the full guideline). [2004]

4.10.15.4 When AED treatment is being discontinued in an individual who has
been seizure free, it should be carried out slowly (at least 2–3 months) and
one drug should be withdrawn at a time. [2004]

4.10.15.5 Particular care should be taken when withdrawing benzodiazepines
and barbiturates (may take up to 6 months or longer) because of the
possibility of drug-related withdrawal symptoms and/or seizure recurrence.
[2004]

4.10.15.6 There should be a failsafe plan agreed with individuals and their
families and/or carers as appropriate, whereby if seizures recur, the last
dose reduction is reversed and medical advice is sought. [2004]

4.10.16 Referral for complex or refractory epilepsy

4.10.16.1 All individuals with epilepsy should have access via their specialist to a
tertiary service when circumstances require. [2004]

4.10.16.2 Information should be provided to individuals and families and/or
carers as appropriate about the reasons for considering surgery. The benefits
and risks of the surgical procedure under consideration should be fully
explained before the individual's informed consent is obtained. [2004]

4.10.16.3 If seizures are not controlled and/or there is diagnostic uncertainty or
treatment failure, individuals should be referred to tertiary services soon\(^1\) for
further assessment. Referral should be considered when one or more of the
following criteria are present:

- the epilepsy is not controlled with medication within 2 years
- management is unsuccessful after two drugs
- the individual is aged under 2 years

\(^1\) Appendix H of the full guideline provides tables for the prognosis for remission of seizures in
adults.
\(^{k}\) The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.
• an individual experiences, or is at risk of, unacceptable side effects from medication

• there is a unilateral structural lesion

• there is psychological and/or psychiatric co-morbidity

• there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. [2004]

4.10.16.4 In children, the diagnosis and management of epilepsy within the first few years of life may be extremely challenging. For this reason, children with suspected epilepsy should be referred to tertiary services early, because of the profound developmental, behavioural and psychological effects that may be associated with continuing seizures. [2004]

4.10.16.5 Behavioural or developmental regression or inability to identify the epilepsy syndrome in an individual should result in immediate referral to tertiary services. [2004]

4.10.16.6 Individuals with specific syndromes such as Sturge–Weber syndrome, the hemispheric syndromes, Rasmussen’s encephalitis and hypothalamic hamartoma should be referred to a tertiary epilepsy service. [2004]

4.10.16.7 Psychiatric co-morbidity and/or negative baseline investigations should not be a contraindication for referral to a tertiary centre. [2004]

4.10.16.8 The tertiary service should include a multidisciplinary team, experienced in the assessment of individuals with complex epilepsy, and have adequate access to investigations and treatment by both medical and surgical means. [2004]

4.10.16.9 The expertise of multidisciplinary teams involved in managing complex epilepsy should include psychology, psychiatry, social work, occupational therapy, counselling, neuroradiology, clinical nurse specialists, neurophysiology, neurology, neurosurgery and neuroanaesthesia. Teams should have MRI and video telemetry facilities available to them. [2004]

4.10.16.10 The neurosurgeon in the multidisciplinary team should have specialist experience of and/or training in epilepsy surgery and have access to invasive EEG recording facilities. [2004]

4.11 Psychological interventions

4.11.1 Psychological interventions (relaxation, cognitive behaviour therapy, biofeedback) may be used in conjunction with AED therapy in adults where either the individual or the specialist considers seizure control to be inadequate with optimal AED therapy. This approach may be associated with an improved quality of life in some individuals. [2004]

4.11.2 Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children with drug-resistant focal epilepsy. [2004]
4.11.3 Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]

4.12 Ketogenic diet

4.12.1 The ketogenic diet should not be recommended for adults with epilepsy. [2004]

4.12.2 Refer children with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of a ketogenic diet. [new 2011]

4.13 Vagus nerve stimulation (VNS)

4.13.1 Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures. [2004]

4.13.2 Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures. [2004]

4.14 Prolonged or repeated seizures and convulsive status epilepticus

4.14.1 Follow local or national protocols for treating status epilepticus in children. [new 2011]

4.14.2 First-line treatment for people with prolonged or repeated generalised, convulsive (tonic-clonic, tonic or clonic) seizures in the community

4.14.2.1 Give immediate emergency care and treatment to adults and children who have prolonged (lasting 5 minutes or more) or repeated (three or more in an hour) convulsive seizures in the community. [new 2011]

4.14.2.2 Use buccal midazolam* as first-line treatment to adults and children with prolonged or repeated seizures. Use rectal diazepam if buccal midazolam* is not available. If intravenous access is already established and resuscitation facilities are available, offer intravenous lorazepam. [new 2011]

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* Evidence from NICE Interventional Procedure Guidance no. 50 (March 2004)
* Please see appendix K for licensing details.
4.14.2.3 Only prescribe rectal diazepam or buccal midazolam* for adults and children who have had a previous episode of prolonged or repeated convulsive seizures. [new 2011]

4.14.2.4 Inform individuals and their families and/or carers that buccal midazolam* is currently unlicensed. [2011]

4.14.2.5 Treatment should be administered by trained clinical personnel or, if specified by an individually agreed protocol drawn up with the specialist, by family members or carers with appropriate training. [2004]

4.14.2.6 Care must be taken to secure the individual’s airway and assess his or her respiratory and cardiac function. [2004]

4.14.2.7 Depending on response to treatment, the person’s situation and any personalised care plan, call an ambulance, particularly if:

- the seizures continue for 5 minutes without response to emergency medication
- there is a high risk of recurrence
- this is the first episode requiring emergency treatment
- there are concerns or difficulties monitoring the person’s condition. [new 2011]

4.14.3 Treatment for adults and children with convulsive status epilepticus in hospitals

4.14.3.1 Convulsive status epilepticus

4.14.3.1.1 For adults and children with ongoing generalised tonic-clonic seizures (status epilepticus) who are in hospital, immediately:

- secure airway
- give high-concentration oxygen
- assess cardiac and respiratory function
- check blood glucose levels using a finger prick test
- secure intravenous access in a large vein. [new 2011]

4.14.3.1.2 Use intravenous lorazepam as a first-line treatment in hospital in adults and children with ongoing generalised tonic-clonic seizures
4.14.3.1.3 If seizures continue, use intravenous phenobarbital, phenytoin or sodium valproate as second-line treatment in hospital in adults and children with ongoing generalised tonic-clonic seizures (status epilepticus). [new 2011]

4.14.3.2 Refractory convulsive status epilepticus

4.14.3.2.1 Follow local or national protocols for treating refractory status epilepticus in secondary care. [2011]

4.14.3.2.2 Use propofol* or thiopental* in adults with refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required. [2004]

4.14.3.2.3 Use midazolam or thiopental* in children with refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required. [2011]

4.14.3.2.4 As the treatment pathway progresses, the expertise of an anaesthetist/intensivist should be sought. [2004]

4.14.3.2.5 If either the whole protocol or intensive care is required in children, a tertiary paediatric epilepsy centre should be consulted. [2004]

4.14.3.2.6 Regular medication should be continued at optimal doses and the reasons for status epilepticus should be investigated. [2004]

4.14.3.2.7 An individual treatment pathway should be formulated for people who have recurrent convulsive status epilepticus. [2004]

4.14.3.3 Non-convulsive status epilepticus

4.14.3.3.1 Non-convulsive status epilepticus is uncommon and management is less urgent. [2004]

4.15 Women with epilepsy

4.15.1 Information and advice for women and young girls with epilepsy

4.15.1.1 In order to enable informed decisions and choice, and to reduce misunderstandings, women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause. [2004]

* Please see appendix K for licensing details.
4.15.1.2 Information about contraception, conception, pregnancy, or menopause should be given to girls and women in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with girls and women with epilepsy. These may include an individual’s family and/or carers. [2004]

4.15.1.3 All healthcare professionals who treat, care for, or support women with epilepsy should be familiar with relevant information and the availability of counselling. [2004]

4.15.1.4 Discuss with women of childbearing potential the risk of AEDs causing malformations and neurodevelopmental delay to an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Risk of continued use of sodium valproate to the unborn child should specifically be discussed. [new 2011]

4.15.1.5 Discuss with girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) and their parents and/or carer the risk of AEDs causing malformations and neurodevelopmental delay to an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Risk of continued use of sodium valproate to the unborn child should specifically be discussed. [new 2011]

4.15.1.6 Be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of childbearing potential. [2011]

4.15.1.7 All women on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. [2004]
4.15.2 Contraception

4.15.2.1 In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. [2004]

4.15.2.2 In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the possibility of interaction with oral contraceptives should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. [2004]

4.15.2.3 In women of childbearing potential, the risks and benefits of different contraceptive methods, including hormone-releasing IUDs, should be discussed. [2004]

4.15.2.4 If a woman taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, a minimum initial dose of 50 micrograms of oestrogen is recommended. If breakthrough bleeding occurs, the dose of oestrogen should be increased to 75 micrograms or 100 micrograms per day, and 'tricycling' (taking three packs without a break) should be considered. [2004]

4.15.2.5 The progesterone-only pill is not recommended as reliable contraception in women taking enzyme-inducing AEDs. [2004]

4.15.2.6 Women taking enzyme-inducing AEDs who choose to use depot injections of progesterone should be informed that a shorter repeat injection interval is recommended (10 weeks instead of 12 weeks). [2004]

4.15.2.7 The progesterone implant is not recommended in women taking enzyme-inducing AEDs. [2004]

4.15.2.8 The use of additional barrier methods should be discussed with women taking enzyme-inducing AEDs and oral contraception or having depot injections of progesterone. [2004]

4.15.2.9 If emergency contraception is required for women taking enzyme-inducing AEDs, the dose of levonorgestrel should be increased to 1.5 mg and 750 micrograms 12 hours apart. [2004]

4.15.2.10 Discuss with women who are taking lamotrigine that taking the combined oral contraceptive pill with lamotrigine can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When a woman starts or stops taking oral contraceptives, the dose of lamotrigine may need to be adjusted. [new 2011]
4.15.2.11 Follow guidance in the ‘British national formulary’ (available at www.bnf.org) on the interactions between AEDs and hormonal contraception. [new 2011]

4.15.3 Pregnancy

4.15.3.1 Women with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women who plan to stop AED therapy (see Section 4.10.15). [2004]

4.15.3.2 All pregnant women with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to the UK Epilepsy and Pregnancy Register (www.epilepsyandpregnancy.co.uk). [2004]

4.15.3.3 The clinician should discuss with the woman the relative benefits and risks of adjusting medication to enable her to make an informed decision. Where appropriate, the woman’s specialist should be consulted. [2004]

4.15.3.4 Women with generalised tonic–clonic seizures should be informed that the foetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency. [2004]

4.15.3.5 Women should be reassured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing foetus adversely unless they fall and sustain an injury. [2004]

4.15.3.6 Women should be reassured that an increase in seizure frequency is generally unlikely in pregnancy or in the first few months after birth. [2004]

4.15.3.7 Generally, women may be reassured that the risk of a tonic–clonic seizure during the labour and the 24 hours after birth is low (1–4%). [2004]

4.15.3.8 Routine monitoring of AED levels in pregnancy is not recommended. If seizures increase, or are likely to increase, monitoring of AED levels may be useful to plan or anticipate the extent of change of dose adjustment needed. [2004]

4.15.3.9 Women with epilepsy should be informed that although they are likely to have healthy pregnancies, their risk of complications during pregnancy and labour is higher than for women without epilepsy. [2004]
4.15.3.10  Care of pregnant women should be shared between the obstetrician and the specialist. [2004]

4.15.3.11  Pregnant women who are taking AEDs should be offered a high-resolution ultrasound scan to screen for structural anomalies. This scan should be performed at 18–20 weeks' gestation by an appropriately trained ultrasonographer, but earlier scanning may allow major malformations to be detected sooner. [2004]

4.15.3.12  The risk of seizures during labour is low, but it is sufficient to warrant the recommendation that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures. [2004]

4.15.3.13  All children born to mothers taking enzyme-inducing AEDs should be given 1 mg of vitamin K parenterally at delivery. [2004]

4.15.3.14  Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has idiopathic epilepsy and a positive family history of epilepsy. [2004]

4.15.3.15  Although there is an increased risk of seizures in children of parents with epilepsy, individuals with epilepsy should be given information that the probability that a child will be affected is generally low. However, this will depend on the family history. [2004]

4.15.3.16  Advanced planning, including the development of local protocols for care, should be implemented in obstetric units that deliver babies of women with epilepsy. [2004]

4.15.3.17  Joint epilepsy and obstetric clinics may be convenient for mothers and healthcare professionals but there is insufficient evidence to recommend their routine use. [2004]

4.15.3.18  It is, however, important that there should be regular follow-up, planning of delivery, and liaison between the specialist or epilepsy team and the obstetrician or midwife. [2004]

4.15.3.19  Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalised tonic-clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of AED for each individual. [new 2011]

4.15.4 Breastfeeding

4.15.4.1  All women with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that best suits her and her family. [2004]
4.15.4.2 Prescribers should consult Appendix 5 of the British National Formulary when prescribing AEDs for women who are breastfeeding. The decision on whether to continue AED therapy should be made between the woman and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. [2004]

4.15.5 After the birth

4.15.5.1 Parents of new babies or young children should be informed that introducing a few simple safety precautions may significantly reduce the risk of accidents and minimise anxiety. An approaching birth can be an ideal opportunity to review and consider the best and most helpful measures to start to ensure maximum safety for both mother and baby. [2004]

4.15.5.2 Information should be given to all parents about safety precautions to be taken when caring for the baby (see Appendix D of the full guideline). [2004]

4.15.5.3 Parents should be reassured that the risk of injury to the infant caused by maternal seizure is low. [2004]

4.16 People with learning disabilities (see also Sections 4.15 and 4.17)

4.16.1 Diagnosis (see also Section 4.5)

4.16.1.1 It can be difficult to diagnose epilepsy in people with learning disabilities, and so care should be taken to obtain a full clinical history. Confusion may arise between stereotypic or other behaviours and seizure activity. [2004]

4.16.1.2 It is important to have an eye witness account supplemented by corroborative evidence (for example, a video account), where possible. [2004]

4.16.1.3 Clear, unbiased reporting is essential. Witnesses may need education to describe their observations accurately. [2004]

4.16.2 Investigations (see also Section 4.6)

4.16.2.1 Those with learning disabilities may require particular care and attention to tolerate investigations. [2004]

4.16.2.2 Facilities should be available for imaging under anaesthesia, if necessary. [2004]

Appendix D of the full guideline provides a checklist for the information needs of women with epilepsy, and practical information for mothers with epilepsy.
4.16.2.3 In the child presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. [2004]

4.16.3 Management (see section 4.9)

4.16.3.1 Enable adults and children who have learning disabilities, and their family and/or carers where appropriate, to take an active part in developing a personalised care plan for treatment of their epilepsy. [new 2011]

4.16.3.2 Allow additional time for consultation to achieve effective management of epilepsy in adults and children with learning difficulties. [new 2011]

4.16.3.3 In making a management plan for an individual with learning disabilities and epilepsy, particular attention should be paid to the possibility of adverse cognitive and behavioural effects of AED therapy. [2004]

4.16.3.4 The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for those with learning disabilities as for the general population. [2004]

4.16.3.5 Do not discriminate against adults and children with learning difficulties and offer the same investigations and therapies as for the general population. [new 2011]

4.16.3.6 Every therapeutic option should be explored in individuals with epilepsy in the presence or absence of learning disabilities. [2004]

4.16.3.7 Healthcare professionals should be aware of the higher risks of mortality for people with learning disabilities and epilepsy and discuss these with individuals, their families and/or carers. [2004]

4.16.3.8 All individuals with epilepsy and learning disabilities should have a risk assessment including:

- bathing and showering
- preparing food
- using electrical equipment
- managing prolonged or serial seizures
- the impact of epilepsy in social settings
- SUDEP
• the suitability of independent living, where the rights of the individual are balanced with the role of the carer. [2004]

4.17 Young people with epilepsy (see also Section 4.15)

4.17.1 The physical, psychological and social needs of young people with epilepsy should always be considered by healthcare professionals. Attention should be paid to their relationships with family and friends, and at school. [2004]

4.17.2 Healthcare professionals should adopt a consulting style that allows the young person with epilepsy to participate as a partner in the consultation. [2004]

4.17.3 Decisions about medication and lifestyle issues should draw on both the expertise of the healthcare professional and the experiences, beliefs and wishes of the young person with epilepsy as well as their family and/or carers. [2004]

4.17.4 During adolescence a named clinician should assume responsibility for the ongoing management of the young person with epilepsy and ensure smooth transition of care to adult services, and be aware of the need for continuing multi-agency support. [2004]

4.17.5 Multidisciplinary services provided jointly by adult and paediatric specialists have a key role in the care of the young person with epilepsy. This can facilitate the transition from paediatric to adult services and aid in the dissemination of information. [2004]

4.17.6 Before the transition to adult services is made, diagnosis and management should be reviewed and access to voluntary organisations, such as support groups and epilepsy charities, should be facilitated. [2004]

4.17.7 The information given to young people should cover epilepsy in general and its diagnosis and treatment, the impact of seizures and adequate seizure control, treatment options including side effects and risks, and the risks of injury. Other important issues to be covered are the possible consequences of epilepsy on lifestyle and future career opportunities and decisions, driving and insurance issues, social security and welfare benefit issues, sudden death and the importance of adherence to medication regimes. Information on lifestyle issues should cover recreational drugs, alcohol, sexual activity and sleep deprivation (see Section 4.3). [2004]

4.17.8 The diagnosis and management of epilepsy should be reviewed during adolescence. [2004]
4.18 Older people with epilepsy

4.18.1 Do not discriminate against older people and offer the same investigations and therapies as for the general population. [new 2011]

4.18.2 Pay particular attention to pharmacokinetic and pharmacodynamic issues with polypharmacy and comorbidity in older people with epilepsy. Consider using lower doses of AEDs and if using carbamazepine, offer modified-release carbamazepine preparations. [new 2011]

4.19 People from black and minority ethnic groups

4.19.1 People from black and minority ethnic groups may have different cultural and communication needs and these should be considered during diagnosis and management. The need for interpretation should be considered alongside other means of ensuring that an individual’s needs are appropriately met. [2004]

4.19.2 An interpreter should have both cultural and medical knowledge. Interpreters from the family are generally not suitable because of issues such as confidentiality, privacy, personal dignity, and accuracy of translation. [2004]

4.19.3 Information, including information about employment rights and driving, should be available in an appropriate format or through other appropriate means for people who do not speak or read English. [2004]

4.20 Review

4.20.1 Adults and children with epilepsy should have a regular structured review and be registered with a general medical practice. [2004]

4.20.2 Adults should have a regular structured review with their GP, but depending on the individual’s wishes, circumstances and epilepsy, the review may be carried out by the specialist. [2004]

4.20.3 Children should have a regular structured review with a specialist. [2004]

4.20.4 For adults, the maximum interval between reviews should be 1 year but the frequency of review will be determined by the individual’s epilepsy and their wishes. [2004]

4.20.5 For children, the maximum interval between reviews should be 1 year, but the frequency of reviews should be determined by the individual’s epilepsy and their wishes and those of the family and/or carers. The interval between reviews should be agreed between the individual, their family and/or carers as appropriate, and the specialist, but is likely to be between 3 and 12 months. [2004]

4.20.6 Adults should have regular reviews. In addition, access to either secondary or tertiary care should be available to ensure appropriate
4.20.7 Adults with well-controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist. [2004]

4.20.8 If the structured review is to be conducted by the specialist, this may be best provided in the context of a specialist clinic. [2004]

4.20.9 Treatment should be reviewed at regular intervals to ensure that individuals with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained. [2004]

4.20.10 Annual review should include an enquiry about side effects and a discussion of the treatment plan to ensure concordance and adherence to medication. [2004]

4.20.11 At the review, individuals should have access to: written and visual information; counselling services; information about voluntary organisations; epilepsy specialist nurses; timely and appropriate investigations; referral to tertiary services including surgery, where appropriate. [2004]
Outline epilepsy care algorithms

Outline care algorithm for adults

Suspected seizure

Primary care

Information obtained about the event
Physical examination

A&E
(protocols in place for assessment)
Initial screening by physician

Diagnostic doubt

Suspected epileptic seizure

Treatment with AEDs only in exceptional circumstances
(see box A)

Referral to epilepsy specialist or other specialist
(e.g. cardiologist)

Referral to specialist as soon as possible
(The GDG recommended within 2 weeks)

Diagnosis by specialist
with investigations as necessary
(see box A)

Uncertain

Epilepsy

Non-epileptic attack disorder

Referral to psychological or psychiatric services

Further investigation, including assessment of other physical causes
(e.g. cardiac) or
Referral to tertiary care
(see box A)

Women with epilepsy
(see box A)

Special groups
- People with learning disabilities
- Black and ethnic minority groups
- Older people
(see box A)

Investigation and classification by seizure type and epilepsy syndrome by specialist
(see box A)

Treatment
(see box A)

Referral to tertiary care
(see box A)

Prolonged or repeated seizures
Status epilepticus
(see box A)

Regular structured review for all
(see box A)

KEY: .......................... As necessary
Outline care algorithm for children

Suspected seizure

Primary care

A&E
(protocol in place for assessment)
Initial screening by paediatrician

Information obtained about the event
Physical examination

Suspected non-febrile seizure

Treatment with AEDs only in exceptional circumstances (see box A)

Referral to specialist as soon as possible
(The GDG recommended within 2 weeks)

Diagnosis by specialist
with investigations as necessary
(see box A)

Uncertain

Epilepsy

Non-epileptic attack disorder

Referral to psychological or psychiatric services

Further investigation, including assessment of other physical causes (e.g. cardiac) or Referral to tertiary care (see box A)

Young women and girls with epilepsy (see box A)

Special groups
- Children with learning disabilities
- Black and ethnic minority groups
- Young people with epilepsy (see box A)

Investigation and classification by seizure type and epilepsy syndrome by specialist (see box A)

Treatment (see box A)

Prolonged or repeated seizures Status epilepticus (see box A)

Referral to tertiary care (see box A)

Regular structured review for all (see box A)

KEY: As necessary
5 Audit Criteria

The audit criteria outlined below may be applied in either primary or secondary care, and, where appropriate, tertiary care, depending on the age of the individual and the level of seizure control. The criteria have not been identified as being relevant to specific settings as it is important that these criteria are assessed for all individuals regardless of where they receive their care.\(^{14}\)

1. The records show that all individuals presenting with suspected recent onset seizures should be seen within 2 weeks of referral.

2. The records show the named specialist who established the diagnosis of epilepsy.

3. The records show whether or not AED therapy was prescribed. If AEDs were prescribed, details of the prescription, including drug, dose and date of initiation should be included.

4. The records show that if AED therapy was prescribed, that the decision to initiate treatment was made in consultation with the individual and family and/or carers.

5. The records show that if individuals decided not to commence the AED therapy offered, this decision was recorded.

6. The records show that all individuals have had their seizures and/or epilepsy syndrome classified using a multi-axial classification scheme.

7. The records show that if combination AED therapy is prescribed, an adequate trial of monotherapy was tried.

8. The records show that all individuals with a diagnosis of epilepsy have an agreed care plan.

9. The records show that all individuals with epilepsy have had a review in the previous 12 months.

10. The records show that seizure frequency has been documented in the past 12 months for all individuals with a diagnosis of epilepsy.

11. The records show a defined percentage of individuals with epilepsy has been seizure-free for the past 12 months.

12. The records show that the information needs of the individual were discussed at the review.

13. The records show that treatment choices have been discussed with all women and girls of childbearing potential.

14. The records show that contraceptive choices have been discussed with all women and girls of childbearing potential taking AED therapy.

15. The records show that if individuals were referred to tertiary services, they were seen within 4 weeks.

\(^{14}\) The audit criteria as applied to primary care are consistent with the Quality Indicators for Epilepsy in Investing in General Practice The New General Medical Services Contract (London: BMA, 2003). See Appendix D of the NICE guideline for more details.
16. The records show that if individuals were referred to tertiary services, referral was appropriate.

17. The records show that all individuals who have indications for referral to tertiary services were referred.
6 Principle of decision making

6.1 Who should be involved in the decision making process for adults and children with epilepsy?

Healthcare professionals should adopt a consulting style that enables the individual with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs. [2004]

It was not possible within the time and resource constraints in preparing this guideline to prepare a review of the literature relating to models of decision-making between health professionals and individuals with epilepsy or other chronic illnesses. It should be noted that there is a much more extensive literature in relation to other chronic illnesses such as diabetes and asthma.

The patient representatives identified a recent publication by the British Epilepsy Association that addressed the issue of decision making specifically for people with epilepsy.

British Epilepsy Association 2000

The issue of individual empowerment was addressed in a toolkit developed by the Epilepsy Advisory Board of the BEA, and was endorsed by the British Epilepsy Association, Joint Epilepsy Council, the Epilepsy Specialist Nurses’ Association, and the Royal College of Nursing. The toolkit did not offer any references in support of their recommendations on decision making and they should be regarded as representing the opinions of respected authorities.

The authors stated that:

‘The modern management of epilepsy includes regimented approaches to patient care which has been developed by clinicians. However, patients themselves should be encouraged to acknowledge their responsibility and their part in the team that is striving to manage a difficult medical condition. The short-hand jargon for this patient involvement is to ‘take ownership of their own epilepsy’ and accept responsibility for their own health. This is the principle underpinning the concept of individual empowerment’.

The doctor-patient relationship

Doctors are not responsible for people with epilepsy, but rather they are responsible to them. This includes:

- ensuring an accurate diagnosis
- providing individuals with the appropriate information regarding their condition
- agreeing a strategy in partnership with the individual, utilising all currently available treatment options with the goal of abolishing seizures.
7 Diagnosis

7.1 Introduction

There are major health, educational and psychosocial implications attached to making a diagnosis of epilepsy in both adults and children. It is vital that the specialist is sensitive to the needs of the individual and their family/carers when communicating a diagnosis of epilepsy. Making a diagnosis of epilepsy, however, can be difficult. Misdiagnosis is a frequent occurrence, particularly when the diagnosis is made by a non-specialist. Individuals misdiagnosed with epilepsy may experience social and financial deprivation as a result of having the wrong diagnostic label and from side-effects of antiepileptic medication. In addition, there may be a risk of unnecessary teratogenicity as a result of AED therapy in women incorrectly diagnosed as having epilepsy. In a small number of cases, individuals may die prematurely because the correct diagnosis was not made, and a serious condition was neither diagnosed nor treated. Individuals who have symptoms due to epileptic seizures but who are wrongly diagnosed as having psychiatric or associated disorders are disadvantaged from being labelled with an incorrect diagnosis and by the effects of continuing seizure activity because AEDs are not used. It is therefore crucial that specialists involved in diagnosing epilepsy take great care to establish the correct diagnosis.

7.2 Establishing the diagnosis of epilepsy

The diagnosis of epilepsy in adults should be established by a specialist medical practitioner with training and expertise in epilepsy. [2004]

The diagnosis of epilepsy in children should be established by a specialist paediatrician with training and expertise in epilepsy. [2004]

It is recommended that all people having a first seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

It is recommended that all children who have had a first non-febrile seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

Evidence statement

Diagnosing epilepsy is not easy, and misdiagnosis occurs in around 25% of cases. (III)

Details

An adequate diagnosis of epilepsy requires differentiation between seizures and other causes of transient neurological disturbance and collapse; differentiation between acute symptomatic and

---

15 For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy.
16 For children, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.
17 The GDG considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.
unprovoked epileptic seizures; and, in people with epilepsy, classification of the disorder and identification of the cause so as to optimise treatment.44

Secondary evidence

No systematic reviews comparing rates of diagnosis by training, title, or position were found.

Primary evidence

Smith 19996

One primary paper was identified that assessed the frequency, causes, and consequences of an erroneous diagnosis of epilepsy. The authors found an overall misdiagnosis rate of 26.1% (n=46/184). Erroneous diagnoses were made by all professional groups, but the majority were made by generalists.

Scheepers 199845

In another population study, 49 of 214 individuals with a primary diagnosis of epilepsy were subsequently found to be misdiagnosed. Of these, 20 were found to have had cardiovascular or cerebrovascular pathology. Seven had only ever experienced one seizure and a further 10 were found to have underlying psychopathology.
7.3 **Key features of the history and examination that allow epilepsy to be differentiated from other diagnoses in adults and children**

A detailed history should be taken from the individual and an eyewitness to the attack, where possible, to determine whether or not an epileptic seizure is likely to have occurred. [2004]

The clinical decision as to whether an epileptic seizure has occurred should then be based on the combination of the description of the attack and different symptoms. Diagnosis should not be based on the presence or absence of single features. [2004]

The information that should be obtained from the individual and/or family or carer after a suspected seizure is contained in Appendix A. [2004]

The information that should be obtained from the child and/or parent or carer after a suspected seizure is contained in Appendix A. [2004]

In an individual presenting with an attack, a physical examination should be carried out. This should address the individual's cardiac, neurological and mental status, and should include a developmental assessment where appropriate. [2004]

It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations and/or referral to a tertiary centre should be considered. Follow-up should always be arranged. [2004]

Where non-epileptic attack disorder is suspected, suitable referral should be made to psychological or psychiatric services for further investigation and treatment. [2004]

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### Evidence statements

A diagnosis of epilepsy can be made in the majority of cases on the basis of information obtained from individual and witness histories and examination of the individual. (III)

A number of clinical features may occur in different types of attack disorder, so diagnosis should be based on a combination of different symptoms and not on the presence or absence of single features. No single symptom is diagnostic of epilepsy. (IIb)

A clinical examination that includes a neurological examination is essential, since an abnormal examination after a first seizure predicts recurrence. (III)

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### Details

#### Methodological issues

In an evidence-based review of diagnosis one would be looking for articles that ‘test’ a clinical diagnosis of epilepsy (e.g. set of particular symptoms) against a validated test for epilepsy (‘gold’ standard). One would hope to determine the sensitivity (proportion of people with epilepsy who have a set of particular symptoms or signs) and specificity (proportion of people who do not have epilepsy who do not have a set of particular symptoms or signs) of the ‘test’. These two measures would then be combined into an overall measure of the efficacy of a diagnostic test called the **likelihood ratio** – the likelihood that a given combination of symptoms would be expected in an...
individual with epilepsy compared with the likelihood that the same result would be expected in
someone without epilepsy. Unfortunately it is difficult to prepare an evidence-based review on
the clinical diagnosis of epilepsy for reasons discussed below.

Secondary evidence

One systematic review that considered how the diagnosis of epilepsy should be made in adults and
children was identified. The authors noted that it was difficult to prepare an evidence-based
review of the predictive value of symptoms and signs in individuals with epilepsy for the following
two reasons:

1. ‘Gold standard’ for diagnosis was loosely construed and included both a clinical component
   and an EEG component.

2. The clinical requirements for diagnosis were highly variable and included such signs and
   symptoms as tonic/clonic movements, with or without post-ictal confusion, tongue biting, sphincter
disturbance, aura, and loss of consciousness. Some studies required the events to be
   unprovoked; others did not. Some studies required the events be witnessed; others did not.

3. The seizure type was usually diagnosed by clinical features and the epilepsy syndrome, by
   seizure type and EEG findings.

4. Only a minority of studies referred to established classification schemas, for example, the
   International League Against Epilepsy (ILAE).

The authors made the following evidence statements from their review of the evidence:

'The literature supports the diagnostic role of a complete history, especially in diagnosing JME
(juvenile myoclonic epilepsy), to elucidate an adequate description of the seizures to permit
categorizing by seizure type, since a history suggestive of a focal seizure predicts recurrence.
A clinical examination that includes a careful neurologic examination is essential, since an
abnormal examination after a first seizure also predicts recurrence.'

This systematic review provided an evidence summary of relevant primary papers. Six papers
were identified as helping answer the question as to the role of history and physical examination.

- Berg and colleagues reported that 609 of 613 children were assigned a syndromic
diagnosis on the basis of clinical features.

- Arts, Geerts, Brouwer, and colleagues reported on 466 children suggested the history
alone yielded a 29 percent sensitivity and 89 percent specificity.

- Hoefnagels, Padbleg, Overweg, and colleagues noted that it was impossible to find a
gold standard for the diagnosis of epilepsy and therefore developed their own to
distinguish epilepsy from syncope. Sensitivity and specificity of several components of a
history were computed, e.g., particular symptoms before, during, and after the paroxysmal
event. Those before the event had the highest sensitivity (88% to 98%), and those during
the event, the highest specificity (64% to 94%).

- Camfield, Camfield, Dooley and colleagues reported that in a retrospective analysis of
168 children seen after their first seizure, an abnormal neurologic examination (in 30
children) was predictive of recurrence, as was seizure type (partial seizure associated with increased risk). Neither the sleep-wake status at the first seizure nor a history of febrile seizures predicted recurrence. In three additional retrospective studies, the utility of various interventions in diagnosis and/or prediction of recurrence was reported.

- Ambrosetto, Giovanardi, and Tassinari\textsuperscript{54} reported on history (and EEG findings) in 72 individuals and concluded that only generalized seizures as the sole ictal phenomenon, and a long interval between the first and second seizures, were predictive of seizure frequency subsequently.

Other primary papers

Sheldon 2002\textsuperscript{55}

Since the AHRQ review\textsuperscript{48}, an additional study prospectively sought evidence-based criteria that distinguished between seizures and syncope in a population of adults (n=671) who were referred to three academic centres in Canada and the UK (Wales) for assessment of transient loss of consciousness.\textsuperscript{55}

In this study the causes of loss of consciousness were known satisfactorily in 539 adults and included seizures (19%, 102/539, of these focal epilepsy 49% and generalized epilepsy 51%) and syncope (81%, 437/539; of these tilt-positive vasovagal syncope 67% and cardiac causes of syncope 33%).

The point score based on symptoms alone correctly classified 94% of individuals, diagnosing seizures with 94% sensitivity and 94% specificity.\textsuperscript{42}

They propose the use of the following questions:

Questions used that, if positive, support a diagnosis of epileptic seizure:

- At times do you wake up with a cut tongue after your spells?
- At times do you have a sense of déjà vu or jamais vu before your spells?
- At times is emotional stress associated with losing consciousness?
- Has anyone noticed your head turning during a spell?
- Has anyone ever noted that you are unresponsive, have unusual posturing or have jerking limbs during your spells or have no memory of your spells afterwards?
- Has anyone noticed that you are confused after a spell?

Questions used that, if positive, support a diagnosis of syncope:

- Have you ever had light-headed spells?
- At times do you sweat before your spells?
- Is prolonged sitting or standing associated with your spells?
7.4 What are the key features of the history and examination that allow an epileptic seizure to be differentiated from other causes of attack disorder in adults?

This KCQ was not subject to a full evidence review for reasons set out in chapter 2.

Expert reviews on the key features of the history and examination can be found in Appendix A.

7.5 The role of attack/seizure diaries in diagnosis in adults & children

No published papers were identified that addressed the question of the use of seizure diaries to make the diagnosis of epilepsy. This is in contrast to the existing literature relating to their use in monitoring seizure control in individuals with epilepsy.

7.6 The role of home video recording in making the diagnosis of epilepsy in adults and children?

Prospective recording of events, including video recording and written descriptions, can be very helpful in reaching a diagnosis. [2004]

Evidence statements

There is an absence of evidence to support the claim that home video recording can aid the diagnosis of epilepsy.

No evidence on the use of seizure diaries in diagnosis was found.

Details

Methodological issues

The differentiation between epileptic and non-epileptic seizures is made primarily on the basis of the clinical history. One could hypothesise that the direct recording of attack episodes at home (by use of hand-held home video recorder) could help facilitate the diagnosis of epilepsy by the physician/paediatrician to whom the adult/child with a diagnosis of 'possible epileptic seizure?' is referred.

A review of the evidence, however, identified papers of limited validity (case series) and questionable generalisability. Three papers were identified that looked at the use of home video recordings as an aid to the diagnosis of epilepsy in adults and children. One paper looked at the use of a hand-held video camcorder in a tertiary centre to assist in the evaluation of seizures, but it was excluded on the grounds it did not relate to direct recording of attacks at home.
Primary evidence

Newmark 1981

Newmark reported a single case history of a 66 year old woman with a 21 month history of undiagnosed attacks in whom hospital monitoring had been unsuccessful. A diagnosis of ‘secondary generalised tonic-clonic seizures’ was made by analysis of the home video-tape.

Sheth 1994

Sheth and Bodensteiner reported a single case history of a 2 year old boy who was evaluated by a paediatrician and a neurologist for ‘stereotypic paroxysmal events’ which his parents had recorded with a video camera. The neurologist made an initial diagnosis of ‘seizures’ and phenobarbitone was prescribed. The seizures continued and a repeat video 6 weeks later revealed the diagnosis to be ‘infantile masturbation’ and therapy was discontinued.

Woody 1985

Woody reported two cases of children (10 month old boy & 8 year-old girl) who had been previously investigated for undiagnosed attacks using EEG and inpatient assessment. The home video recordings were of sufficient quality to allow a correct diagnosis to be made in each case (‘complex partial seizure’ and ‘reflex micturition epilepsy’).

Health economics

There is a lack of health economics evidence on the areas related to diagnosis in epilepsy. In the present guideline misdiagnosis was viewed as a huge problem not only in terms of human suffering but also in terms of waste of resources for the NHS and society as a whole. With the purpose of highlighting the magnitude of the problem, an economic analysis was carried out to estimate the costs of misdiagnosis (see Appendix G).
8 Investigations

8.1 Introduction
A range of investigations, chiefly EEG and brain imaging, are available to assist clinicians to make a multi-axial classification (Classification of seizures and epilepsy syndromes) of epilepsy in individuals suspected as having epilepsy on the basis of information obtained from the individual and/or witness histories and physical examination.

Great caution is required in performing investigations such as EEG when the clinical history offers limited support for a diagnosis of epilepsy as the risk of a false positive result may lead to misdiagnosis.

8.2 The role of EEG in making a diagnosis of epilepsy

8.2.1 How good is the standard EEG at differentiating between individuals who have had an epileptic seizure and those who have had a non-epileptic seizure?

<table>
<thead>
<tr>
<th>Evidence statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>An EEG should be performed only to support a diagnosis of epilepsy in adults in whom the clinical history suggests that the seizure is likely to be epileptic in origin. [2004]</td>
</tr>
<tr>
<td>An EEG should be performed only to support a diagnosis of epilepsy in children. If an EEG is considered necessary, it should be performed after the second epileptic seizure but may, in certain circumstances, as evaluated by the specialist, be considered after a first epileptic seizure. [2004]</td>
</tr>
<tr>
<td>An EEG should not be performed in the case of probable syncope because of the possibility of a false positive result. [2004]</td>
</tr>
<tr>
<td>The EEG should not be used to exclude a diagnosis of epilepsy in an individual in whom the clinical presentation supports a diagnosis of a non-epileptic event. [2004]</td>
</tr>
<tr>
<td>The EEG should not be used in isolation to make a diagnosis of epilepsy. [2004]</td>
</tr>
<tr>
<td>Individuals requiring an EEG should have the test performed soon after it has been requested.</td>
</tr>
</tbody>
</table>

Evidence statements

The standard EEG has variable sensitivity and specificity in determining whether an individual has had an epileptic seizure. In the primary papers reviewed the sensitivity ranged from 26% to 56% and specificity from 78% to 98%. The likelihood ratio for a positive test ranged from 2.5 to 13 and for a negative test from 0.5 to 0.76. (III; IIb children)

The finding of interictal epileptiform activity on EEG can be used to help confirm the clinical diagnosis of an epileptic seizure. A negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure. (III)

Individuals with a clinical diagnosis of a non-epileptic seizure disorder are unlikely to have, but may occasionally have, epileptiform abnormalities on EEG. (III)

18 The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.
Details

A recent definition of what constitutes a standard/routine interictal EEG has been provided in guidelines produced by the International League Against Epilepsy. Recommendations for routine EEG investigation were that:

- The ‘modified combined nomenclature’ derived from the 10-20 system should be used for electrode location
- The minimum number of electrodes should be 21 for adults and 9 for children
- At least bipolar montages with longitudinal and transverse chains should be included
- Artefacts of eye movement should be excluded using eye-opening, eye-closing, and blink procedures
- Activation procedures, such as hyperventilation and photic stimulation, should be used.

Secondary evidence

Linzer 1997

In this US systematic review, the authors reviewed the literature on diagnostic testing in syncope in order to provide recommendations for a comprehensive, cost-effective approach to establishing its cause.

The authors noted that in the early 1980s EEG was commonly used in the US to investigate individuals with syncope. However, six studies conclusively showed that EEG monitoring is of little use in unselected individuals with syncope. The authors qualitatively summarized the results of these six studies. In the absence of a history of seizure activity, EEG did not provide a diagnosis in more than 500 cases reported in the literature. Eight of 534 individuals were diagnosed (diagnosis not stated) using EEG; 2 of these 8 had clinical data provided, and both people had a history of seizures.

Fowle 2000

One UK paper used systematic literature searching to identify relevant primary studies. However, this paper did not meet systematic review criteria as it did not address a specific clinical question: it presented a general overview of the uses of the EEG in epilepsy.

The authors made the important point that EEG is a diagnostic test with variable sensitivity and specificity. Thus, the EEG may be abnormal in normal people (in one study of male RAF personnel who are all 'screened' using EEG, 0.5% (69/13658), of the sample had ‘epileptiform’ discharges). It may also be normal in people with epilepsy.

Gilbert 2000

A systematic review of the use of EEG after a first unprovoked seizure in children identified four relevant primary studies. From these, the sensitivity and specificity of the EEG was calculated to be at best 61% and 71% respectively.
A US systematic review considered the role of the EEG in making a diagnosis of epilepsy. The authors noted that it was difficult to prepare an evidence-based review of diagnosis in epilepsy, including the role of the EEG, for the following reasons:

- ‘Gold standard’ for diagnosis was loosely construed and included both a clinical component and an EEG component.
- The clinical requirements for diagnosis were highly variable and included such signs and symptoms as tonic/clonic movements, with or without post-ictal confusion, tongue biting, sphincter disturbance, aura, and loss of consciousness. Some studies required the events to be unprovoked; others did not. Some studies required the events be witnessed; others did not.
- The seizure type was usually diagnosed by clinical features and the epilepsy syndrome, by seizure type and EEG findings.
- Only a minority of studies referred to established classification schemas, for example, the ILAE.

Primary evidence

The primary papers reviewed here had methodological deficiencies according to criteria for diagnostic tests proposed by the Evidence Based Medicine Working Group.

One US study involved a retrospective review of the initial EEG (interictal) reports of several categories of people referred for study in the previous 6 years to determine the proportion with epileptiform abnormalities.

The results have been extracted from the paper and tabulated below.
Table 8.1 Results from a review of 948 individuals with various non-epileptic neurological and psychiatric disorders referred for EEG and 764 individuals with epilepsy

A) Results of interictal EEG

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=764)</th>
<th>Not epilepsy (n=948)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptiform activity</td>
<td>397</td>
<td>38</td>
</tr>
<tr>
<td>Normal</td>
<td>367</td>
<td>910</td>
</tr>
</tbody>
</table>

B) Diagnostic value of epileptiform activity for epilepsy

- **Sensitivity**: 0.52 (397/764)
- **Specificity**: 0.96 (910/948)
- **Likelihood ratio for positive test**: 13.0
- **Likelihood ratio for negative test**: 0.5

In those with a diagnosis of non-epileptic neurological and psychiatric disorders only 4% (38/948) had epileptiform activity on the initial EEG. In those with a clinical diagnosis of epilepsy 52% (397/764) had epileptiform activity on the initial EEG.

The results can be interpreted as follows. Epileptiform activity in the EEG is specific, but not sensitive, for the diagnosis of epilepsy. A positive interictal EEG can be used to help confirm the diagnosis of epilepsy but a negative result cannot be used to rule out the diagnosis of epilepsy.

Hoefnagels 1991

A Dutch study assessed the diagnostic value of a single interictal EEG in people presenting with transient loss of consciousness.

The study population consisted of 119 consecutive people (aged 15 or over) referred to a neurological department with one or more episodes of transient loss of consciousness. The authors were able to classify all individuals on clinical grounds as having had either an epileptic seizure (38%) or syncope (62%). Their findings for the test characteristics of interictal EEG are presented below (presented in this form in the paper).

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19 Result defined as a large increase in pre-test to post-test probability
20 Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)
Table 8-2: Results of EEG in 119 individuals referred to a neurological department with one or more episodes of transient loss of consciousness

<table>
<thead>
<tr>
<th>A) Results of interictal EEG</th>
<th>Seizure (n=45)</th>
<th>Syncope (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Localised epileptiform activity</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Generalised epileptiform activity</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Localised slow activity</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

B) Diagnostic value of epileptiform activity for a seizure

<table>
<thead>
<tr>
<th></th>
<th>Seizure (n=45)</th>
<th>Syncope (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.40 (18/45)</td>
<td>0.95 (69/73)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.95 (69/73)</td>
<td>(0.5 – 0.8)</td>
</tr>
<tr>
<td>Likelihood ratio for positive test (CI)</td>
<td>7.3 $^{23}$ (2.6 – 20.3)</td>
<td></td>
</tr>
<tr>
<td>Likelihood ratio for negative test (CI)</td>
<td>0.6 $^{22}$ (0.5 – 0.8)</td>
<td></td>
</tr>
</tbody>
</table>

The results can be interpreted as follows. Epileptiform activity in the EEG is specific, but not sensitive, for the diagnosis of a seizure as the cause of transient loss of consciousness. A positive interictal EEG can be used to confirm the clinical diagnosis of a seizure but a negative result cannot be used to rule out the clinical diagnosis of a seizure.

Camfield 2000

A Canadian study explored the question as to how often routine EEG results can be correctly predicted from the EEG requisition form in children.

Five hundred consecutive initial EEG requests were examined (child mean age 5 years 11 months). Based only on the requisition (demographics, referring physician, and reason for EEG), the authors coded their prediction of the result and then the actual result. When results were discordant from prediction, a judgment was made about the potential importance of the result.

Overall, EEG results were correctly predicted in 81%. Prediction for all non-epilepsy reasons was accurate in 91% (n=320). The highest rate of correct prediction was in the group with non-epileptic paroxysmal disorders. Children in this category were almost always (96%, 157/158) predicted to have a normal EEG. In contrast, for children clinically suspected as having epilepsy the correct EEG findings were correctly predicted in 59% of cases (n=141) (comparison of prediction for paroxysmal vs epileptic disorders, p<0 0001 chi squared).

Jan 2002

A Saudi Arabian study examined the relationship between clinical indications and EEG results in children and assessed the predictability of a normal result.

Four hundred and thirty eight consecutive paediatric EEGs were included prospectively. One certified electroencephalographer (EEGer) reviewed EEG requisitions and recorded his prediction of a normal result. EEGs were reviewed separately and the relationship between the clinical indications and EEG abnormalities was recorded. The children’s mean age was 5 years (sd 4.2).

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$^{21}$ Result defined as a moderate increase in pre-test to post-test probability

$^{22}$ Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)

$^{23}$ CI- confidence interval
The first EEG was studied in 65% of cases. Overall, 55% of the EEGs were abnormal. Repeat EEGs were twice as likely to be abnormal (95% CI 1.3-3, p=0.001). Established epilepsy, using antiepileptic drugs, and sleep record highly correlated with an abnormal result (p<0.0001). The EEGer predicted 26% of the EEGs to be normal.

A normal EEG was correctly predicted in 98% of non-epileptic paroxysmal events, however, epileptiform activity on the EEG (see Table ) was correctly predicted in only 26% of children with seizures. EEGs of 15 (3.4%) children with established epilepsy revealed unexpected findings that completely changed their management.

The results have been extracted from the paper and tabulated below (only subgroups of seizure versus non-epileptic paroxysmal event included: 44%, 194/438 of all EEG requests).

**Table 8-3: Results of EEG for seizures vs non-epileptic paroxysmal events**

<table>
<thead>
<tr>
<th></th>
<th>Seizure (n=154)</th>
<th>Non-epileptic paroxysmal event (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal/multifocal spikes on EEG</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Generalised epileptiform discharges</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Background EEG disturbances (focal &amp; diffuse)</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>95</td>
<td>39</td>
</tr>
</tbody>
</table>

**B) Diagnostic value of epileptiform activity for a seizure**

- Sensitivity: 0.26 (40/154)
- Specificity: 0.98 (39/40)
- Likelihood ratio for positive test: 13
- Likelihood ratio for negative test: 0.76

Stroink 2003

A prospective, multi-centre hospital based study of children with newly-diagnosed possible single or multiple seizures assessed the accuracy of the initial diagnosis after one or more paroxysmal events.

760 children were included with mean age of 5.4 years, of whom 48.3% were boys. In the group of 174 children with a final diagnosis of an epileptic seizure or epilepsy, 97 had epileptiform EEGs, giving a sensitivity of 55.7% (95% CI 48.0% to 63.2%). In the 50 children with other diagnoses or in whom doubt remained, 11 had epileptiform EEGs (specificity of 78.0%, 95% CI 63.7% to 88.0%). The likelihood ratio for a positive test is therefore 2.5 and for a negative test 0.5.

---

24 Result defined as a large increase in pre-test to post-test probability
25 Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)
8.2.2 How good is the EEG at differentiating between individuals who have different epilepsy seizure types and epilepsy syndromes?

An EEG may be used to help determine seizure type and epilepsy syndrome in individuals in whom epilepsy is suspected. This enables individuals to be given the correct prognosis. [2004]

Evidence statement

The standard EEG can help classify individuals with a clinical diagnosis of an epileptic seizure into different epilepsy seizure types and epilepsy syndromes. (III)

Details

Secondary evidence

Hirtz 2000

An evidence-based review of approaches for evaluating a first non-febrile seizure in children was identified. This stated that the majority of studies confirmed that an EEG helps in determination of seizure type and epilepsy syndrome in children.

Primary evidence

King 1998

A prospective Australian study investigated whether it was possible to diagnose specific epilepsy syndromes promptly by use of standard clinical methods, EEG and MRI in individuals presenting with a first epileptic seizure.

The study population was 300 consecutive adults and children (aged 5 and over) who presented with a first unprovoked epileptic seizure with no readily apparent cause (e.g., stroke, head injury). Clinical data from individuals and witnesses was systematically collected and a preliminary classification of the epilepsy type was made: generalised epilepsy; partial (focal) epilepsy or seizure unclassified. The authors attempted to obtain an EEG within 24 hours of the seizure. Where the EEG was negative, a sleep-deprived EEG was done. MRI was done electively. It is not clear if the EEG assessor was blinded to the clinical assessment.

A generalised or partial (focal) epilepsy syndrome was clinically diagnosed in 141 (47%) individuals with 159 (53%) cases unclassified. Subsequent analysis showed that only three of these clinical diagnoses were incorrect. Addition of the EEG data enabled the authors to diagnose an epilepsy syndrome in the majority of cases (77%, 232/300); with only 68 (23%) remaining unclassified.

Neuroimaging showed 38 epileptogenic lesions, including 17 tumours. There were no lesions in those with EEG-confirmed idiopathic generalised epilepsy or in children with benign rolandic epilepsy. The authors’ final diagnoses were: generalised epilepsy (23%); partial epilepsy (58%); and unclassified (19%).
8.2.3 How can the diagnostic yield of the standard interictal EEG be improved?

For individuals in whom epilepsy is suspected, but who present diagnostic difficulties, specialist investigations should be available. [2004]

Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful. [2004]

Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. [2004]

When a standard EEG has not contributed to diagnosis or classification a sleep EEG should be performed. [2004]

In children, a sleep EEG is best achieved through sleep deprivation or the use of melatonin [2004]

Evidence

There is insufficient high quality evidence to determine whether performing an EEG within the first 24 hours after a seizure increases the likelihood of obtaining epileptiform activity. (III)

Repeating a standard EEG in a selected adult population has been shown to increase the likelihood of obtaining epileptiform activity. (III)

Recording of the EEG whilst asleep or after sleep deprivation increases the likelihood of obtaining epileptiform activity. (III)

The use of melatonin may be used to induce sleep in children who are to undergo a sleep EEG. (III)

Details

As reviewed in the preceding section, the sensitivity of standard interictal EEG is low. This section reviews the evidence for increasing the diagnostic yield of EEG by the following additional techniques:

- early recording of EEG after seizure;
- repeatedly performing EEGs
- sleep: sleep EEGs and sleep deprivation EEGs.

The following general reviews were consulted. Specific review articles are discussed below.
8.2.3.1 Early recording of EEG after seizure

Secondary evidence

No systematic reviews were identified.

Primary evidence

King 1998\textsuperscript{71}

A prospective Australian study investigated whether it was possible to diagnose specific epilepsy syndromes promptly by use of standard clinical methods, EEG and MRI in individuals presenting with a first epileptic seizure.

The selected study population was 300 consecutive adults and children (aged 5 and over) who presented with a first unprovoked epileptic seizure with no readily apparent cause (e.g., stroke, head injury). Clinical data from individuals and witnesses were systematically collected and a preliminary classification of the epilepsy type was made: generalised epilepsy; partial (focal) epilepsy or seizure unclassified. The authors attempted to obtain an EEG within 24 hours of the seizure. Where the EEG was negative, a sleep-deprived EEG was done. MRI was done electively. It was not clear if the EEG assessor was blinded to the clinical assessment. The participants were not subject to randomisation.

The first EEG was performed within 12 hours of the seizure in 89 (30%) individuals, between 12–24 hours in 67 (22%) individuals, and after more than 24 hours in 144 (48%) individuals.

Epileptiform abnormalities were observed in 80 (51%) of the 156 who had an EEG within the first 24 hours, compared with 49 (34%) of the 144 who had a later EEG (95% CI for difference in proportions 6%–28%).

Sundaram and colleagues investigated various factors affecting interictal spike discharges in the EEGs of 203 consecutive cases with seizures.

Participants were all adults (aged 16 years and over) with definite or suspected seizures who were referred for an EEG. Adults with a history suggesting non-specific blackouts, syncope, pseudoseizures or alcohol withdrawal seizures, undergoing assessment for surgery or those who had any surgery for epilepsy were excluded.

Interictal spike discharges were correlated with age, number of seizures in the previous 12 months, timing of the EEG with relation to the last seizure, AED treatment, aetiology, and neurological status. Blinding was not documented.

77% (n=27/35) of those EEGs performed within 2 days of the last seizure showed ISDs compared with 33% (n=5/15) for EEGs within 2 to 7 days, and 41% (n=62/153) for EEGs more than 7 days after the last seizure.
8.2.3.2 Repeatedly performing EEGs

Secondary evidence

No systematic reviews were identified.

Primary evidence

Salinsky 1987

One US study retrospectively reviewed the EEG data on 429 adults to determine the probability of finding interictal epileptiform activity (IEA) on EEG. Blinding was not documented.

The study population was highly selected, comprising of adult male veterans (army personnel) with epilepsy (95% of whom had complex partial seizures).

In 50% of adults with IEA, the abnormality was present on the first EEG, in 84% by the third EEG and in 92% by the fourth EEG.

8.2.3.3 Sleep and sleep deprivation EEGs

A narrative review which considered the earlier literature and a recent critical review of the literature were consulted. There was consensus that natural sleep and sleep deprivation increase the diagnostic yield of EEG in children and adults. The following issues, however, were identified:

- Poor quality of research studies addressing impact of sleep and sleep-deprivation EEGs on diagnostic yield. Many studies are retrospective; not blinded and confound the effect of repeat EEG recordings with the effects of sleep and sleep deprivation;

- Uncertainty as to whether sleep itself or sleep deprivation causes the observed increased diagnostic yield;

- Conflicting advice on the role of sleep and sleep-deprivation EEGs in ‘authoritative’ reviews likely to be consulted by practitioners.

Two prospective studies of the role of sleep and sleep deprivation were identified, both included in the Agency for Healthcare Research & Quality systematic review.

Secondary evidence

No systematic reviews were identified.
Primary evidence

Carpay 1997

A prospective Dutch study aimed to assess the diagnostic yield of a repeated EEG after partial sleep deprivation in children and adolescents with one or more seizures who had previously had a standard EEG.

The study population was 552 children (age: range 1 month – 16 years; mean 6 years) with one or more newly diagnosed seizures. Intermittent photic stimulation was performed on all EEGs, and hyperventilation was induced when the child was co-operative. A routine interictal EEG was recorded. When the standard-EEG was classified to be without epileptiform activity, a sleep deprived-EEG was recorded by using an age-dependent protocol for sleep deprivation. The assessor of the EEGs was blinded to the clinical assessment.

Fifty six percent (309/552) of the sample had a positive standard-EEG and 44% (243/552) had an EEG without epileptiform activity. In 177 (73% of all eligible children) of these negative cases, sleep deprived-EEGs were recorded. Sleep deprived-EEGs added 11% (61/552) more diagnoses to the 56% of children with epileptiform activity on the standard-EEG (67% in total).

King 1998

An Australian study (prospective) investigated whether it is possible to diagnose specific epilepsy syndromes promptly by use of standard clinical methods, EEG and MRI in individuals presenting with a first epileptic seizure.

The study population was 300 consecutive adults and children (aged 5 and over) who presented with a first unprovoked epileptic seizure with no readily apparent cause (e.g., stroke, head injury). Clinical data from individuals and witnesses were systematically collected and a preliminary classification of the epilepsy type was made: generalised epilepsy; partial (focal) epilepsy or seizure unclassified. The authors attempted to obtain an EEG within 24 hours of the seizure. Where the EEG was negative, a sleep-deprived EEG was done. MRI was done electively. It is not clear if the EEG assessor was blinded to the clinical assessment.

Epileptiform abnormalities were shown in 43% (129/300) of the first EEG records. A majority of those with a negative first EEG (92%, 158/171) underwent a sleep-deprived EEG. A sleep-deprived EEG added 18% (55/300) more diagnoses to the 43% of those with epileptiform activity on the first EEG (61% in total).

Schreiner 2003

Schreiner and Pohlmann-Eden aimed to evaluate the predictive value of standard EEG and EEG with sleep deprivation for seizure recurrence in adults after a first unprovoked seizure. 157 adults were included and were aged between 17 and 84 years. 61.8% were male. A standard EEG was performed within 48 hours of the first seizure. A sleep deprived EEG was performed 3 to 7 days after the first seizure for those in whom the standard EEG was normal or was inconclusive. 46 adults (29.3%) had a normal EEG. Of the 60 whose initial EEG was normal or was inconclusive, the sleep deprived EEG showed abnormalities in 9 adults. Conversely, in 10 adults, sleep deprived EEG did not detect abnormalities already identified by the standard EEG.
8.2.3.4 What is the role of melatonin for children undergoing a sleep EEG?

In children, sleep EEGs have traditionally been undertaken by depriving children of sleep the night before the EEG study. This procedure, however, has been shown to be of limited acceptability to parents of children with epilepsy.\textsuperscript{79} As an alternative, children can be given oral melatonin to induce sleep.\textsuperscript{80}

No RCT evidence on the effectiveness of melatonin in children undergoing EEG assessment was identified.

8.2.4 What are the roles of long-term video-EEG and ambulatory EEG?

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG. [2004]

Evidence statements

Long-term video-EEG and ambulatory EEG can help differentiate between epileptic and non-epileptic seizures in individuals who present diagnostic difficulties following clinical assessment and standard EEG. (III)

Long-term video-EEG and ambulatory EEG can help classify seizure type and seizure syndrome in individuals who present diagnostic difficulties following clinical assessment and standard EEG. (III)

Details

Inpatient video-EEG has an important role in the diagnosis of epilepsy when the clinical history and standard EEG have been unhelpful. The inpatient video-EEG can aid with:

- Differentiating between epileptic and non-epileptic seizures
  Individuals with non-epileptic seizures are an important group and account for 20% of referrals to tertiary centres for assessment of treatment-refractory ‘seizures’. To complicate matters, epilepsy and non-epileptic attack disorder can co-exist. To establish the diagnosis it may be necessary to document ictal events, both clinical and EEG, by means of long-term video-EEG. The inpatient video-EEG is viewed as the ‘gold standard’ investigation for the diagnosis of non-epileptic events.

- Classification of seizure type and epilepsy syndrome
  Long-term video-EEG recording can aid with both classification of seizure type and epilepsy syndrome.

Three narrative reviews were consulted: one on the use of long-term video-EEG monitoring in adults\textsuperscript{81} and two on the diagnosis of non-epileptic attack disorders (NEAD).\textsuperscript{82,83}
Secondary evidence

AHRQ 2001

Eight primary studies (4 prospective and 4 retrospective) of the role of long-term video-EEG in the diagnosis of epilepsy were reviewed in the Agency for Healthcare Research & Quality review. These are summarised below. The authors of the review concluded that inpatient video-EEG and ambulatory EEG were discretionary tests and that the evidence was inconclusive on the value of any added information.

Prospective studies:

- An Australian study reported a case series of 82 children (age 2 months – 16 years, median 6 years) who underwent inpatient EEG-video telemetry. The commonest reason for referral was to determine whether an event was ictal (76%, 62/82). Other reasons included seizure frequency, classification or localisation of onset. Events occurred during the recording in 80% (66/82) of subjects. Of these, 35% (23/66) were judged to be epileptic and the seizure type identified.

- A US study reported a case series of 100 infants, children and adolescents who had outpatient video-EEG. Of the 36 who were referred to determine whether the events were epileptic, an overall diagnosis was made in 32, of whom 8 had seizures and 6 had pseudoseizures.

- An Italian case series evaluated the role of long-term video-EEG with or without sleep deprivation in children and adults with suspected nocturnal frontal lobe epilepsy (n=23). Daytime video-EEG was not diagnostic, however, after sleep deprivation a diagnosis of nocturnal frontal lobe epilepsy was made in 12 cases.

- A US case series evaluated the ability of combined ambulatory cassette-EEG and video monitoring to establish a diagnosis in 125 individuals with attacks of unknown nature (previous standard EEG negative and, where performed, CT/MRI negative). Attacks were recorded in 80% (101/125). Of these, a diagnosis was made in 80% (80/101), of which 25% (20/80) had epilepsy, 75% (60/80) had ‘psychogenic seizures’, and a dual diagnosis was present in 3 cases.

Retrospective studies:

- One US study reviewed the case notes of:
  - 138 children who underwent long-term video-EEG to differentiate between seizure versus non-seizure. A diagnosis was made in 70% (90/138) of cases.
  - 68 children who underwent long-term video-EEG to classify their seizure type. A classification could be made in 88% (60/68).

- Another US study reviewed the case notes of 444 adults and children (age range 1 week to 71 years; mean 22 years) who underwent diagnostic long-term video-EEG. Cases of known refractory focal epilepsy undergoing surgical assessment were excluded. A diagnosis was achieved in 72% (321/444) of cases. Of these, 56% (180/321) had epileptic seizures and 44% (141/321) had ‘psychogenic seizures’.

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In another US study, the case notes of 60 children aged under 10 years who were referred
to a tertiary centre with suspected epilepsy but who had a normal interictal EEG were
reviewed.\textsuperscript{90} The children underwent inpatient video EEG. A diagnosis was achieved in 33
cases. Of these, 24 had non-epileptic attacks and 9 had epileptic seizures.

The diagnostic utility of long-term video and ambulatory EEG was assessed in 102
individuals. The video EEG led to a diagnosis in 57 cases, of which 19 cases were
epilepsy.\textsuperscript{91}

\textbf{8.2.5 What is the role of provocation techniques and induction protocols?}

\begin{quote}
Provocation by suggestion may be used in the evaluation of non-epileptic attack disorder.
However, it has a limited role and may lead to false positive results in some individuals. [2004]

Photic stimulation and hyperventilation should remain part of standard EEG assessment. The
individual and family and/or carer should be made aware that such activation procedures may
induce a seizure and they have a right to refuse. [2004]
\end{quote}

\textbf{Evidence statements}

There is conflicting evidence in adults as to the role of induction protocols (there is no evidence for
children). (III)

Photic stimulation is necessary to determine if the individual is photo-sensitive but carries a small risk of
inducing a seizure. (III)

Hyperventilation is routinely employed to increase the sensitivity of an interictal EEG. (IV)

\textbf{Details}

Prolonged inpatient video-EEG monitoring may not yield a diagnosis if the interval between
seizures is long. Techniques have been developed (provocation techniques/induction protocols) to
shorten monitoring time. These methods can be divided into two groups:

- those which influence physiological processes to increase the likelihood of an epileptic
  seizure occurring (for example, standard activation procedures such as hyperventilation,
  photic stimulation, sleep deprivation and withdrawal of medication);

- those using psychological methods such as direct or indirect suggestion to induce a non-
  epileptic seizure.

The use of provocation techniques is controversial.

A narrative review on the diagnosis of psychogenic non-epileptic seizures was consulted. This
reviewed the literature on provocation techniques prior to 1996.\textsuperscript{83}

The scope of this guideline does not include the diagnosis of non-epileptic seizures. However, there
are appropriate investigations and effective treatment that can be used in the diagnosis and
management of non-epileptic seizures.\textsuperscript{82,92}
Secondary evidence

No systematic reviews were identified.

Primary evidence

One RCT and four non-randomised studies were identified.

McGonigal 2002

A UK study aimed to assess the yield of recorded habitual non-epileptic seizures during outpatient video-EEG, using simple suggestion techniques based on hyperventilation and photic simulation. The study design was a randomised controlled trial of ‘suggestion’ versus ‘no suggestion’. The setting was a tertiary centre.

The participants were 30 individuals (22 female, 8 male), aged over 16 years, with a probable clinical diagnosis of non-epileptic seizures; 15 were randomised to each group.

The main outcome measures were: yield of habitual non-epileptic seizures recorded, and requirement for additional inpatient video EEG.

Ten out of 15 individuals had habitual non-epileptic seizures with suggestion; 5/15 had non-epileptic seizures with no suggestion (p = 0.058; not significant); 8/9 individuals with a history of previous events in medical settings had non-epileptic seizures recorded during study. Logistic regression analysis with an interaction clause showed a significant effect of suggestion in those with a history of previous events in medical settings (p = 0.003). An additional inpatient video-EEG was avoided in 14 of the 30 (47%).

Bhatia 1997

Another study considered the usefulness of short-term recording of video electroencephalography (VEEG) as an outpatient procedure with placebo induction and intravenous saline in cases of pseudoseizures.

Fifty cases of suspected pseudoseizures were enrolled. They were divided into 2 groups: Group 1 consisted of individuals with frank pseudoseizures; Group 2 those where diagnosis was uncertain. VEEG recording was done and 10 ml of saline used for placebo-induction. Of 50 cases, 24 (48%) were in Group 1 and 26 (52%) in Group 2. Fifteen (15/50, 30%) had a spontaneous event during VEEG. A further 15 (15/45, 33%) had an event only on placebo induction.

Parra 1998

A US study aimed to determine the timing of spontaneous psychogenic non-epileptic events during video-EEG telemetry (VEEG), and the need to use induction protocols.

One hundred consecutive cases (75 females, 25 males) admitted to their inpatient VEEG unit from July 1994 to June 1996 for differential diagnosis of paroxysmal events were studied.

The time to the first diagnostic spontaneous event, identified by the individual or a family member as typical, was recorded. Episodes were classified as psychogenic non-epileptic events, physiologic non-epileptic events, and epileptic seizures.
The mean duration of VEEG was 74+/−SD 54.1 hours. In 82 individuals, a diagnostic event occurred spontaneously. The first event was an epileptic seizure in 22, a psychogenic non-epileptic event in 53, and a physiologic non-epileptic event in 7. The time to first diagnostic event was significantly shorter for a psychogenic non-epileptic event than for an epileptic seizures [15.0+/−sd 16.3 hours (range 5 min to 58 hours) vs. 28.6+/−sd 34.0 hours (range 1-110 hours) F=15.621, p<0.0001]. In the first 24 hours, 77.4% of those with a psychogenic non-epileptic event had an event. By 48 hours, all but 2 (96.2%) had had diagnostic events. After the first 58 hours of monitoring, all individuals with a psychogenic non-epileptic event experienced a spontaneous diagnostic event.

One study aimed to determine the benefit of provocation methods (IV saline or verbal suggestion) in individuals suspected as having non-epileptic seizures. The study population was 72 people (50 female; 22 male; age range 16 – 56) who were referred to a comprehensive epilepsy centre in Turkey between January 1992 to June 1996. Individuals had an outpatient EEG and induction with either IV saline or verbal suggestion.

Non-epileptic seizures were observed in 52 (72.2%) individuals. Thirteen of these still had risk factors for epilepsy. The authors could not decide whether all of their previous attacks were non-epileptic because 10-30% of people with non-epileptic seizures also have epileptic seizures. For a more accurate diagnosis the authors decided that these 13, together with the 20 individuals who did not have seizures with induction, needed video-EEG monitoring. Thirty-nine people who had non-epileptic seizures and no risk factors for epilepsy were thought to have pure non-epileptic seizures.

A US study described the use of a multimodality provocative technique that did not use a placebo (did not use IV saline).

Twenty one individuals with a clinical suspicion for psychogenic non-epileptic seizures were eligible to undergo an activation procedure using suggestion, hyperventilation, and photic stimulation during the study period. Of 19 inductions performed, 16 (16/19, 84%) were successful in inducing the habitual episode.

8.2.6 Does an abnormal EEG predict seizure recurrence?

In individuals presenting with a first unprovoked seizure, unequivocal epileptiform activity shown on EEG can be used to assess the risk of seizure recurrence. [2004]

Evidence statement

Individuals presenting with a first unprovoked seizure who have epileptiform activity on their initial EEG have an increased risk of seizure recurrence. (IIb children, III adults)

The specificity of an epileptiform EEG in predicting further seizures ranges from 0.13 to 0.99, and sensitivity from 0.20 to 0.91. (II)
Four systematic reviews were identified.

**Berg 1991**

Factors predictive of seizure recurrence following a first unprovoked seizure were explored in this systematic review of 16 studies.

All studies that reported on EEG results found there was a higher risk of recurrence associated with the presence of any abnormalities. The relative risk (abnormal/normal) ranged from 1.2 to 4.1. The pooled risk of recurrence at 2 years was 27% (95% CI 21% to 33%) with a normal EEG, 58% (95% CI 49% to 66%) with epileptiform abnormalities, and 37% (95% CI 27% to 48%) with non-epileptiform abnormalities. The relative risk associated with an abnormal EEG was 1.9 (95% CI 1.5 to 2.4) in the idiopathic group, and 1.4 (95% CI 1.0 to 1.9) in the remote symptomatic group.

Both seizure aetiology and EEG results clearly and consistently separated cases into higher and lower risk groups.

**Gilbert 2000**

In this review, the authors aimed to quantify and analyse the value of the information from an EEG after a first unprovoked seizure in children.

Four studies involving 831 children were included.

The pre-test probability of recurrence in all studies was found to be below the lower range of the rational testing region; that is, the expected value of the information gained from the EEG was too low to affect treatment recommendations in most children.

**Hirtz 2000**

An evidence-based practice parameter stated that the EEG helps in determination of risk of recurrence of seizures in children after a first unprovoked seizure.
The aim of the meta-analysis was to calculate the sensitivity and specificity of an epileptiform EEG in predicting further seizures. Studies using standard EEGs and where follow up was for at least one year were included.

Nineteen studies were included in which epileptiform EEGs were related with subsequent seizures in 4,288 individuals. The specificity of an epileptiform EEG in predicting further seizures ranged from 0.13 to 0.99, and sensitivity from 0.20 to 0.91.

Twelve studies were included in which abnormal EEGs were related with subsequent seizures in 1,856 individuals. The specificity of an epileptiform EEG in predicting further seizures ranged from 0.24 to 0.90, and sensitivity from 0.23 to 0.86.

The diagnostic accuracy of the EEG and the thresholds for classifying an EEG as positive varied widely. However, the authors were not able to identify any characteristic of the study participants that accounted for this variation. The factor that did account for 37% of the variation was reader threshold for classifying the EEG as epileptiform. Due to the presence of significant heterogeneity, it was not possible to calculate summary statistics for the sensitivity and specificity of the EEG in predicting further seizures.
### 8.3 The role of neuroimaging in the diagnosis of epilepsy

| Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. [2004] |
| MRI should be the imaging investigation of choice in individuals with epilepsy. [2004] |
| MRI is particularly important in those: |
| • who develop epilepsy before the age of 2 years or in adulthood |
| • who have any suggestion of a focal onset on history, examination or EEG (unless clear evidence of benign focal epilepsy) |
| • in whom seizures continue in spite of first-line medication. [2004] |
| Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made. [2004] |
| CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children in whom a general anaesthetic or sedation would be required for MRI but not CT. [2004] |
| In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness. [2004] |
| Individuals requiring MRI should have the test performed soon. [2004] |

#### Evidence statements

- Both Magnetic Resonance Imaging (MRI) scanning and Computed Tomography (CT) scanning can identify structural abnormalities in the brain that are thought to be aetiologically relevant to a diagnosis of epilepsy. (III)
- Magnetic Resonance Imaging (MRI) scanning is more sensitive and specific than Computed Tomography (CT) scanning in identifying structural abnormalities. (III)
- Individuals diagnosed as having idiopathic generalised epilepsy who undergo CT and/or MRI scanning are unlikely to have any aetiologically relevant structural abnormalities. (III)

#### Details

This review summarises the evidence for the use of magnetic resonance imaging (MRI) and computed tomography (CT) scans in the diagnosis of epilepsy.

Both MRI and CT scans are used principally in the identification of structural abnormalities in the brain that underlie seizure disorders and thus are helpful in determining the aetiology of the disorder (axis 4 – classification).

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26 The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.
Secondary evidence

Two systematic reviews of the literature were identified.\textsuperscript{48,70}

AHRQ 2001\textsuperscript{48}

Nine studies discussed the role of neuroimaging in the diagnosis of epilepsy, and the evidence suggested that the role of MRI in first diagnosis is best established in individuals in whom the CT is non-diagnostic.

Hirtz 2000\textsuperscript{70}

Nine studies addressed the use of neuroimaging in children presenting with a first non-febrile seizure. The evidence consistently demonstrated that MRI was more sensitive than CT scanning. However, the studies showed that only 1.9\% of images revealed clinically significant findings that contributed to treatment or management.

Primary evidence

As for evidence on EEG, the primary papers reviewed here have methodological deficiencies according to criteria for diagnostic tests.

Diagnosis of epilepsy

Berg \textsuperscript{2000}\textsuperscript{99}

Berg and colleagues described the use of imaging in 613 children with newly diagnosed epilepsy. Data were collected prospectively over a 4 year period. Of the 613 children, 488 (79.6\%) had imaging: 388 (63.3\%) magnetic resonance imaging, 197 (32.1\%) computed tomography scans, and 97 (15.8\%) both. Half of children with idiopathic generalized epilepsy had imaging studies compared with 70\% to 100\% of children with other forms of epilepsy, depending on the specific type.

A summary of results is presented in Table .

Aetiologically relevant abnormalities were found in 62 (12.7\% of those imaged). Fourteen of these children had otherwise completely normal presentations and histories. Their abnormalities included tuberous sclerosis (n=4), tumours (n=2), an arteriovenous malformation later diagnosed as a tumour, a cavernous angioma, cerebral malformations (n=3), and other abnormalities (n=3). Thirteen of the 14 had partial seizures and 12 had focal electroencephalographic (EEG) findings. Only one had neither.

In 18 of the 62 children with aetiologically related abnormalities, both a CT and an MRI were performed. In 15 cases, the abnormality was identified by the CT and confirmed by the MRI. In 3 cases, the CT was normal and the MRI abnormal.
### Table 8-3: Frequency of neuroimaging and yield by epilepsy syndrome

- Modified with permission from Berg at al 2009

<table>
<thead>
<tr>
<th>Epilepsy Syndrome*</th>
<th>Total</th>
<th>Any Neuroimaging N (%)</th>
<th>MRI (±CT) N (%)</th>
<th>Abnormal† N(%) ‡</th>
<th>Etiologically Relevant † N(%) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic localisation-related §</td>
<td>61</td>
<td>48 (78.7)</td>
<td>29 (47.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Symptomatic localisation-related</td>
<td>195</td>
<td>177 (90.8)</td>
<td>151 (77.4)</td>
<td>50 (28.3)</td>
<td>43 (24.3)</td>
</tr>
<tr>
<td>Cryptogenic localisation-related</td>
<td>103</td>
<td>87 (84.5)</td>
<td>103 (64.1)</td>
<td>4 (4.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Idiopathic generalised (all) II</td>
<td>126</td>
<td>62 (49.2)</td>
<td>51 (40.5)</td>
<td>5 (8.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Childhood absence</td>
<td>74</td>
<td>31 (41.9)</td>
<td>26 (35.1)</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Juvenile absence</td>
<td>15</td>
<td>8 (53.3)</td>
<td>7 (46.7)</td>
<td>2 (25.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>12</td>
<td>7 (58.3)</td>
<td>6 (50.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All other idiopathic generalised</td>
<td>25</td>
<td>16 (64.0)</td>
<td>13 (52.0)</td>
<td>2 (12.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cryptogenic / symptomatic generalised</td>
<td>52</td>
<td>48 (92.3)</td>
<td>41 (78.8)</td>
<td>15 (31.3)</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>24</td>
<td>22 (91.7)</td>
<td>18 (75.0)</td>
<td>7 (31.8)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Lennox Gastaut</td>
<td>4</td>
<td>4 (100)</td>
<td>2 (50.0)</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Doose’s syndrome</td>
<td>10</td>
<td>9 (90.0)</td>
<td>9 (90.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other cryptogenic / symptomatic generalised</td>
<td>14</td>
<td>13 (92.9)</td>
<td>12 (85.7)</td>
<td>7 (53.8)</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Undetermined (all)</td>
<td>76</td>
<td>66 (86.8)</td>
<td>51 (67.1)</td>
<td>6 (9.1)</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td>With both focal and generalised features</td>
<td>5</td>
<td>5 (100)</td>
<td>3 (60.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>With neither clearly focal or generalised features</td>
<td>71</td>
<td>61 (85.9)</td>
<td>47 (66.2)</td>
<td>6 (9.8)</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td>Total</td>
<td>613</td>
<td>488 (79.6)</td>
<td>388(63.3)</td>
<td>80 (16.4)</td>
<td>62 (12.7)</td>
</tr>
</tbody>
</table>

* Because of small numbers, some hierarchically related syndromes were collapsed into a single category.
† Abnormal indicates any abnormality and includes pineal cysts and mild Chari I malformations. Etiologically relevant indicates abnormalities that were associated with increased risk of epilepsy and which were presumed to be relevant to the child’s epilepsy.
‡ % of those in syndrome category who had neuroimaging.
§ One child initially thought to have benign rolandic epilepsy was classified under symptomatic localisation-related epilepsy as a result of an abnormal neuroimaging finding. Re-review 2 years later revealed the abnormality to be choroids fissure cyst incidental to the epilepsy.
II Of 5 children with IGE, 3 had mild Chari I malformations, 1 had mesial temporal sclerosis, and 1 had a choroids fissure cyst.

---

**Bunn 2002**

One study aimed to compare the clinical benefit of CT with MRI for children investigated at a district general hospital.

A retrospective case note review of two one year periods (1992-1993 and 1996-1997) was undertaken. All children aged 18 or under who had a CT scan or MRI of the head, neck, or spine requested by a paediatrician were included.

A definitive diagnosis was made with CT in 12% of children who presented with seizures, and in 27% with MRI.

**Dam 1985**

The aim of the study was to compare the diagnostic value of the history, clinical examination, and EEG with the CT scan in the identification of people with brain tumours.

The cause of epilepsy in 221 individuals with late-onset of epilepsy (25 years or older) was determined by history, clinical examination, EEG recording, and CT scan.

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Brain tumour, as diagnosed by the CT scan, was the cause of epilepsy in 16% (n=36). The cause
(using history, neurological examination, and CT) could not be identified in 38% of individuals
(n=84).

Holt-Seitz 1999\textsuperscript{103}

The aetiology, early mortality, predictors of prognosis, and diagnostic yields of EEG and CT scans
in new-onset seizures in older people were examined in adults aged 60 or older.

Participants were identified by reviewing records of all EEG recordings undertaken in a two year
period (Jan 1994 – Dec 1995) at a single hospital. 88 people with definite or probable seizure
were identified, but 4 refused to participate. The initial EEG was abnormal in 61 people (73%).

CT was performed in all individuals and were abnormal in 57 (68%). Only 11 individuals
underwent MRI scanning and abnormalities were detected in 7, three of whom had no abnormality
detected in CT.

Jallon 1997\textsuperscript{104}

A Swiss study aimed to determine the incidence of first seizures in a population of 384,657.

In the year of study, 418 people were referred for an EEG with a first suspected epileptic seizure.
After excluding 133 individuals (insufficient data, unclear diagnosis, lived outside study area), 273
participants remained.

All participants by definition had an EEG recording. 199 individuals (67%) underwent CT scanning
of which 61 (32%) were normal. 56 people (19.7%) underwent MRI scanning, which was normal in
30.4%. MRI was abnormal in 16% of those with normal CT scans.

Kilpatrick 1991\textsuperscript{105}

The diagnostic value of MRI was investigated in adults with late-onset epilepsy.

50 individuals with newly diagnosed late-onset epilepsy (seizures beginning after age 25 years)
were included. Only those in whom the CT scan was normal, did not allow a definitive diagnosis to
be made, or showed a lesion believed to be irrelevant were included. An age-sex matched group
of 20 people without seizures was used to assess the incidence of MRI infarcts and lesions.

Of the 32 with normal CT, MRI was normal in 20, showed irrelevant lesions in 8, and showed the
cause of seizures in 4. In the 12 people with non-diagnostic CT, MRI clarified the diagnosis in 5
and was normal in 2. The incidence of MRI detected lesions was no greater than in the age-sex
matched group without seizures. MRI was diagnostic in 32% (10/31) of individuals with partial
seizures and/or focal EEG findings as compared with 0% (0/19) of those without focal seizures.

King 1998\textsuperscript{71}

A prospective study of people presenting with a first seizure was undertaken to assess the
diagnostic value of early EEG, sleep-deprived EEG, and MRI.

300 individuals were included who presented for the first time with an unprovoked seizure with no
readily apparent cause. Individuals were excluded mainly for non-epileptic events or provoked
seizures.

Neuroimaging was done for 277 participants (92%); 263 MRI and 14CT alone. 49 of the 50 with
generalized epilepsy had normal MRI scans. Among the 154 with partial epilepsy, MRI revealed
26 (17%) epileptogenic lesions. For the 61 unclassified individuals, 9 lesions were revealed by MRI and 2 lesions by CT scan, giving a total of 11/61 (18%). CT was done in 28 of the 38 cases with lesions on MRI, but the lesion was only detected in 12. After MRI, one diagnosis was revised from generalised to partial epilepsy. Eleven unclassified individuals with focal lesions were reclassified as having partial epilepsy. A final diagnosis of epilepsy was made in 243 (81%) of the initial group.71

Ramirez-Lassepas 1984106
The role of the CT scan in the evaluation of adults after their first seizure(s) was determined in this US study.

The hospital records of 148 individuals, aged 16 to 90 years, hospitalised for evaluation of a first acute seizure were reviewed. Included individuals had a complete neurological exam, complete metabolic workup, EEG recording, and CT scan.

Aetiology was determined in 71 participants (48%), with a structural lesion identified by CT in 55 (37%) and 16 (11%) had metabolic seizures. CT findings agreed with the results of the neurological exam in 82% of cases. CT revealed structural lesions in 14 (15%) people with non-focal findings and in 12 (22%) with generalised EEG abnormalities.

Roberts 1988107
A prospective study of CT scans in adults with late-onset epilepsy was set up to search for evidence of cerebrovascular disease.

The case notes of 132 consecutive new outpatients with a history of one or more epileptic seizures with age of onset 40 years or older were reviewed. Individuals were excluded if there were other neurological symptoms or there was doubt about the diagnosis. Control scans were obtained from 132 control subjects of appropriate age and sex.

15 of those with epilepsy had infarcts on CT compared with 2 of the controls (p=0.003). However, there was no difference between the groups in the presence of relevant clinical features of systemic vascular and cardiac disease. The CT evidence of cerebral atrophy was the same in both groups.

Syndromic diagnosis and classification
Atakli 1998108
One study aimed to identify and analyse pitfalls in the diagnosis of juvenile myoclonic epilepsy (JME). The notes of 76 individuals with well-documented diagnoses of JME (as assessed using the Panayiotopoulos diagnostic criteria) were retrospectively analysed.

All of the CT (n=33) and MRI (n=3) investigations were normal.

Harvey 1997109
A community based cohort of children with new-onset temporal lobe epilepsy (TLE) were recruited to study the presentation and natural history of the disorder.

318 children with a history of 2 or more unprovoked partial seizures of suspected TLE origin with onset before aged 15 were recruited (Jan 1991 to Mar 1993). Of these, 63 were diagnosed with TLE. MRI was performed in 58 of the 63 (92%) children and CT in 48 of the 63 (76%). Five
children did not undergo MRI because the CT was normal and their parents did not wish them to undergo MRI.

MRI revealed structural abnormalities of the temporal lobe in 24 of the 63 children (38%).

Jallon 2001110

One study described first unprovoked seizures and newly diagnosed epilepsies at initial presentation in a large cohort.

Individuals were referred to the study if they were older than one month, had at least one unprovoked epileptic seizure diagnosed between May 1995 and June 1996, and were likely to be followed up for at least 2 years. After exclusions (previous diagnosis of unprovoked seizures, acute symptomatic seizures, those likely to be lost to follow-up) 1,942 people were included.

One or more imaging studies were performed in 1,418 individuals (73.0%). In the first-seizure group (n=926), a neuroimaging study was performed in 78.2% of the participants (CT scan only 57.9%; MRI only 6.5%; CT scan + MRI 13.8%). This rate varied according to the epileptic syndrome: 55.0% for idiopathic localization-related, 63.5% for idiopathic generalized, 82.1% for isolated seizures, 86.0% for cryptogenic localization-related, and 88.6% for symptomatic localization-related. For those with newly-diagnosed epilepsy (n=1,016), a neuroimaging study was performed in 68.3% (CT scan only 42.9%; MRI only 12.2%; CT scan + MRI 13.2%). This rate varied according to the epileptic syndrome: 40.3% for idiopathic generalized, 60.4% for idiopathic localization-related, 65.4% for symptomatic generalized, 74.4% for cryptogenic or symptomatic generalized, 78.0% for undetermined whether focal or generalized, 78.1% for cryptogenic localization-related, and 94.2% for symptomatic localization-related.

These high rates of imaging permitted classification of seizures in 78.1% of the first-seizure group and 88.0% of the newly-diagnosed-epilepsy group; classification of syndromes in all the first seizures and 98.6% of those with newly diagnosed epilepsy; and classification of aetiology in all the first seizures and 98.8% of those with newly diagnosed epilepsy, with a reasonably high degree of certainty at the time of initial diagnosis.

Lee 2002111

The role of MRI in the process of classification of epilepsies was investigated in this study. The registry forms of 300 consecutive individuals registered at the Yonsei Epilepsy Clinic were examined for clinical information and investigations performed. 51 people were excluded (did not have epilepsy, single seizure only, and no EEG or MRI). Three diagnoses were made for the 249 included participants: first step diagnosis (clinical information), second step diagnosis (clinical and EEG correlation) and third step diagnosis (clinical, EEG, and MRI correlation).

MRI revealed structural lesions in 106 (43%) of the 249. Lesions were found in 47 (38%) of 125 individuals with negative EEGs and in 59 (48%) of 124 individuals with positive interictal epileptiform discharges. Both EEG and MRI were negative in 78 (31%) and positive in 59 (24%) participants. The incidence of MRI lesions in different syndromes of the second step diagnosis was 47% in localization related epilepsy, 6% in generalised epilepsy, and 31% in undetermined epilepsy. Among the 199 with a second step diagnosis, MRI changed the diagnosis in 30 (12%), however none of these had a second step diagnosis of generalised epilepsy. MRI also decreased the proportion of individuals in non-specific categories from 37% to 29%.

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8.4 The role of prolactin levels and other blood tests as an aid to diagnosis

Measurement of serum prolactin is not recommended for the diagnosis of epilepsy. [2004]

In adults, appropriate blood tests (for example, plasma electrolytes, glucose, calcium) to identify potential causes and/or to identify any significant co-morbidity should be considered. [2004]

In children, other investigations, including blood and urine biochemistry, should be undertaken at the discretion of the specialist to exclude other diagnoses, and to determine an underlying cause of the epilepsy. [2004]

All investigations should be performed in a child centred environment. [2004]

Evidence statement

There is conflicting evidence as to the value of blood tests, such as serum prolactin levels, in differentiating between epileptic and non-epileptic seizures. (III)

Details

This section presents the evidence for the use of blood tests in making the diagnosis of epilepsy, and in differentiating between epilepsy and other conditions, particularly syncope. Blood tests discussed are levels of serum prolactin, neuron-specific enolase, serum creatine kinase, and white blood count.

Secondary evidence

AHRQ 200148

This systematic review identified two relevant papers (Anzola112 and Neufeld113 discussed below).

Primary evidence

The primary papers reviewed here have methodological deficiencies according to criteria for diagnostic tests proposed by the Evidence Based Medicine Working Group. The main concerns were lack of a ‘gold standard’ for reference, and lack of blinding of investigators or assessors.47,65

Diagnosis of epilepsy

Fein 1997114

The utility of serum and cerebrospinal fluid (CSF) prolactin levels was assessed in the diagnosis of children with seizures. Serum samples were analysed if the samples were taken within 90 minutes of the seizure, and CSF samples within 4 hours of the seizure. The comparison group was children who had not experienced a seizure but who otherwise required a lumbar puncture.
The positive predictive value of age-adjusted dichotomous levels (elevated and normal) of serum prolactin was 68% (95% CI 47-85%) and the negative predictive value was 76% (95% CI 61-87%).

Shah 2001

One study aimed to analyse the relationship between different types of seizures and non-epileptic events, seizure duration, time of sampling and serum prolactin levels and peripheral white blood count. Seizure classification and baseline plus both post-event white blood count and prolactin levels were available for 174 events.

Serum prolactin level increased above twice the level at baseline after a complex partial seizure or a generalized seizure. Peripheral WBC count was elevated above the upper limit of normal in 36% of cases after a generalized seizure. In generalized seizures, the length of a seizure is positively associated, whereas the lapse time between the seizure onset and blood draw is negatively correlated with the increase in WBC count.

Tumani 1999

The temporal profile of serial levels of neuron-specific enolase (NSE) and serum prolactin were compared in 21 individuals with single seizures. Measurements were taken at one, three, six and 24 hours after the event.

There was a significant decrease of NSE and prolactin levels over time (p<0.001). At one hour after the event, only 38% of individuals had increased NSE compared with abnormal prolactin levels in 81%.

Differential diagnosis between epileptic and non-epileptic attacks

Alving 1998

This study aimed to evaluate the discriminative power of serum prolactin measurements in the differential diagnosis between epileptic (ES) and pseudo-epileptic seizures (PES). Blood samples were taken from 58 participants both 15 minutes after the seizure and 2 hours after the first sample.

Sensitivity for the maximal rise of serum prolactin in pseudoseizures (5.5 times baseline level) was only 20% and the negative predictive value 40%. For the cut-off in absolute level, (1025 µU/ml), the figures were 34% and 44% respectively.

Epilepsy vs syncope

Anzola 1993

The clinical usefulness of plasma prolactin in the differential diagnosis between epilepsy and syncope was studied in 59 cases. Plasma prolactin levels were measured as soon as possible after the event (P1), one hour after P1 (P2), and in the morning for the next two days (P3,P4).

Levels were significantly increased in those who had a seizure when P1 was sampled within 60 minutes of an attack. In people who had a syncopal attack, plasma levels did not increase. For those assessed within 60 minutes of the attack, the positive predictive value of the cut-off (P1

* These figures cannot be reconciled with the tables/data in the original paper.
The use of serum prolactin levels in the differential diagnosis between epileptic and syncopal attacks was examined in individuals with complex partial seizures (CPS) and individuals with vasovagal syncopal attacks (VVS). The serum levels in 33 people were measured as soon as possible after the event (within 60 minutes), one hour after the first sample, and 24 hours later. Mean values of prolactin levels in both groups were increased immediately after the event (CPS: $1142 \pm 305$ mIU/l, VVS: $874 \pm 208$ mIU/l). Elevated levels immediately after the event were found in 78% of in the CPS group, and 60% of the VVS group.

The objective of this study was to determine the role of sequential serum creatine kinase (CK) levels in differentiating between generalised tonic-clonic seizures and vaso-vagal syncope in people presenting with first events of loss of consciousness. Serum levels were taken in 16 individuals on admission (i.e. within a few hours of the event) and 24-26 hours later.

Using the criteria of CK levels > 200mU/ml (3.33µkat/l) (on either admission or 24-26 hours later) and/or the elevation from the first to the second measurement of >=15mU/ml (0.25µkat/l), there were only 12% false negatives and 12% false positives.

### 8.5 Cardiovascular tests as an aid to diagnosis

A 12 lead ECG should be performed in adults with suspected epilepsy. [2004]

In children a 12 lead ECG should be considered in cases of diagnostic uncertainty. [2004]

In cases of diagnostic uncertainty, a referral to a cardiologist should be considered. [2004]

### Evidence statement

Seizure-like attacks with a cardiovascular cause may be misdiagnosed as epilepsy. (III)

### Details

This was not subject to a full evidence review for reasons given in Chapter 2.

Zaidi and colleagues conducted cardiovascular tests in 74 people with a previous diagnosis of epilepsy. Participants were included if attacks continued despite adequate AED therapy, or there was clinical uncertainty based on the seizure description. Each individual underwent a head-up tilt test and carotid sinus massage during continuous electrocardiography, electroencephalography and blood pressure monitoring.
An alternative diagnosis was made in 31 people (42%). After follow-up (10.3±6.7 months), 19 (61%) of the 31 with an alternative diagnosis were symptom free and all 31 had subjectively improved. Of the 13 people who were taking AEDs, 11 (85%) had successfully stopped AED therapy.

8.6 What is the role of neuropsychological assessment in the diagnosis and management of epilepsy?

Neuropsychological assessment should be considered in individuals in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory. [2004]

Referral for a neuropsychological assessment is indicated:
- when an individual with epilepsy is having educational or occupational difficulties
- when an MRI has identified abnormalities in cognitively important brain regions
- when an individual complains of memory or other cognitive deficits and/or cognitive decline. [2004]

Evidence statement

Neuropsychological deficits are commonly associated with epilepsy and its treatment. Awareness of these problems may facilitate education, social integration and employment. (IV)

Details

This section was not subject to a full evidence review for reasons set out in Chapter 2.

Narrative reviews

Two expert reviews were consulted.

Buelow 2002

The arguments for and against neuropsychological (NP) assessment in all children with epilepsy were presented in this review. Arguments for the testing of all children were:
- NP testing should not be restricted only to children considered for epilepsy surgery.
- Children with epilepsy may have academic and learning disabilities that may go unrecognised, unless screened for early identification of such problems.
- Undetected learning disabilities could lead to lifelong learning problems and poor social adaptive functioning.
• NP testing could identify children with a borderline or low IQ who may have specific learning needs.

• Systematic behavioural assessment would facilitate the development of management strategies for such problems as poor self-concept or stigma.

• NP testing can track cognitive changes in the child with epilepsy.

Conversely, they argued that NP testing should be limited because:

• NP testing may not be cost-effective for all children.

• False-positive results may lead to a child being labelled with a diagnosis that is not accurate.

• Expectations of children labelled as ‘learning disabled’ may be lower, and children may be stigmatised.

• Testing of children may create more feelings of being different than their peers without epilepsy and alter their self-perception in a negative way.

• NP testing is a specialist skill that may not be easily available to all children with epilepsy.

• Testing should be performed for a specific reason, as there are resource implications.

The authors concluded that the need for NP testing should be raised and considered in the initial evaluation of every child with epilepsy.\textsuperscript{120}

The GDG considered that neuropsychological assessment provides a systematic and standardised evaluation of an individual's cognitive abilities and:

• may be useful in identifying cognitive deficits such as memory and language impairments that will have implications for educational, occupational and independent living goals and medical management, such as adherence to prescription

• may provide information regarding the likely cause of cognitive impairment (medication, brain lesion, seizures, mood)

• repeat assessments may provide information regarding the likely prognosis of cognitive function in the future.

\textsuperscript{Kwan 2001\textsuperscript{121}}

This review considered the cause and neuropathology of epilepsy, neuronal discharges, AED treatment and the associated effects on cognition and behaviour. Psychosocial factors were also discussed.

The authors concluded that a better understanding of the complex cognitive and behavioural dimensions of epilepsy would allow clinicians to provide a more holistic, person centred approach to management. They recommended that each individual with epilepsy should be assessed individually with respect to factors unique to their seizure disorder and treatment.
9 Classification of seizures and epilepsy syndromes

9.1 Introduction
It is inadequate to simply diagnose an individual as having ‘epilepsy’. Epilepsy should be viewed as a feature or symptom of an underlying neurological disorder and not as a single disease entity. It is important that specialists and generalists who treat individuals with epilepsy understand that epilepsy should be classified according to seizure type and epilepsy syndrome. The need to consider age-related epilepsy syndromes is particularly important in children with epilepsy.

It is axiomatic that the correct classification of seizure type and epilepsy syndrome should lead to the individual with epilepsy receiving appropriate investigations, appropriate treatment, and information about the likely prognosis of the seizure type and/or syndrome.

9.2 Classification of the epilepsies
Epileptic seizures and epilepsy syndromes in individuals should be classified using a multi-axial diagnostic scheme. The axes that should be considered are: description of seizure (ictal phenomenology); seizure type; syndrome and aetiology. [2004]

The seizure type(s) and epilepsy syndrome, aetiology, and co-morbidity should be determined, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment and persistence of seizures. [2004]

Individuals with epilepsy should be given information about their seizure type(s) and epilepsy syndrome, and the likely prognosis. [2004]

Evidence statements
The classification of epilepsy relies on evidence from expert committee reports (International League Against Epilepsy). At present the established classification system is undergoing review and current proposals have the status of ‘work in progress’. (IV)

Failure to correctly classify the epilepsy syndrome can lead to inappropriate treatment and persistence of seizures. (III)

Details
Overview of classification systems
The classification of epilepsy has long been a subject of contention. The problem is due to the fact that epilepsy is not a single disease entity; rather, it is a symptom of a range of underlying neurological disorders. The clinical presentation depends on a number of factors, chiefly: the part of the brain affected, the pattern of spread of epileptic discharges through the brain, the cause of the epilepsy and the age of the individual. Classification has thus tended to focus on both the clinical presentation (type of epileptic seizure), and on the underlying neurological disorder (epilepsies and epileptic syndromes).4
The first epilepsy classifications did not distinguish between syndromes and seizures. Terms such as grand mal and petit mal were used, respectively, to classify epilepsy presenting with tonic-clonic seizures and those with ‘small attacks’ such as absences. The first attempt to classify the epilepsies was carried out by Gastaut. His work formed the basis for the Commission on the Classification and Terminology of the International League against Epilepsy (ILAE) standardised classifications and terminology for epileptic seizures and the epilepsies and epileptic syndromes developed in the 1970s and 1980s. (Table , Table ).

Although the ILAE 1981 and 1989 classifications remain in common use they have been the subject of criticism and debate. They have been criticised for:

- being unsatisfactory for epidemiological research
- placing undue emphasis on the types of case referred to tertiary centres
- placing undue emphasis on the role of the EEG at the expense of newer techniques such as MRI
- not classifying epileptic seizures according to what an individual or eyewitness reports happens during a seizure (ictal semiology).

In response to concerns about the existing classification systems the ILAE in 1997 undertook to make a revision of classification a priority and set up a Task Force of experts in the field to address this issue. This group first reported in 2001. The Task Force argued that it was not possible to replace the current international classifications with similar revised and updated classifications that would be universally accepted and meet all the clinical and research needs such a formal organizational system would be expected to provide. Instead, they proposed that clinicians and researchers should use a multi-axial diagnostic scheme (Table ). Epileptic seizures and epilepsy syndromes are to be described and categorised in individuals according to a system that uses standardised terminology, and that is sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

1. Some individuals cannot be given a recognized syndromic diagnosis;
2. Seizure types and syndromes change as new information is obtained;
3. Complete and detailed descriptions of ictal phenomenology are not always necessary;
4. Multiple classification schemes can, and should, be designed for specific purposes (for example, communication and teaching; therapeutic trials; epidemiologic investigations; selection of candidates for surgery; basic research; genetic characterizations).

There is also scope to simplify or expand the classification system depending on whether it is to be used by a neurologist with particular expertise in epilepsy or by a general physician or paediatrician.

The specific areas covered by this scheme are presented in Table , Table and Table . The Task Force also made suggestions as to how current terminology should be changed so as to make it more usable (Table ) and these have been incorporated into the guideline glossary of terms.
# Table 9.1 Classification of epileptic seizures according to clinical type

<table>
<thead>
<tr>
<th>1. Partial (focal, local) seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Simple partial seizures (consciousness not impaired)</td>
</tr>
<tr>
<td>1.1. With motor signs</td>
</tr>
<tr>
<td>1.1.2. With somatosensory or special-sensory symptoms (simple hallucinations, for example, tingling, light flashes, buzzing)</td>
</tr>
<tr>
<td>1.1.3. With autonomic symptoms or signs (for example, epigastric sensation, pallor, sweating, flushing, piloerection and papillary dilatation)</td>
</tr>
<tr>
<td>1.1.4. With psychic symptoms (disturbance of higher cerebral function) (for example, déjà vu, distortion of time sense, fear. NB these rarely occur without impairment of consciousness and are much more commonly experienced as 1.2 complex partial seizures)</td>
</tr>
<tr>
<td>1.2. Complex partial seizures (with impairment of consciousness)</td>
</tr>
<tr>
<td>1.2.1. With simple partial onset followed by impairment of consciousness</td>
</tr>
<tr>
<td>1.2.2. With impairment of consciousness at onset</td>
</tr>
<tr>
<td>1.3. Partial seizures evolving to secondarily generalized seizures (may be generalized tonic-clonic, tonic, or clonic)</td>
</tr>
<tr>
<td>1.3.1. Simple partial seizures evolving to generalized seizures</td>
</tr>
<tr>
<td>1.3.2. Complex partial seizures evolving to generalized seizures</td>
</tr>
<tr>
<td>1.3.3. Simple partial seizures evolving to complex partial seizures and then evolving to generalized seizures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Generalized seizures (convulsive or non-convulsive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1. Absence seizures (impairment of consciousness alone or with mild clonic, atonic or tonic components, automatisms and/or autonomic symptoms or signs)</td>
</tr>
<tr>
<td>2.2. Atypical absence</td>
</tr>
<tr>
<td>2.3. Myoclonic seizures</td>
</tr>
<tr>
<td>2.4. Clonic seizures</td>
</tr>
<tr>
<td>2.5. Tonic-clonic seizures</td>
</tr>
<tr>
<td>2.6. Atonic seizures</td>
</tr>
</tbody>
</table>

Modified from: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures\(^{124}\) Reprinted by permission of the journal *Epilepsia*
### Table 9-2: Classification of epilepsies and epileptic syndromes

<table>
<thead>
<tr>
<th>1. Localization-related (focal, local, partial) epilepsies and syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. <strong>Idiopathic</strong> (listed in order of age of onset)</td>
</tr>
<tr>
<td>1.1.1. Benign childhood epilepsy with centrotemporal spike</td>
</tr>
<tr>
<td>1.1.2. Childhood epilepsy with occipital paroxysms</td>
</tr>
<tr>
<td>1.2. <strong>Symptomatic</strong></td>
</tr>
<tr>
<td>1.3. <strong>Cryptogenic</strong></td>
</tr>
<tr>
<td>2. <strong>Generalized epilepsies and syndromes</strong></td>
</tr>
<tr>
<td>2.1. <strong>Idiopathic</strong> (listed in order of age of onset)</td>
</tr>
<tr>
<td>2.1.1. Benign neonatal familial convulsions</td>
</tr>
<tr>
<td>2.1.2. Benign neonatal convulsions</td>
</tr>
<tr>
<td>2.1.3. Benign myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>2.1.4. Childhood absence epilepsy (pyknolepsy)</td>
</tr>
<tr>
<td>2.1.5. Juvenile absence epilepsy</td>
</tr>
<tr>
<td>2.1.6. Juvenile myoclonic epilepsy (impulsive petit mal)</td>
</tr>
<tr>
<td>2.1.7. Epilepsy with grand mal (generalized tonic-clonic) seizures on awakening</td>
</tr>
<tr>
<td>2.2. <strong>Cryptogenic or symptomatic</strong> (listed in order of age of onset)</td>
</tr>
<tr>
<td>2.2.1. West syndrome (infantile spasms)</td>
</tr>
<tr>
<td>2.2.2. Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>2.2.3. Epilepsy with myoclonic-astatic seizures</td>
</tr>
<tr>
<td>2.2.4. Epilepsy with myoclonic absences</td>
</tr>
<tr>
<td>2.3. <strong>Symptomatic</strong></td>
</tr>
<tr>
<td>2.3.1. Non-specific etiology</td>
</tr>
<tr>
<td>2.3.1.1. Early myoclonic encephalopathy</td>
</tr>
<tr>
<td>2.3.1.2. Early infantile epileptic encephalopathy with suppression burst</td>
</tr>
<tr>
<td>2.3.1.3. Other symptomatic generalized epilepsies not defined above</td>
</tr>
<tr>
<td>2.3.2. Specific syndromes</td>
</tr>
<tr>
<td>2.3.2.1. Epileptic seizures may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature</td>
</tr>
<tr>
<td>2.3.3. Epilepsies and syndromes undetermined whether focal or generalized</td>
</tr>
<tr>
<td>2.3.3.1. With both generalized and focal seizures</td>
</tr>
<tr>
<td>2.3.3.1.1. Neonatal seizures – excluded from G/L</td>
</tr>
<tr>
<td>2.3.3.1.2. Severe myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>2.3.3.1.3. Epilepsy with continuous spike-waves during slow wave sleep</td>
</tr>
<tr>
<td>2.3.3.1.4. Acquired epileptic aphasia (Landau-Kleffner syndrome)</td>
</tr>
<tr>
<td>2.3.3.2. Without unequivocal generalized or focal features</td>
</tr>
</tbody>
</table>

All cases with generalized tonic-clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization related, such as in many cases of sleep-grand mal are considered not to have unequivocal generalized or focal features.

### Special syndromes

- **Febrile convulsions**
- **Isolated seizures or isolated status epilepticus**
- **Seizures occurring only when there is an acute metabolic or toxic event**

---

*Modified from: Commission on Classification and Terminology of the International League Against Epilepsy.*

Proposal for revised classification of epilepsies and epileptic syndromes. Reprinted by permission of the journal *Epilepsia.*

**Idiopathic:** No underlying cause other than a possible hereditary predisposition.

**Symptomatic:** The consequence of a known or suspected disorder of the central nervous system.

**Cryptogenic:** A disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic, but the aetiology is not known.
### Table 9-3: A proposed diagnostic scheme for people with epileptic seizures and with epilepsy

| Axis 1: Ictal phenomenology | from the Glossary of Descriptive Ictal Terminology (Blume, 1991) to describe ictal events with any degree of detail needed. |
| Axis 2: Seizure type | from the List of Epileptic Seizures (Table ) Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate. |
| Axis 3: Syndrome | from the List of Epilepsy Syndromes (Table ), with the understanding that a syndromic diagnosis may not always be possible. |
| Axis 4: Aetiology | from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies (Table ). |
| [Axis 5: Impairment, this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from an impairment classification adapted from the WHO ICIDH-2.] |

*Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology*  
Reprinted by permission of the journal *Epilepsia*
Table 9-4: Axis 2 – Epilepsy seizure types (and precipitating stimuli for reflex seizures)

- **Self-limited seizure types**
  - **Generalized seizures**
    - Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)
    - Clonic seizures
    - Typical absence seizures
    - Atypical absence seizures
    - Myoclonic absence seizures
    - Tonic seizures
    - Spasms
    - Myoclonic seizures
    - Eyelid myoclonia
    - Myoclonic atonic seizures
    - Negative myoclonus
    - Atonic seizures
  - Reflex seizures in generalized epilepsy syndromes
    - Focal seizures
      - Focal sensory seizures
      - Focal motor seizures
      - Gelastic seizures
      - Hemiclonic seizures
      - Secondarily generalized seizures
      - Reflex seizures in focal epilepsy syndromes

- **Continuous seizure types**
  - **Generalized status epilepticus**
    - Generalized tonic-clonic status epilepticus
    - Focal status epilepticus
  - **Precipitating stimuli for reflex seizures**
    - **Visual stimuli**
      - Flickering light - colour to be specified when possible
      - Patterns
      - Other visual stimuli
    - **Thinking**
    - **Music**
    - **Eating**
    - **Praxis**
    - **Somatosensory**
    - **Proprioceptive**
    - **Reading**
    - **Hot water**
    - **Startle**

---

*Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology*[^2]  
Reprinted by permission of the journal *Epilepsia*[^4]
### Table 9-5: Axis 3 – Epilepsy syndromes and related conditions

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benign familial neonatal seizures</td>
</tr>
<tr>
<td>• Early myoclonic encephalopathy</td>
</tr>
<tr>
<td>• Ohtahara syndrome</td>
</tr>
<tr>
<td>• Migrating partial seizures of infancy</td>
</tr>
<tr>
<td>• West syndrome</td>
</tr>
<tr>
<td>• Benign myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>• Benign familial infantile seizures</td>
</tr>
<tr>
<td>• Benign infantile seizures (non-familial)</td>
</tr>
<tr>
<td>• Dravet's syndrome</td>
</tr>
<tr>
<td>• Hemiplegic Hemiatriphy syndrome</td>
</tr>
<tr>
<td>• Myoclonic status in non-progressive encephalopathies</td>
</tr>
<tr>
<td>• Benign childhood epilepsy with centrotemporal spikes</td>
</tr>
<tr>
<td>• Early onset benign childhood occipital epilepsy (Panayiotopoulos type)</td>
</tr>
<tr>
<td>• Late onset childhood occipital epilepsy (Gastaut type)</td>
</tr>
<tr>
<td>• Epilepsy with myoclonic absences</td>
</tr>
<tr>
<td>• Epilepsy with myoclonic-astatic seizures</td>
</tr>
<tr>
<td>• Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>• Landau-Kleffner syndrome</td>
</tr>
<tr>
<td>• Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)</td>
</tr>
<tr>
<td>• Childhood absence epilepsy</td>
</tr>
<tr>
<td>• Progressive myoclonus epilepsies</td>
</tr>
<tr>
<td>• Idiopathic generalized epilepsies with variable phenotypes</td>
</tr>
<tr>
<td>• Juvenile absence epilepsy</td>
</tr>
<tr>
<td>• Juvenile myoclonic epilepsy</td>
</tr>
<tr>
<td>• Epilepsy with generalized tonic-clonic seizures only</td>
</tr>
<tr>
<td>• Reflex epilepsies</td>
</tr>
<tr>
<td>• Idiopathic photosensitive occipital lobe epilepsy</td>
</tr>
<tr>
<td>• Other visual sensitive epilepsies</td>
</tr>
<tr>
<td>• Primary reading epilepsy</td>
</tr>
<tr>
<td>• Startle epilepsy</td>
</tr>
<tr>
<td>• Autosomal dominant nocturnal frontal lobe epilepsy</td>
</tr>
<tr>
<td>• Familial temporal lobe epilepsies</td>
</tr>
<tr>
<td>• Generalized epilepsies with febrile seizures plus</td>
</tr>
<tr>
<td>• Familial focal epilepsy with variable foci</td>
</tr>
<tr>
<td>• Symptomatic (or probably symptomatic) focal epilepsies</td>
</tr>
<tr>
<td>• Limbic epilepsies</td>
</tr>
<tr>
<td>• Mesial temporal lobe epilepsy with hippocampal sclerosis</td>
</tr>
<tr>
<td>• Mesial temporal lobe epilepsy defined by specific aetiologies</td>
</tr>
<tr>
<td>• Other types defined by location and aetiology</td>
</tr>
<tr>
<td>• Neocortical epilepsies</td>
</tr>
<tr>
<td>• Rasmussen syndrome</td>
</tr>
<tr>
<td>• Other types defined by location and aetiology</td>
</tr>
</tbody>
</table>

**CONDITIONS WITH EPILEPTIC SEIZURES THAT DO NOT REQUIRE A DIAGNOSIS OF EPILEPSY**

- Benign neonatal seizures
- Febrile seizures
- Reflex seizures
- Alcohol withdrawal seizures
- Drug or other chemically-induced seizures
- Immediate and early post traumatic seizures
- Single seizures or isolated clusters of seizures
- Rarely repeated seizures (oligo-epilepsy)

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2 Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Reprinted by permission of the journal Epilepsia.
Table 9-6: Axis 4 - Aetiology. Classification of groups of diseases frequently associated with epilepsy seizures or syndromes

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Myoclonic Epilepsies</td>
<td>for example, Ceroid lipofuscinosis</td>
</tr>
<tr>
<td>Neurocutaneous Disorders</td>
<td>for example, Tuberous Sclerosis Complex; Neurofibromatosis</td>
</tr>
<tr>
<td>Malformations Due to Abnormal Cortical Developments</td>
<td></td>
</tr>
<tr>
<td>Other Cerebral Malformations</td>
<td></td>
</tr>
<tr>
<td>Tumours</td>
<td>for example, Gangliocytoma</td>
</tr>
<tr>
<td>Chromosomal Abnormalities</td>
<td>for example, Partial Monosomy 4P or Wolf-Hirschorn Syndrome</td>
</tr>
<tr>
<td>Monogenic Mendelian Diseases with complex Pathogenic Mechanisms</td>
<td>for example, Fragile X Syndrome</td>
</tr>
<tr>
<td>Inherited Metabolic Disorders</td>
<td>for example, Nonketotic Hyperglycinemia</td>
</tr>
<tr>
<td>Prenatal or Perinatal Ischemic or Anoxic Lesions or Cerebral Infections Causing Nonprogressive Encephalopathies</td>
<td>for example, Porencephaly</td>
</tr>
<tr>
<td>Postnatal Infections</td>
<td>for example, Herpes Encephalitis; Bacterial Meningitis</td>
</tr>
<tr>
<td>Other Postnatal Factors</td>
<td>for example, Head Injury; Alcohol and Drugs Abuse; Stroke</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
</tbody>
</table>

Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Reprinted by permission of the journal Epilepsia
**Table 9-7: Definition of key terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Change Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy seizure type</td>
<td>An ictal event believed to represent a unique pathophysiologic mechanism and anatomical substrate. This is a diagnostic entity with aetiologic, therapeutic, and prognostic implications. (new concept)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy syndrome</td>
<td>A complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type: thus frontal lobe seizures per se, for instance, do not constitute a syndrome. (changed concept)</td>
<td></td>
</tr>
<tr>
<td>Epileptic disease</td>
<td>A pathologic condition with a single specific, well-defined etiology. Thus progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundborg is a disease. (new concept)</td>
<td></td>
</tr>
<tr>
<td>Epileptic encephalopathy</td>
<td>A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. (new concept)</td>
<td></td>
</tr>
<tr>
<td>Benign epilepsy syndrome</td>
<td>A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. (clarified concept)</td>
<td></td>
</tr>
<tr>
<td>Reflex epilepsy syndromes</td>
<td>A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that also are associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures also can occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures. (changed concept)</td>
<td></td>
</tr>
<tr>
<td>Focal seizures and syndromes</td>
<td>Replaces the terms partial seizures and localization-related syndromes. (changed terms)</td>
<td></td>
</tr>
<tr>
<td>Simple and complex partial epileptic seizures</td>
<td>These terms are no longer recommended, nor will they be replaced. Ictal impairment of consciousness will be described when appropriate for individual seizures, but will not be used to classify specific seizure types. (new concept)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic epilepsy syndrome</td>
<td>A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurologic signs or symptoms. These are presumed to be genetic and are usually age-dependent. (unchanged term)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic epilepsy syndrome</td>
<td>A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. (unchanged term)</td>
<td></td>
</tr>
<tr>
<td>Probably symptomatic epilepsy syndrome</td>
<td>Synonymous with, but preferred to, the term cryptogenic; used to define syndromes that are believed to be symptomatic, but no aetiology has been identified. (new term)</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology*
9.3 What is the role of classification in adults and children with epilepsy?

This KCQ was not subject to a full evidence review for reasons set out in chapter 2.

The example presented below shows the importance of correct diagnosis and classification in juvenile myoclonic epilepsy (JME).

Delgado-Escueta 1984

In one study, 43 individuals, aged 15 to 69 years, were referred for uncontrolled convulsive seizures. After the diagnosis of JME was established, 86% were either seizure-free or satisfactorily controlled on valproate alone, or with other AEDs.

Grunewald 1992

In a London-based case series, 15 definite cases of JME were identified from 180 consecutive referrals to an epilepsy clinic. Diagnoses on referral were usually vague and non-syndromic. In many cases, the syndromic features were accurately recorded in the notes, but the referring physician appeared to be unaware of JME and a correct diagnosis not made. Following the diagnosis of JME and optimisation of drug treatments, myoclonic jerks improved or disappeared in 13 of the 15 individuals. The authors suggested that a syndromic classification should be recorded for all people with epilepsy, and this should be regularly reviewed particularly if seizures are poorly controlled.

Montalenti 2001

Montalenti and colleagues found that only 31.3% of individuals (n=20/63) were correctly diagnosed on referral to the Epilepsy Service. The remainder were either classified as having idiopathic generalised epilepsy (n=10), or diagnosed as having partial epilepsy, or were not classified (n=33). The most frequent reason for misdiagnosis was an underestimation or misinterpretation of myoclonic jerks by both the individual or the referring physician, suggesting that the correct diagnosis is dependent on the knowledge of the physician.

This has also been identified in other studies. Another factor associated with misdiagnosis was a failure to seek a history of myoclonic jerks, again associated with the knowledge of the referring physician of the syndrome.

9
10 Pharmacological treatment of epilepsy

10.1 Introduction

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) taken daily to prevent the recurrence of epileptic seizures. It is important that the treatment strategy and suitability of the AED is determined by the prescriber, in collaboration with the individual with epilepsy and/or carer, before drug therapy is commenced. Factors determining suitability include: type of seizure and/or epilepsy syndrome; childbearing potential; the presence of co-morbidity; individual and/or carer preferences; the presence of contraindications to the drug; potential interactions with other drugs; potential adverse effects and the licensed indication of the drug.

This chapter first considers the most appropriate therapy for particular seizure types and epilepsy syndromes and the treatment is presented both by drug and by epilepsy syndrome. It is also noted whether the evidence base refers to the use of a single AED in an individual with epilepsy (monotherapy) or whether more than one AED is used in combination (adjunctive therapy).

The next section considers, in turn, the questions of when should AED therapy be started and when it should it be discontinued. The issue of monitoring AED blood levels and the use of other blood tests is also considered.

Pharmacological treatment of epilepsy

**Adults and children:**

The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the individual’s lifestyle, and the preferences of the individual and their family and/or carers as appropriate (see Appendix E). [2004]

The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first-line AED. [2004]

Changing the formulation or brand of AED is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects. [2004]

10.2 Monotherapy for newly diagnosed Focal Seizures

10.2.1 Introduction

Focal seizures are the most commonly encountered seizure type in adult and paediatric practice. Focal seizures are by definition those that originate in one area of the brain. The most recent proposal of a classification of the epilepsies by the ILAE suggest that focal seizures originate within networks limited to one hemisphere, for each seizure type ictal onset is consistent with preferential propagation patterns which can involve the contralateral hemisphere, and in some cases where there is more than one seizure type each has a consistent site of onset (Berg et al 2010) 13. The seizures are then described according to severity (eg with or without impairment of consciousness, or whether they proceed to a bilateral convulsive seizure) and possible site of origin.

When individuals first present, aims of treatment should be seizure freedom with one medication. The term monotherapy here refers to the use of one initial drug with no previous trial of such.
10.2.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence review. For this review we included adults and children with focal seizures. For studies in which both partial and primary generalized seizures were combined, a 20% threshold was used as a threshold for “contamination” for the outcome of seizure freedom and a 50% threshold for the outcomes of adverse events.

10.2.3 Matrix of the evidence for adults

We searched for RCTs comparing the effectiveness of different monotherapy pharmacological interventions for epilepsy in a population with focal seizures. The interventions we included in our search were pregabalin, zonisamide, lacosamide, lamotrigine, gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbitone, felbamate, clobazam, clonazepam, acetazolamide, primidone, sodium valproate, sulphiamide and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
10.2.4 Monotherapy for adults with newly diagnosed focal seizures

10.2.4.1 Carbamazepine versus lamotrigine

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N.

Network meta-analysis

Carbamazepine and lamotrigine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The results of this analysis are presented in section 10.2.5.

Health economic evidence

Two economic evaluations of AEDs, including carbamazepine and lamotrigine, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, we developed an original economic model to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The results of these studies and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking carbamazepine were seizure free compared to participants taking lamotrigine, however there is uncertainty over the clinical importance of this effect. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of participants achieving seizure freedom. (NCGC network meta-analysis)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of participants withdrew due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants taking carbamazepine withdrew due to adverse events compared to participants taking lamotrigine. (VERY LOW QUALITY)

Significantly more participants taking carbamazepine withdrew due to adverse events compared to participants taking lamotrigine. (NCGC network meta-analysis)

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more rapidly on participants taking carbamazepine compared to participants taking lamotrigine. (VERY LOW QUALITY)

Health Related Quality of Life outcomes – statistically non-significant results

No significant difference was found on the mean scores of quality of life between lamotrigine and carbamazepine.

Cost-effectiveness

One economic evaluation conducted alongside a randomised controlled trial showed lamotrigine to be cost-effective compared to carbamazepine (directly applicable and potentially serious limitations). One economic evaluation based on a decision analytic model showed lamotrigine to be more costly and less effective than carbamazepine (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:
- time to first seizure
- incidence of adverse events
- cognitive outcomes

10.2.4.2 Lamotrigine versus phenytoin

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Lamotrigine and phenytoin were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence

No studies were identified in the economic literature search. Lamotrigine was included in the original economic model developed to compare AEDs used as monotherapy in newly diagnosed adult patients, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the proportion of participants having treatment withdrawn due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to first seizure. (VERY LOW QUALITY)
Adverse events – statistically significant results

1. Significantly less participants taking lamotrigine monotherapy had an incidence of somnolence compared to participants in phenytoin monotherapy (VERY LOW QUALITY)

2. Significantly more participants taking phenytoin monotherapy had an incidence of ataxia compared to participants in lamotrigine monotherapy (VERY LOW QUALITY)

Adverse events – statistically non-significant results

3. No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the incidence of the following adverse events:
   - asthenia (VERY LOW QUALITY)
   - rash (VERY LOW QUALITY)
   - headache (VERY LOW QUALITY)
   - dizziness (VERY LOW QUALITY)

Health related quality of life outcomes – statistically significant results

4. Significantly more participants in lamotrigine had improvement in the overall score of SEALS compared to phenytoin in 24 weeks treatment (VERY LOW QUALITY)

Cost-effectiveness

5. No economic evidence comparing lamotrigine monotherapy to phenytoin monotherapy was identified.

Outcomes with no evidence

6. There were no studies that reported:
   - withdrawal due to adverse events
   - time to exit/withdrawal of allocated treatment
   - cognitive outcomes

10.2.4.3 Lamotrigine versus sodium valproate

Direct clinical evidence

7. For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

8. Lamotrigine and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence

9. One economic evaluation of AEDs, including lamotrigine and sodium valproate, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The
complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

**Evidence statements**

**Adverse events – statistically significant results**

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

Significantly less participants taking lamotrigine monotherapy had an incidence of tremor compared to participants in sodium valproate monotherapy. (LOW QUALITY)

Significantly less participants taking lamotrigine monotherapy had an incidence of alopecia compared to participants in sodium valproate monotherapy. (LOW QUALITY)

**Adverse events – statistically non-significant results**

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the incidence of the following adverse events:

- dizziness (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- blurred vision (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

**Cost-effectiveness**

Two economic evaluations based on decision analytic models showed lamotrigine to be more costly and less effective than sodium valproate. Both studies were directly applicable, but one had minor limitations and the other had potentially serious limitations.

**Outcomes with no evidence**

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.2.4.4 Levetiracetam versus controlled release Carbamazepine

**Direct clinical evidence**

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Network meta-analysis**

Levetiracetam and controlled release carbamazepine were not among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy as they
did not connect to the network of evidence at any point. For detail on the criteria for inclusion in the network meta-analysis, see appendix O.

Health Economic Evidence

No studies were identified in the economic literature search. As this left a gap in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5) and the results of Brodie 2007. The complete results of the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically significant results
Significantly more participants in levetiracetam monotherapy withdrew due to lack of efficacy compared to carbamazepine monotherapy (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between levetiracetam monotherapy and carbamazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)
No significant difference between levetiracetam monotherapy and carbamazepine monotherapy for the withdrawal due to adverse events. (VERY LOW QUALITY)

Adverse events – statistically non-significant
No significant difference between levetiracetam monotherapy and carbamazepine monotherapy for the incidence of:

- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed levetiracetam to be more costly and less effective than controlled release carbamazepine. The study was directly applicable and had potentially serious limitations for this comparison.

Outcomes with no evidence
There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.2.4.5 Carbamazepine versus gabapentin

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis
Carbamazepine and gabapentin were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
One economic evaluation of AEDs, including carbamazepine and gabapentin, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements
Efficacy - statistically significant results
Significantly more patients taking carbamazepine monotherapy were seizure free compared to gabapentin monotherapy. (LOW QUALITY)
Significantly fewer patients withdrew due to lack of efficacy with carbamazepine monotherapy compared to gabapentin monotherapy. (LOW QUALITY)
Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly more rapidly on participants taking gabapentin monotherapy compared to participants taking carbamazepine monotherapy. (LOW QUALITY)

Efficacy - non-statistically significant results
No significant difference between carbamazepine monotherapy and gabapentin monotherapy for the proportion of participants achieving seizure freedom. (NCGC network meta-analysis)

Adverse events - statistically significant results
Significantly fewer patients withdrew due to adverse events with gabapentin monotherapy compared to carbamazepine monotherapy. (LOW QUALITY)
Significantly fewer patients withdrew due to adverse events with gabapentin monotherapy compared to carbamazepine monotherapy. (NCGC network meta-analysis)
Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly less rapidly on participants taking gabapentin monotherapy compared to participants taking carbamazepine monotherapy. (LOW QUALITY)

Cost-effectiveness
Two economic evaluations, one conducted alongside a randomised controlled trial and one based on a decision analytic model, showed gabapentin to be more costly and less effective than carbamazepine. Both studies were directly applicable, but one had potentially serious limitations and the other had minor limitations.

Outcomes with no evidence
There were no studies that reported:
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes
10.2.4.6 Vigabatrin versus carbamazepine

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Vigabatrin and carbamazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in newly diagnosed adult patients, but vigabatrin was not. Vigabatrin was excluded owing to its potential for long term adverse effects.

Evidence statements

Efficacy- statistically significant results
Significantly fewer patients withdrew due to lack of efficacy with carbamazepine monotherapy than vigbatrin monotherapy. (MODERATE QUALITY)
Carbamazepine monotherapy is significantly more effective than vigabatrin monotherapy in prolonging time to first seizure. (MODERATE QUALITY)

Efficacy – statistically non-significant results
No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)
No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the proportion of seizure free participants. (NCGC network meta-analysis)
No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for time to exit/withdrawal of allocated treatment. (VERY LOW QUALITY)

Adverse events- statistically significant results
Significantly more participants in carbamazepine monotherapy compared to vigabatrin monotherapy withdrew due to adverse events, however there is uncertainty over the magnitude of the clinical effect. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the proportion of patients withdrawing due to adverse events (NCGC network meta-analysis)
There was no significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the incidence of the following adverse events:
- drowsiness (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- appendages (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
Cost-effectiveness

No economic evidence comparing vigabatrin and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- cognitive outcomes
- quality of life outcomes.

10.2.4.7 Clonazepam versus carbamazepine

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Clonazepam and carbamazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. As the only data available for clonazepam compared to carbamazepine concerned withdrawal due to adverse events, this comparison was only included in the network assessing AEDs on that outcome. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence

No studies were identified in the economic literature search and clonazapem was not included in the NCGC adults monotherapy model due to the lack of efficacy data reported in the trial.

Evidence statements

Adverse events – statistically non-significant results

No significant difference between clonazepam monotherapy and carbamazepine monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

No significant difference between clonazepam monotherapy and carbamazepine monotherapy for the proportion of participants withdrawing due to adverse events. (NCGC network meta-analysis)

Cost-effectiveness

No economic evidence comparing clonazepam and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes
10.2.4.8 Oxcarbazepine versus phenytoin

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Oxcarbazepine and phenytoin were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
No studies were identified in the economic literature search. Oxcarbazepine was included in the original economic model developed to compare AEDs used as monotherapy in newly diagnosed adult patients, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Adverse effects – statistically significant results
Significantly fewer participants in oxcarbazepine withdrew due to adverse events compared to participants in phenytoin. (LOW QUALITY)

Cost-effectiveness
No economic evidence comparing oxcarbazepine and phenytoin was identified.

Outcomes with no evidence
There were no studies that reported:
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• cognitive outcomes
• quality of life outcomes

10.2.4.9 Oxcarbazepine versus sodium valproate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Oxcarbazepine and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.
Health Economic Evidence

One economic evaluation of AEDs, including oxcarbazepine and sodium valproate, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

**Efficacy – statistically non-significant results**
No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

**Adverse events – statistically non-significant results**
No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

**Cost-effectiveness**
Two economic evaluations, both based on decision analytic models, showed oxcarbazepine not to be cost-effective compared to sodium valproate. One showed oxcarbazepine to be more costly and less effective than sodium valproate (directly applicable and minor limitations) and the other showed oxcarbazepine to be more costly and more effective, but with an unacceptably high incremental cost-effectiveness ratio (>£150,000 per QALY) (directly applicable and potentially serious limitations).

**Outcomes with no evidence**
There were no studies that reported:
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.4.10 Carbamazepine versus phenytoin

**Direct clinical evidence**
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Network meta-analysis**
Carbamazepine and phenytoin were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

**Health Economic Evidence**
No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in newly diagnosed epilepsy.
adult patients, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic
window.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between carbamazepine monotherapy and phenytoin monotherapy for
the proportion of seizure-free participants. (NCGC network meta-analysis)

Adverse effects – statistically non-significant results
No significant difference between carbamazepine monotherapy and phenytoin monotherapy for
the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)
No significant difference between carbamazepine monotherapy and phenytoin monotherapy for
the proportion of participants withdrawing due to adverse events. (NCGC network meta-analysis)

Cost-effectiveness
No economic evidence comparing carbamazepine and phenytoin was identified.

Cognitive outcomes – statistically non-significant results
No significant difference between carbamazepine monotherapy and phenytoin monotherapy for
any of the cognitive outcomes:

- digit symbol
- digit span forward
- digit span backward
- Consistent Long Term Retrieval Score
- Finger Tap
- Grooved Pegboard
- Choice Reaction Time
- P3 latency
- P3 amplitude

Outcomes with no evidence
There were no studies that reported:
- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

Updated 2011
10.2.4.11 Carbamazepine versus sodium valproate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Carbamazepine and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
One economic evaluation of AEDs, including carbamazepine and sodium valproate, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (NCGC network meta-analysis)

Adverse effects – statistically non-significant results
No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawing due to adverse events. (NCGC network meta-analysis)

Cognitive outcomes – statistically non-significant results
No significant differences between carbamazepine and sodium valproate for any of the following cognitive outcomes: motor, speed and integration, memory, concentration and mental flexibility after 6 months of treatment.

Cost-effectiveness
Two economic evaluations, both based on decision analytic models, showed sodium valproate to be cost-effective compared to carbamazepine. One study showed sodium valproate to be more costly and more effective with an incremental cost-effectiveness ratio of £11,731 (directly applicable and potentially serious limitations) and the other study showed sodium valproate to be less costly and more effective than carbamazepine (directly applicable and minor limitations).
Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- quality of life outcomes

10.2.4.12 Sodium valproate versus phenytoin

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Sodium valproate and phenytoin were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence

No studies were identified in the economic literature search. Sodium valproate was included in the original economic model developed to compare AEDs used as monotherapy in newly diagnosed adult patients, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Adverse effects – statistically non-significant results

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate and phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes
10.2.4.13 Carbamazepine versus topiramate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Carbamazepine and topiramate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
Two economic evaluations of AEDs, including carbamazepine and topiramate, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically significant results
Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly more rapidly on topiramate monotherapy compared to carbamazepine monotherapy, however there is uncertainty over the clinical magnitude of its effect. (VERY LOW QUALITY)

Efficacy – statistically non significant results
No significant difference between carbamazepine monotherapy and topiramate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Adverse events – statistically non significant results
No significant difference between carbamazepine monotherapy and topiramate monotherapy for the proportion of seizure-free participants. (NCGC network meta-analysis)

Cost-effectiveness
One economic evaluation conducted alongside a randomised controlled trial showed that topiramate was likely to be cost-effective compared to carbamazepine, but that topiramate was more costly and less effective than oxcarbazepine (directly applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed topiramate to be more costly and more effective with an unacceptably high incremental cost-effectiveness ratio (£89,736 per QALY) (directly applicable and potentially serious limitations).

One economic evaluation based on decision analytic model showed topiramate to be more costly and less effective than carbamazepine (directly applicable and minor limitations).
Outcomes with no evidence
There were no studies that reported:
• withdrawal due to lack of efficacy
• time to first seizure
• incidence of adverse events
• cognitive outcomes
• quality of life outcomes

10.2.4.14 Topiramate versus sodium valproate

Direct Clinical Evidence
No direct clinical evidence was identified.

Network meta-analysis
Topiramate and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
One economic evaluation of AEDs, including topiramate and sodium valproate, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Cost-effectiveness
Two economic evaluations, both based on decision analytic models, showed topiramate not to be cost-effective compared to sodium valproate. One study showed topiramate to be more costly and less effective than sodium valproate (directly applicable and minor limitations) and another study showed topiramate to be more costly and more effective than sodium valproate but with an unacceptably high incremental cost-effectiveness ratio (£126,519 per QALY) (directly applicable and potentially serious limitations).

10.2.4.15 Carbamazepine versus oxcarbazepine

Direct Clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Carbamazepine and oxcarbazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
Two economic evaluations of AEDs, including carbamazepine and oxcarbazepine, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients.
Evidence statements

Efficacy – statistically non-significant results
No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for proportion of seizure-free participants. (VERY LOW QUALITY)
No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for proportion of seizure-free participants (NCGC network meta-analysis).
No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

Adverse effects – statistically non-significant results
No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)
No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for proportion of participants withdrawing due to adverse events (NCGC network meta-analysis).

Cost-effectiveness
One economic evaluation conducted alongside a randomised controlled trial showed oxcarbazepine to be cost-effective compared to carbamazepine, with an incremental cost-effectiveness ratio of £6,200 per QALY (directly applicable and potentially serious limitations).
Two economic evaluations, both based on decision analytic models, showed oxcarbazepine unlikely to be cost-effective compared to carbamazepine. Both studies showed oxcarbazepine to be more costly and more effective than carbamazepine but with an unacceptably high incremental cost-effectiveness ratio: £64,615 in one study (directly applicable and minor limitations) and £81,130 in the other (directly applicable and potentially serious limitations).

Outcomes with no evidence
There were no studies that reported:
- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.4.16 Gabapentin versus lamotrigine

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Gabapentin and lamotrigine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.
Health Economic Evidence
One economic evaluation of AEDs, including gabapentin and lamotrigine, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

**Efficacy – statistically significant results**

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less rapidly on participants taking lamotrigine monotherapy compared to participants taking gabapentin monotherapy. (LOW QUALITY)

**Efficacy – statistically non-significant results**

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

**Adverse effects – statistically non-significant results**

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

**Cost-effectiveness**

Two economic evaluations, one conducted alongside a randomised controlled trial and one based on a decision analytic model, showed gabapentin to be more costly and less effective than lamotrigine. Both studies were directly applicable, but one had potentially serious limitations and the other had minor limitations.

**Outcomes with no evidence**

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.4.17 Gabapentin versus topiramate

**Direct clinical evidence**

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Network meta-analysis**

Gabapentin and topiramate were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

**Health Economic Evidence**

One economic evaluation of AEDs, including gabapentin and topiramate, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed.
to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on
clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this
study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically significant results
Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less
rapidly on participants taking topiramate monotherapy compared to participants taking
gabapentin monotherapy. (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between gabapentin monotherapy and topiramate monotherapy for the
proportion of seizure free participants. (VERY LOW QUALITY)

Adverse effects – statistically significant results
Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more
rapidly on participants taking topiramate monotherapy compared to participants taking
gabapentin monotherapy. (LOW QUALITY)

Adverse effects – statistically non-significant results
No significant difference between gabapentin monotherapy and topiramate monotherapy for the
proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation conducted alongside a randomised controlled trial showed gabapentin to
be more costly and less effective than topiramate (directly applicable and potentially serious
limitations).

One economic evaluation based on a decision analytic model showed topiramate to be more costly
and more effective than gabapentin, with an incremental cost-effectiveness ratio of £13,457 per
QALY. However, in this analysis, both topiramate and gabapentin were more costly and less
effective than sodium valproate and carbamazepine (directly applicable and minor limitations).

Outcomes with no evidence
There were no studies that reported:
- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.4.18 Lamotrigine versus topiramate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper
identified in the literature search please refer to Appendix L.

Network meta-analysis
Lamotrigine and topiramate were among AEDs included in a network meta-analysis of AEDs used
as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis
are presented in section 10.2.5.
Health Economic Evidence

Two economic evaluations \(^{134,150}\) of AEDs, including lamotrigine and topiramate, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically non significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and topiramate monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

Adverse effects – statistically significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more rapidly on participants taking topiramate monotherapy compared to participants taking lamotrigine monotherapy. (LOW QUALITY)

Cost-effectiveness

One economic evaluation conducted alongside a randomised controlled trial showed lamotrigine to be more costly and more effective than topiramate with an incremental cost-effectiveness ratio of £6,727 per QALY (directly applicable and potentially serious limitations). However, both topiramate and lamotrigine were more costly and less effective than oxcarbazepine in this analysis and the unit cost of lamotrigine has come down considerably since the analysis was undertaken.

Two economic evaluations based on decision analytic models showed topiramate unlikely to be cost-effective compared to lamotrigine, with high incremental cost-effectiveness ratios of £35,521 per QALY and £240,571 per QALY, respectively. Both studies were directly applicable, but one has potentially serious limitations and the other minor limitations.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.4.19 Gabapentin versus oxcarbazepine

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis
Gabapentin and oxcarbazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence
One economic evaluation of AEDs, including oxcarbazepine and gabapentin, used as monotherapy in the treatment of newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of this study and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically significant results
Significantly more participant taking oxcarbazepine monotherapy compared to participants taking gabapentin monotherapy were seizure free. (LOW QUALITY)
Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less rapidly on participants taking oxcarbazepine monotherapy compared to participants taking gabapentin monotherapy. (LOW QUALITY)

Adverse effects – statistically non-significant results
No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)
No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation conducted alongside a randomised controlled trial showed gabapentin to be more costly and less effective than oxcarbazepine (directly applicable and potentially serious limitations).
One economic evaluation based on a decision analytic model showed oxcarbazepine to be more costly and more effective than gabapentin with an incremental cost-effectiveness ratio of £3,207 per QALY. However, in this analysis, neither gabapentin nor oxcarbazepine are cost-effective compared to sodium valproate or carbamazepine (directly applicable and minor limitations).

Outcomes with no evidence
There were no studies that reported:
• withdrawal due to lack of efficacy
• time to first seizure
• incidence of adverse events
• cognitive outcomes
• quality of life outcomes

10.2.4.20 Lamotrigine versus oxcarbazepine

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
**Network meta-analysis**

Lamotrigine and oxcarbazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

**Health Economic Evidence**

Two economic evaluations \(^{134,150}\) of AEDs, including lamotrigine and oxcarbazepine, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.2.6.

**Evidence statements**

**Efficacy – statistically non-significant results**

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

**Adverse effects – statistically non-significant results**

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

**Cost-effectiveness**

Three economic evaluations, one conducted alongside a randomised controlled trial and two based on decision analytic models, showed oxcarbazepine to be cost-effective compared to lamotrigine. In one study, oxcarbazepine is less costly and more effective than lamotrigine (directly applicable and potentially serious limitations). In the other two studies, oxcarbazepine is more costly and more effective than lamotrigine with incremental cost-effectiveness ratios of £4,879 per QALY and £13,474 per QALY, respectively. Both of these two studies are directly applicable, but one has potentially serious limitations and the other minor limitations.

**Outcomes with no evidence**

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

**10.2.4.21 Topiramate versus oxcarbazepine**

**Direct clinical evidence**

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis

Topiramate and oxcarbazepine were among AEDs included in a network meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal epilepsy. The complete results of this analysis are presented in section 10.2.5.

Health Economic Evidence

Two economic evaluations of AEDs, including topiramate and oxcarbazepine, used as monotherapy in the treatment of newly diagnosed focal epilepsy were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed adult patients. This was based on clinical evidence from the network meta-analysis (see section 10.2.5). The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.2.6.

Evidence statements

Efficacy – statistically non-significant results

- No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)
- No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

Adverse effects – statistically non-significant results

- No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)
- No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

Three economic evaluations, one conducted alongside a randomised controlled trial and two based on decision analytic models, showed topiramate not to be cost-effective compared to oxcarbazepine. In two studies, oxcarbazepine is less costly and more effective than topiramate. Both of these two studies are directly applicable, but one has potentially serious limitations and the other minor limitations. In the other study, topiramate is more costly and more effective than oxcarbazepine with an unacceptably high incremental cost-effectiveness ratio of £102,933 per QALY (directly applicable and potentially serious limitations).

Outcomes with no evidence

- withdrawal due to lack of efficacy
- time to first seizure
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.5 Network meta-analysis of AEDs used as monotherapy for focal epilepsy

Our analyses were based on a total of 12 studies, randomised to nine different interventions used as monotherapy treatment. These studies formed the first two networks of evidence; proportion of participants achieving seizure freedom and proportion of participants withdrawn due to adverse events. For details on these networks, please see pages 24-32 of Appendix 0. The baseline risk for
these two networks was calculated by aggregating the number of people achieving seizure freedom or withdrawing due to adverse events across the carbamazepine arms of the studies included in the monotherapy networks and dividing by the aggregate sample size from the same arms. Thus, carbamazepine was assigned the position of baseline drug (control group), as carbamazepine is the standard AED for monotherapy in newly diagnosed focal seizures.

The results of the network meta-analysis for newly diagnosed focal seizures showed that no single AED in monotherapy is significantly more effective in achieving seizure freedom compared to carbamazepine. However, based on point estimates, distribution of rank and proportion of simulations in which they are the most effective AEDs in monotherapy, valproate and phenytoin were the most effective AEDs in achieving seizure freedom with a probability of 38.5% and 33.9% respectively. The results from the second network showed that gabapentin and lamotrigine were the most tolerable AEDs with a probability of 39.6% and 26.3% respectively.

For detailed explanation on methodology and results of NMA refer to Appendix O.

10.2.6 Health economic evidence of AEDs used as monotherapy for adults with newly diagnosed focal epilepsy

2 studies\textsuperscript{134,150} assessing the cost-effectiveness of AEDs used as monotherapy were included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability. Following the review of the clinical and cost-effectiveness literature, it was considered that most AEDs were broadly similar in their efficacy, but evidence of their cost-effectiveness was limited and, at times, conflicting. Given these limitations in the evidence base, an original economic model was developed to compare AEDs used as first-line monotherapy in adults with newly diagnosed focal epilepsy. This was based on evidence from the network meta-analysis (see section 10.2.5) and clinical review detailed above. See appendix P for full details and results of modelling.
### Economic study characteristics

Table 10-1: Monotherapy for adults with newly diagnosed focal epilepsy - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC Model - adult monotherapy (see Appendix P for details)</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; comparators included carbamazepine, carbamazepine controlled release, oxcarbazepine, sodium valproate, lamotrigine, topiramate and levetiracetam; time horizon 15 years; clinical data based on NCGC network meta-analysis and Brodie 2007 (see appendix P for details)</td>
</tr>
<tr>
<td>Marson (2007) – after June 2001&lt;sup&gt;134&lt;/sup&gt;</td>
<td>Potentially serious limitations (a, b)</td>
<td>Directly applicable</td>
<td>Economic evaluation alongside randomised controlled trial; other comparators included carbamazepine, lamotrigine, gabapentin, topiramate and oxcarbazepine; 2-year time horizon; includes data collected after June 2001 when oxcarbazepine was introduced</td>
</tr>
<tr>
<td>Marson (2007) – after June 2001&lt;sup&gt;134&lt;/sup&gt;</td>
<td>Potentially serious limitations (a, b)</td>
<td>Partially applicable (c)</td>
<td>Economic evaluation alongside randomised controlled trial; other comparators included carbamazepine, lamotrigine, gabapentin, topiramate and oxcarbazepine; 2-year time horizon; no NICE threshold for cost per seizure avoided; includes data collected after June 2001 when oxcarbazepine was introduced</td>
</tr>
<tr>
<td>Hawkins (2005)&lt;sup&gt;150&lt;/sup&gt;</td>
<td>Potentially serious limitations (a, d)</td>
<td>Partially applicable (e)</td>
<td>Decision analytic model; comparators included carbamazepine, oxcarbazepine, sodium valproate, lamotrigine and topiramate; time horizon 15 years; clinical data based on network meta-analysis that included several studies with mixed focal and generalised epilepsy populations</td>
</tr>
</tbody>
</table>

(a) Unit costs of interventions are from 2002/03 (in Hawkins) and 2005 (in Marson) and since publication, lamotrigine has come off patent and the non-proprietary price is dramatically lower

(b) Responders to EQ-5D questionnaires at 2 year follow-up were ‘healthier’ than non-responders

(c) Analysis based on seizures avoided, not QALYs
(d) Effectiveness data was derived from a network meta-analysis that included at least two unblinded studies that have not been included in the NCGC clinical review (Nieto Barrera 2001; Beunanen 1996).

(e) Costs and effects discounted at 6% and 1.5% per annum, respectively.

**Economic study results**

**NCGC Model – adult monotherapy (directly applicable, minor limitations)**

For full details of base case and all sensitivity analyses, see appendix P.

**Table 10-2: Monotherapy for adults with newly diagnosed focal epilepsy – Results of NCGC model**

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>£7,971</td>
<td>8.018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>£9,338</td>
<td>7.882</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>£9,898</td>
<td>7.843</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>£10,169</td>
<td>7.745</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>£10,666</td>
<td>7.900</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>£11,582</td>
<td>7.850</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>LEV</td>
<td>£12,112</td>
<td>7.877</td>
<td>Dominated</td>
<td></td>
</tr>
</tbody>
</table>
Evidence statements

1 Sodium valproate is the most effective and least cost among AEDs evaluated as monotherapy (directly applicable and minor limitations).

2 Carbamazepine (normal or controlled-release preparations) is likely to be cost-effective if sodium valproate is contraindicated (directly applicable and minor limitations).

3 Lamotrigine and oxcarbazepine may be cost-effective if sodium valproate is contraindicated (directly applicable and minor limitations).

4 Gabapentin, levetiracetam and topiramate are not cost-effective compared to alternative AEDs evaluated as monotherapy (directly applicable and minor limitations).

5 Gabapentin, levetiracetam and topiramate may be cost-effective if carbamazepine, lamotrigine, oxcarbazepine and sodium valproate are all contraindicated (directly applicable and minor limitations). In this situation, levetiracetam is the most cost-effective of the three AEDs given a threshold willingness to pay of £20,000 per QALY.

Marson 2007\textsuperscript{134} (directly applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Table 10-3: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Marson 2007\textsuperscript{134}

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>£1,095</td>
<td>1.491</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective compared to: OXC: 17% TPM: 42% LTG: 41% GBP: 86%</td>
</tr>
<tr>
<td>OXC</td>
<td>£1,839</td>
<td>1.611</td>
<td>£6,200</td>
<td>At £20K per QALY threshold, 83% probability most cost-effective compared to CBZ</td>
</tr>
<tr>
<td>TPM</td>
<td>£1,930</td>
<td>1.541</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, 58% probability most cost-effective compared to CBZ</td>
</tr>
<tr>
<td>LTG</td>
<td>£2,078 (a)</td>
<td>1.563</td>
<td>Dominated (b)</td>
<td>At £20K per QALY threshold, 59% probability most cost-effective compared to CBZ</td>
</tr>
<tr>
<td>GBP</td>
<td>£2,573</td>
<td>1.480</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, 14% probability most cost-effective compared to</td>
</tr>
</tbody>
</table>
Evidence statements

Oxcarbazepine is the most cost-effective AED evaluated as monotherapy, less costly and more
effective than gabapentin, lamotrigine and topiramate (directly applicable and potentially serious
limitations).

Carbamazepine is the least cost and second least effective AED evaluated as monotherapy
(directly applicable and potentially serious limitations).

Gabapentin is the most costly and least effective AED evaluated as monotherapy (directly
applicable and potentially serious limitations).

Lamotrigine and topiramate are more costly and less effective than oxcarbazepine (directly
applicable and potentially serious limitations).

When oxcarbazepine was excluded from the analysis in order to use data from the entire trial
period, lamotrigine was the most cost-effective AED evaluated as monotherapy. Also, it is likely
that if current costs of lamotrigine were used, it would be cost-effective compared to alternative
AEDs evaluated as monotherapy.

Marson 2007 134 (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Drug cost of LTG has decreased significantly since this evaluation was undertaken.
In analysis of entire trial period and thus excluding oxcarbazepine from analysis, LTG is cost-effective compared
to CBZ (£11,851 per QALY)

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Updated 2011
### Table 10-4: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Marson 2007

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (seizures)</th>
<th>ICER (£ / seizure avoided) (a)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>£1,151</td>
<td>50.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>£1,815</td>
<td>32.0</td>
<td>£35</td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>£2,059</td>
<td>59.4</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>£1,946 (b)</td>
<td>50.9</td>
<td>Dominated (c)</td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>£2,594</td>
<td>85.3</td>
<td>Dominated</td>
<td></td>
</tr>
</tbody>
</table>

At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to:
- OXC: 15%, 10%, 10%, 9%
- TPM: 73%, 67%, 65%, 63%
- LTG: 59%, 52%, 50%, 48%
- GBP: 95%, 92%, 90%, 90%

At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ:
- OXC: 85%, 90%, 90%, 91%
- TPM: 27%, 33%, 35%, 37%
- LTG: 41%, 48%, 50%, 52%

At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ:
- OXC: 85%, 90%, 90%, 91%
- GBP: 5%, 8%, 10%, 10%

(a) No willingness to pay threshold for seizures avoided exists.
(b) Drug cost of LTG has decreased significantly since this evaluation was undertaken.
(c) In analysis of entire trial period and thus excluding oxcarbazepine from analysis, LTG may be cost-effective compared to CBZ (£80 per seizure avoided)

### Evidence statements

Oxcarbazepine is more costly and more effective in terms of total seizures experienced than carbamazepine, with each additional seizure avoided costing £35 (partially applicable and potentially serious limitations). Without an explicit willingness to pay per seizure avoided threshold, it is indeterminable as to whether oxcarbazepine would be considered cost-effective compared to carbamazepine.

Patients taking gabapentin, lamotrigine and topiramate experienced more total seizures and incurred higher costs than patients taking carbamazepine, indicating that these AEDs may not be cost-effective (partially applicable and potentially serious limitations).

Hawkins 2005\(^{150}\) (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.
Table 10-5: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Hawkins 2005

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>£4,428</td>
<td>9.392</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 42%</td>
</tr>
<tr>
<td>VPA</td>
<td>£4,572</td>
<td>9.404</td>
<td>£11,731</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 46%</td>
</tr>
<tr>
<td>LTG</td>
<td>£6,133 (a)</td>
<td>9.382</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 0%</td>
</tr>
<tr>
<td>OXC</td>
<td>£6,294</td>
<td>9.415</td>
<td>£117,519</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 12%</td>
</tr>
<tr>
<td>TPM</td>
<td>£7,838</td>
<td>9.430</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 0%</td>
</tr>
</tbody>
</table>

(a) Drug cost of LTG has decreased significantly since this evaluation was undertaken.

Evidence statements

Sodium valproate is the most cost-effective AED evaluated as monotherapy given a threshold willingness to pay of £20,000 per QALY (partially applicable and potentially serious limitations).

Lamotrigine was the least effective among AEDs evaluated as monotherapy and was more costly than carbamazepine and sodium valproate (partially applicable and potentially serious limitations).

Oxcarbazepine and topiramate are not cost-effective compared to alternative AEDs evaluated as monotherapy (partially applicable and potentially serious limitations).

10.2.7 Monotherapy for children with newly diagnosed focal epilepsy

10.2.7.1 Matrix of the evidence for children

Placebo (Pla) Carbamazepine (CBZ) Phenobarbitone (PHB) Lamotrigine (LTG) Phenytoin (PHT) Sodium valproate (VPA) Oxcarbazepine (OXC) Vigabatrin (VGB) Clobazam (CLB)
10.2.7.2 Lamotrigine versus Carbamazepine

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation of AEDs, including carbamazepine and lamotrigine, used as monotherapy in the treatment of children with newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed children. This was based on clinical evidence from Nieto-Barerra and Guerreiro. The complete results of this study and the NCGC children monotherapy model are presented in section 10.2.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of seizure-free children. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more children taking lamotrigine monotherapy had an infection compared to children taking carbamazepine monotherapy, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY).

Significantly more children taking carbamazepine monotherapy experienced dizziness compared to children taking lamotrigine monotherapy. (MODERATE QUALITY).

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of children withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the incidence of the following adverse events:

- headache (LOW QUALITY)
- pharyngitis (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed first line treatment with lamotrigine might be cost-effective compared to first line treatment with carbamazepine, but there was considerable uncertainty in this result (directly applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed lamotrigine monotherapy to be more costly and less effective than carbamazepine monotherapy (directly applicable and potentially serious limitations).
Outcomes with no evidence
There were no studies that reported:
  • withdrawal due to lack of efficacy
  • time to first seizure
  • time to exit/withdrawal of allocated treatment
  • cognitive outcomes
  • quality of life outcomes

10.2.7.3 Phenobarbitone versus carbamazepine

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Adverse events – statistically significant results
Significantly more children in phenobarbitone monotherapy withdrew due to adverse events compared to carbamazepine monotherapy, however there is uncertainty over the magnitude of clinical effect. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenobarbitone and carbamazepine in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence
There were no studies that reported:
  • seizure freedom
  • withdrawal due to lack of efficacy
  • time to first seizure
  • time to exit/withdrawal of allocated treatment
  • incidence of adverse events
  • cognitive outcomes
  • quality of life outcomes

10.2.7.4 Phenobarbitone versus phenytoin

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.
Evidence statements

Adverse events – statistically significant results
Significantly more children in phenobarbitone monotherapy withdrew due to adverse events compared to phenytoin monotherapy. (VERY LOW QUALITY)

Significantly more children taking phenobarbitone monotherapy experienced an incidence of behavioural disorder compared to children taking phenytoin monotherapy, however there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenobarbitone and phenytoin in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.2.7.5 Phenobarbitone versus sodium valproate

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Adverse events – statistically significant results
Significantly more children in phenobarbitone monotherapy withdrew due to adverse events compared to sodium valproate monotherapy, however there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Significantly more children taking phenobarbitone monotherapy experienced an incidence of behavioural disorder compared to children taking sodium valproate monotherapy, however there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenobarbitone and sodium valproate in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• cognitive outcomes
• quality of life outcomes

10.2.7.6 Phenytoin versus carbamazepine

Clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Adverse effects – statistically non-significant results
No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the proportion of children withdrawn due to adverse events (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenytoin and carbamazepine in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence
There were no studies that reported:
• seizure freedom
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• cognitive outcomes
• quality of life outcomes

10.2.7.7 Phenytoin versus sodium valproate

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Adverse effects – statistically non-significant results
No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the proportion of children withdrawn due to adverse events (VERY LOW QUALITY)
Cost-effectiveness

No economic evidence comparing phenytoin and sodium valproate in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.7.8 Carbamazepine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Adverse effects – statistically non-significant results

No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for the proportion of children withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing carbamazepine and sodium valproate in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.2.7.9 Oxcarbazepine versus phenytoin

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (LOW QUALITY)

Adverse effects – statistically significant results

Significantly fewer participants on oxcarbazepine monotherapy withdrew due to adverse events compared to phenytoin monotherapy. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing oxcarbazepine and phenytoin in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcome

10.2.7.10 Vigabatrin versus carbamazepine

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the proportion of seizure free children (VERY LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the proportion of children withdrawn due to adverse events (VERY LOW QUALITY).

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the incidence of irritability/excitability (VERY LOW QUALITY).

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the incidence of weight increase (VERY LOW QUALITY).

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the incidence of excessive sedation (VERY LOW QUALITY).
No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the incidence of urticarial rash (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing vigabatrin and carbamazepine in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.2.8 Health economic evidence of AEDs used as monotherapy for children with newly diagnosed focal epilepsy

One study\textsuperscript{155} assessing the cost-effectiveness of AEDs used as monotherapy was included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessment of the methodology and applicability. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as first-line monotherapy in children with newly diagnosed focal epilepsy. This was based on clinical evidence from Nieto-Barrera 2001\textsuperscript{152} and Guerreiro 1997\textsuperscript{153}. See appendix P for full details and results of modelling.
### Economic study characteristics

#### Table 10-6: Monotherapy for children with newly diagnosed focal epilepsy - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC Model – children monotherapy (see Appendix P for details)</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; comparators included carbamazepine, lamotrigine and oxcarbazepine; time horizon 15 years starting age 2 years; clinical data based on clinical review</td>
</tr>
<tr>
<td>Frew 2007\textsuperscript{155}</td>
<td>Potentially serious limitations</td>
<td>Directly applicable</td>
<td>Patient simulation decision model; comparators for first-line monotherapy included standard drugs (CBZ, VPA and PHT) and LTG; time horizon varied between 3 months and 15 years.</td>
</tr>
</tbody>
</table>

### Economic study results

**NCGC Model – children monotherapy (directly applicable, minor limitations)**

For full details of base case and all sensitivity analyses, see appendix P.

#### Table 10-7: Monotherapy for children with newly diagnosed focal epilepsy – Results of NCGC model

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>£15,170</td>
<td>10.343</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
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<td>Base case: 86.74%</td>
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<td>Cohort starting age =10 yrs: 73.38%</td>
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<td></td>
<td>At £30K per QALY threshold: 86.72%</td>
</tr>
<tr>
<td>LTG</td>
<td>£15,612</td>
<td>10.251</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>At £20K per QALY threshold, probability most cost-effective</td>
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<td></td>
<td>Base case: 12.16%</td>
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<td></td>
<td>Cohort starting age =10 yrs: 26.12%</td>
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<td></td>
<td></td>
<td>At £30K per QALY threshold: 11.88%</td>
</tr>
<tr>
<td>OXC</td>
<td>£16,467</td>
<td>10.183</td>
<td>Dominated</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
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<td>Base case: 1.1%</td>
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<td>Cohort starting age =10 yrs: 0.5%</td>
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<td></td>
<td>At £30K per QALY threshold: 1.4%</td>
</tr>
</tbody>
</table>

### Evidence statements

- Carbamazepine is the most effective and least costly among the AEDs evaluated as monotherapy in children with newly diagnosed focal epilepsy (directly applicable and minor limitations).
- Lamotrigine and oxcarbazepine are more costly and less effective than carbamazepine (directly applicable and minor limitations).

**Frew (2007)\textsuperscript{155} (directly applicable, potentially serious limitations)**

See economic evidence table in appendix M for study details.
Table 10-8: Monotherapy for children with newly diagnosed focal epilepsy – Results of Frew 2007\textsuperscript{155}

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (no new AEDs)</td>
<td>Point estimates cannot be determined from the data provided</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG (first line monotherapy)</td>
<td>Point estimates cannot be determined from the data provided</td>
<td>More costly and possibly more effective, but ICER cannot be determined from the data provided.</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 40%</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence statements**

In 40\% of simulations, first line monotherapy with lamotrigine was optimal compared to a strategy involving only older drugs (carbamazepine, sodium valproate and/or phenytoin). Therefore, lamotrigine monotherapy may be cost-effective, but there is considerable uncertainty in this decision (directly applicable and potentially serious limitations). If current costs for lamotrigine were used, first line monotherapy with lamotrigine may be optimal in a greater proportion of simulations.
10.2.9 Recommendations and link to evidence

First-line treatment in adults and children with newly diagnosed focal seizures

**Recommendation**
Offer carbamazepine, lamotrigine, oxcarbazepine or sodium valproate as first-line treatment to adults and children with newly diagnosed focal seizures, unless contraindicated. If the first AED is ineffective or not tolerated, offer an alternative from these four AEDs. If the second well-tolerated AED is ineffective, consider adjunctive treatment. [new 2011]

**Relative values of different outcomes**
In adults and children seizure freedom, withdrawal due to adverse events and time to treatment failure due to adverse events were the most clinically important outcomes for this recommendation.

**Trade off between clinical benefits and harms**
The efficacy at reducing seizures has to be balanced against the potential side effects for each of these drugs.

No statistically significant difference was observed between drugs in the network meta-analysis but sodium valproate was most effective in the greatest proportion of simulations.

Lamotrigine has a better adverse events profile than carbamazepine. Lamotrigine requires slow titration to reduce risk of rash, which may make it unsuitable for individuals requiring rapid control. The network meta-analysis and the meta-analysis of direct evidence found significantly more participants on carbamazepine compared to lamotrigine withdrew due to adverse events and the meta-analysis of direct outcomes found carbamazepine to have a shorter time to withdrawal than lamotrigine. Oxcarbazepine has a similar adverse events profile to carbamazepine and lamotrigine.

Carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations.

Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity.

In children, lamotrigine and carbamazepine have similar efficacy and adverse events profiles, with the exception of incidence of dizziness which is more prominent with carbamazepine.

None of the four drugs were considered to be both more effective and present a low enough side effect profile to mean that one could be recommended over the other. The GDG decided that they were roughly equivalent and there should be a choice of which to give.

Topiramate and phenytoin showed no significant difference compared to carbamazepine in the network meta-analysis and phenytoin had a relatively high probability of effectiveness in
the network meta-analysis simulations. However they have disadvantages due to drug interactions and their adverse events profiles. Gabapentin was less effective than other AEDs. Vigabatrin is discounted because of its adverse effects in long-term use. Phenobarbitone is not recommended because of adverse effects. Clobazam is discounted because of the risk of tolerance. Therefore these drugs were not thought to be appropriate to recommend as first-line treatment.

**Economic considerations**

The GDG considered multiple sources of economic data in generating this recommendation. Marson 2007 indicated that oxcarbazepine is a very cost-effective first line AED both in terms of QALYs gained and total seizures avoided. The GDG also considered that although lamotrigine was not shown to be cost-effective in the study, the significant reduction in its unit cost since it was evaluated is likely to improve its relative cost-effectiveness on both of these outcomes. Although the time horizon on the SANAD economic evaluation was relatively short (2 years), it is likely to have captured much of the substantial resource use that comes with initiating treatment in a population with newly diagnosed epilepsy. This resource use entails extra appointments to refine diagnosis, adjust dose and manage side effects.

The GDG also considered the original analyses undertaken for this guideline which was an update to the models presented by Hawkins (2005)\textsuperscript{150} for adults and Frew (2007)\textsuperscript{155} for children. The results of the two analyses for adults indicated sodium valproate to be a very cost-effective first line AED for focal epilepsy and that carbamazepine, either in normal or controlled release formulation, was likely to be an effective alternative if sodium valproate was contraindicated. Among children, the two analyses showed that a strategy of using older drugs such as carbamazepine or sodium valproate is likely to be most cost-effective, but that lamotrigine or oxcarbazepine might be cost-effective if older drugs were contraindicated.

Other AEDs licensed for use as monotherapy, including gabapentin, levetiracetam and topiramate, were not shown to be cost-effective in at least one economic analysis. Phenytoin is not considered in the economic analysis because it has a narrow therapeutic window.

**Quality of evidence**

In adults, the two studies included in the evidence were of very low quality due to serious limitations in the study design, serious inconsistency and serious indirectness. Brodie’s study (1995)\textsuperscript{136} was a double blinded trial and SANAD (Marson, 2007)\textsuperscript{39} was an unblinded study. In the SANAD trial, there was no allocation concealment and the randomisation was based on clinician’s preferred first treatment. Brodie (1995)\textsuperscript{136} had high dropout rates in the carbamazepine arm and no information on randomisation nor allocation concealment. In children, one unblinded study was included (Nieto-Barrera, 2001)\textsuperscript{152}.
Other considerations

The GDG found no evidence to refute the drugs listed as first-line in the original guideline except for topiramate which has been advised as adjunctive therapy.

Sodium valproate inhibits metabolism of lamotrigine. This needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be concomitant increase in the lamotrigine dose.

Oxcarbazepine and carbamazepine are hepatic enzyme-inducing drugs and may interact with other medications; this may influence the choice of AED in some individuals. The metabolism of lamotrigine may be increased by oestradiol in the OCP.

In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration.

There is increased risk of side effects with carbamazepine in older people. Carbamazepine had a higher incidence of death in old people compared to lamotrigine. The GDG suggested the use of the controlled release preparation of carbamazepine or use low doses and escalate very cautiously. Otherwise use an alternative first-line therapy in this population. It is better to use non-enzyme inducing AEDs as this population are likely to be taking other medications.

The GDG considered that different patients react differently to the different drugs and there may be a need to try different options with the hope of getting the balance right between seizure freedom and side effects. If the first AED is ineffective, a second AED should be added alongside the initial AED and, if seizures are controlled, the first AED may be withdrawn, recognising that some patients will prefer to remain on two AEDs if seizure-free. The GDG considered that it is generally preferable to avoid polytherapy.

Recommendation

Only offer levetiracetam to adults and children with focal seizures if first-line treatments (see recommendation 4.10.3.1) are contraindicated. [new 2011]

Relative values of different outcomes

Seizure freedom, withdrawal due to adverse events and withdrawal due to lack of efficacy were considered to be the most important outcomes.

Trade off between clinical benefits and harms

Although both levetiracetam and carbamazepine-extended release had very similar findings in terms of efficacy, levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine-extended release which is why it was not recommended as the drug of first choice. However it may be useful for people where the first line AEDs are contraindicated.
The GDG considered that levetiracetam has a lack of interaction with other drugs. However it was considered generally better to titrate levetiracetam slowly.

**Economic considerations**

When carbamazepine, lamotrigine, oxcarbazepine and sodium valproate were removed from the analysis, gabapentin, levetiracetam and topiramate were all likely to be considered cost-effective. However, levetiracetam was likely to be most cost-effective and therefore optimal in the situation where all first line drugs are contraindicated. The GDG also considered that in the situation where all first line drugs are contraindicated, there is a likelihood that gabapentin and topiramate might not be appropriate either, thus lending further weight to the choice of levetiracetam.

**Quality of evidence**

One trial with high dropout rates in both arms showed there was no significant difference between levetiracetam and carbamazepine in the proportion of seizure free participants and withdrawal due to adverse events. However, significantly higher proportion of participants on levetiracetam withdrew due to lack of efficacy compared to carbamazepine.

**Other considerations**

This is a partly GDG consensus opinion based recommendation. Levetiracetam is only licensed for people over 16 year olds. It is useful because it does not interact with hormonal contraception. The GDG opinion was that the limited evidence currently available suggests that levetiracetam does not carry increased risk of teratogenicity.

10.2.10 **Research Recommendations (for full list see section 2.11)**

10.2.10.1 **Newly diagnosed seizures (focal & generalised) - monotherapy**

**Question:** How do the newer AEDs compare in efficacy to the standard AEDs (in the treatment of newly diagnosed epilepsy

a. Focal seizures: carbamazepine, eslicarbazepine, lamotrigine, lacosamide, levetiracetam, pregabalin and zonisamide.

b. Generalised seizures: lamotrigine, levetiracetam, sodium valproate and zonisamide.

**Why is this important?**

Levetiracetam and other AEDS licensed for the treatment of focal and generalised seizures since publication of the original guideline in 2004 have not been evaluated as first line monotherapy.

**Research should include:**

- Prospective randomised controlled trial
- All ages
- Primary outcome seizure freedom
- Secondary outcomes should include seizure-reduction, quality of life and cognitive outcomes

**Attempt to obtain some data on pharmaco-resistance**
10.3 Monotherapy and Adjunctive Treatment for Focal Seizures for refractory population

10.3.1 Introduction

Focal seizures, as stated in the previous section, originate from one area of the brain. They are the most common seizure type in adults and children. Refractory in this context refers to the fact monotherapy has been trialled and seizures continue. Although seizure freedom remains the goal of therapy, in this population optimal seizure control may be more achievable. Treatment success has been most recently defined by the ILAE as a seizure free duration that is at least three times the longest seizure free interval prior to starting the new treatment with a sustained response over 12 months (Kwan et al 2009)156.

10.3.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with focal seizures. For studies in which both partial and primary generalised seizures were combined, a 20% threshold was used as a threshold for “contamination” for the outcome of seizure freedom and a 50% threshold for the outcomes of adverse events.
10.3.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy in adults with refractory focal epilepsy. The interventions we included in our search were pregabalin, zonisamide, lacosamide, lamotrigine, gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbitone, felbamate, clobazam, clonazepam, acetazolamide, primidone, sodium valproate, sulthiame and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

### Monotherapy for adults with refractory focal epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Tiagabine</th>
<th>Oxcarbazepine</th>
<th>Sodium valproate</th>
<th>PLA</th>
<th>LTG</th>
<th>TGB</th>
<th>OXC</th>
<th>VPA</th>
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</thead>
<tbody>
<tr>
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<td>Oxcarbazepine</td>
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<td>Sodium valproate</td>
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</tbody>
</table>

Updated 2011
### Adjunctive therapy for adults with refractory focal epilepsy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>Carbamazepine</td>
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<td>Clobazam</td>
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<td>Eslicarbazepine</td>
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<td>Felbamate</td>
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<tr>
<td>Lacosamide</td>
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### Adjunctive therapy for children with refractory focal epilepsy

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<tr>
<td>LEV</td>
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</tr>
<tr>
<td>TOP</td>
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<td></td>
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<tr>
<td>GBP</td>
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</tr>
</tbody>
</table>
Adjunctive therapy for infants with refractory focal epilepsy

Placebo

Topiramate

PCB  TPM

Placebo (PLA)  Clobazam (CIB)  Eslicarbazepine(ECBZ)  Felbamate(FBM)
Gabapentin (GBP)  Lacosamide(LAC)  Lamotrigine (LTG)  Lamotrigine XR (LTG-XR)
Levetiracetam (LEV)  Levetiracetam XR (LEV-XR)  Oxcarbazepine (OXC)  Topiramate (TPM)
Tiagabine (TGB)  Vigabatrin (VGB)  Zonisamide(Zon)
10.3.4 Monotherapy for adults with refractory focal epilepsy

10.3.4.1 Lamotrigine versus sodium valproate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
One economic evaluation of lamotrigine, sodium valproate and carbamazepine as monotherapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. The results of this study are presented in full in section 10.3.5.

Evidence statements

Adverse events – statistically non-significant results
No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)
No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the incidence of headache. (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed lamotrigine monotherapy to be more costly and equally effective as sodium valproate monotherapy in a population with refractory focal epilepsy (partially applicable and very serious limitations). In this analysis, carbamazepine monotherapy was less costly and more effective than both sodium valproate and lamotrigine.

Outcomes with no evidence
There were no studies that reported:

• seizure freedom
• at least 50% reduction in seizure frequency
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• cognitive outcomes
• quality of life outcomes

10.3.4.2 Tiagabine versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.
Evidence statements

Efficacy – statistically non-significant results
No significant difference between tiagabine monotherapy and placebo for the proportion of participants withdrawn due to lack of efficacy. (LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between tiagabine monotherapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between tiagabine monotherapy and placebo for the incidence of the following adverse events:

- dizziness (VERY LOW QUALITY)
- abnormal thinking (difficulty in concentration) (VERY LOW QUALITY)
- insomnia (VERY LOW QUALITY)
- paresthesia (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- amnesia (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing tiagabine monotherapy to placebo was identified.

Outcomes with no evidence
There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.4.3 Oxcarbazepine versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Significantly more participants on oxcarbazepine monotherapy experienced seizure freedom compared to placebo. (VERY LOW QUALITY)

**Adverse events—statistically non-significant results**

No significant difference between oxcarbazepine monotherapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and placebo for the incidence of the following adverse events:

- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- vomiting (VERY LOW QUALITY)
- pruritus (VERY LOW QUALITY)
- diplopia (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)

**Cost-effectiveness**

No economic evidence comparing oxcarbazepine monotherapy to placebo was identified.

**Outcomes with no evidence**

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

**10.3.5 Health Economic Evidence for monotherapy in refractory focal epilepsy**

One study\(^{150}\) assessing the cost-effectiveness of AEDs used as monotherapy in adults with refractory focal epilepsy was included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability.
Economic study characteristics

Table 10-9: Monotherapy in adults with refractory focal epilepsy - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins (2005)(^{150})</td>
<td>Very serious limitations (a)</td>
<td>Partially applicable (b,c)</td>
<td>Decision analytic model; comparators included carbamazepine sodium valproate and lamotrigine; time horizon 15 years; clinical data based on network meta-analysis of data from Gilliam 1998 (^{159}) and Kerr 2001 (^{240})</td>
</tr>
</tbody>
</table>

(a) Unit costs of interventions are from 2002/03 and since then lamotrigine has come off patent and the nonproprietary price is dramatically lower.
(b) Effectiveness data was derived from a network meta-analysis that included at least one unpublished study that was not reviewed as part of our systematic review.
(c) Costs discounted at 6% per annum; QALYs discounted at 1.5% per annum.

Economic study results

Hawkins 2005\(^{150}\) (partially applicable, potentially serious limitations)
See economic evidence table in appendix M for details.

Table 10-10: Monotherapy in refractory focal epilepsy - Economic summary of findings – Hawkins 2005\(^{150}\)

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>£5,599</td>
<td>8.865</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 79%</td>
</tr>
<tr>
<td>VPA</td>
<td>£5,728</td>
<td>8.856</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 21%</td>
</tr>
<tr>
<td>LTG</td>
<td>£6,749</td>
<td>8.856</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0%</td>
</tr>
</tbody>
</table>

Evidence statements

Cost-effectiveness
One economic evaluation based on a decision analytic model showed carbamazepine monotherapy to be the most effective and least costly, and therefore most cost-effective AED used in the treatment of refractory focal epilepsy. The same analysis shows lamotrigine monotherapy and sodium valproate monotherapy not to be cost-effective. This evidence is partially applicable and has very serious limitations.
10.3.6 Adjunctive therapy for adults with refractory focal epilepsy

10.3.6.1 Lamotrigine versus Placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Lamotrigine and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
One economic evaluation of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy – statistically significant results
Significantly more participants on lamotrigine adjunctive therapy compared to placebo had at least a 50% reduction in seizure frequency. (LOW QUALITY)
Significantly more participants on lamotrigine adjunctive therapy compared to placebo had at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Adverse events – statistically significant
Significantly more participants on lamotrigine adjunctive therapy compared to placebo withdrew due to adverse events. (NCGC network meta-analysis)
Significantly more participants on lamotrigine adjunctive therapy compared to placebo had:
- incidence of dizziness (LOW QUALITY)
- incidence of diplopia (LOW QUALITY)
- incidence of ataxia (LOW QUALITY)
- incidence of blurred vision (MODERATE QUALITY)
- incidence of nausea (LOW QUALITY)
- incidence of somnolence (LOW QUALITY)
- incidence of vomiting (LOW QUALITY)
- incidence of pain (LOW QUALITY)

Significantly more participants on placebo compared to lamotrigine adjunctive therapy had:
- Incidence of respiratory disorder (VERY LOW)
Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and placebo for:

- Incidence of headache (VERY LOW)
- Incidence of rash (VERY LOW)
- Incidence of drowsiness (VERY LOW)
- Incidence of faintness (VERY LOW)
- Incidence of dyspepsia (VERY LOW)
- Incidence of nasal congestion (VERY LOW)
- Incidence of fatigue (VERY LOW)
- Incidence of flushing (VERY LOW)
- Incidence of co-ordination abnormality (VERY LOW)
- Incidence of asthenia (VERY LOW)
- Incidence of vision abnormality (VERY LOW)
- Incidence of rhinitis (VERY LOW)
- Incidence of tiredness (VERY LOW)
- Incidence of accidental injury (VERY LOW)
- Incidence of vertigo (VERY LOW)
- Incidence of death (VERY LOW)
- Aggravation of seizures (VERY LOW)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed adjunctive lamotrigine to be cost-effective compared to placebo (directly applicable and minor limitations), but in this same analysis adjunctive lamotrigine was ruled out through extended dominance. Another economic evaluation based on a decision analytic model showed adjunctive lamotrigine not to be cost-effective compared to placebo (directly applicable and very serious limitations).

10.3.6.2 Lamotrigine extended release versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Lamotrigine extended release and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.
Health Economic Evidence

No studies were identified in the economic literature search. Lamotrigine extended release was not included in the original economic model as it is not currently available in the UK.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on lamotrigine extended release adjunctive therapy were seizure free than the placebo. (MODERATE QUALITY)

Significantly more participants on lamotrigine extended release adjunctive therapy than the placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine extended release adjunctive therapy and placebo for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Adverse events – statistically significant

Significantly more participants on lamotrigine extended release adjunctive therapy withdrew due to adverse events compared to those taking placebo although there is uncertainty over the magnitude of its clinical effect. (MODERATE QUALITY)

Significantly more participants on lamotrigine extended release adjunctive therapy withdrew due to adverse events compared to those taking placebo. (NCGC network meta-analysis)

Significantly more participants in the lamotrigine extended release adjunctive therapy than the placebo experienced dizziness. (MODERATE QUALITY)

Significantly fewer participants in the lamotrigine extended release adjunctive therapy experienced nasopharyngitis than the placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant

No significant difference between lamotrigine extended release adjunctive therapy and placebo for the incidence of headache. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine extended release adjunctive therapy to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.3 Lamotrigine versus levetiracetam

Direct clinical evidence

For details of the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis

Lamotrigine and levetiracetam were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

One economic evaluation of AEDs, including lamotrigine and levetiracetam, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for all adverse events. (VERY LOW QUALITY)

Cognitive events and quality of life – statistically significant results

There was a significant improvement in POMS anger-hostility subscale and family/friend completed measure of depressive symptoms for lamotrigine relative to levetiracetam.

Cognitive events and quality of life – statistically non-significant results

No significant improvements for lamotrigine relative to levetiracetam at end of maintenance period for most of the subscales including:

- POMS total mood disturbance, depression-dejection, vigor-activity, fatigue-inertia, confusion-bewilderment and tension-anxiety subscales.
- NDDI-E patient-completed measure of depressive symptoms
- ESS daytime sleepiness measure
- STAXI measure of the experience, expression, and control of anger
- BDI-II measure of severity of depressive symptoms

Cost-effectiveness

Two economic evaluations based on decision analytic models showed adjunctive levetiracetam not to be cost-effective compared to adjunctive lamotrigine. One showed adjunctive levetiracetam to have an unacceptably high incremental cost-effectiveness ratios of £36,482 per QALY (directly applicable and very serious limitations) and another showed adjunctive levetiracetam to be more costly and less effective than adjunctive lamotrigine (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- At least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
10.3.6.4 Lamotrigine versus tiagabine

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Lamotrigine and tiagabine were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
One economic evaluation of AEDs, including lamotrigine and tiagabine, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between lamotrigine adjunctive therapy and tiagabine adjunctive therapy for seizure freedom (LOW QUALITY)
No significant difference between lamotrigine adjunctive therapy and tiagabine adjunctive therapy for 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events – statistically non-significant
No significant difference between lamotrigine adjunctive therapy and tiagabine therapy for incidence of:
- Headache (VERY LOW QUALITY)
- Fatigue (VERY LOW QUALITY)
- Disturbed sleep (VERY LOW QUALITY)
- Dizziness (VERY LOW QUALITY)
- Nervousness (VERY LOW QUALITY)
- Paresthesia (VERY LOW QUALITY)
- Nausea (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed adjunctive tiagabine to be more costly and more effective than adjunctive lamotrigine, with an acceptable incremental cost-effectiveness ratio of £17,250 per QALY (directly applicable and very serious limitations). Another economic evaluation based on a decision analytic model showed adjunctive tiagabine to be more costly and less effective than adjunctive lamotrigine (directly applicable and minor limitations).
Outcomes with no evidence

There were no studies that reported:
 - withdrawal due to adverse events
 - withdrawal due to lack of efficacy
 - time to first seizure
 - time to exit/withdrawal of allocated treatment
 - cognitive outcomes
 - quality of life outcomes

10.3.6.5 Lamotrigine versus topiramate

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Lamotrigine and topiramate were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic evidence

One economic evaluation of AEDs, including lamotrigine and topiramate, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults’ adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on topiramate adjunctive therapy than lamotrigine adjunctive therapy experienced seizure freedom, however there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on topiramate adjunctive therapy compared to lamotrigine adjunctive therapy had:
 - Incidence of headache (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for:
 - Incidence of dizziness (VERY LOW QUALITY)
• Incidence of fatigue (VERY LOW QUALITY)

• Incidence of nausea (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results
Lamotrigine adjunctive therapy had significantly better scores compared to topiramate adjunctive therapy for:

• COWA
• POL test total overall score
• Combined cognitive scores

Topiramate adjunctive therapy had significantly better scores compared to lamotrigine adjunctive therapy for:

• Stroop colour-word interference
• Symbol digit modalities (correct number)

Cognitive outcomes – statistically non-significant results
No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for:

• RAVLT delayed recall
• Lafayette grooved pegboard
• Digit cancellation test

Cost-effectiveness
Two economic evaluations based on decision analytic models showed adjunctive topiramate to be more costly and more effective than adjunctive lamotrigine, with incremental cost-effectiveness ratios of £35,484 per QALY (directly applicable and very serious limitations) and £78,958 per QALY (directly applicable and minor limitations). In both of these analyses adjunctive topiramate was more costly and less effective than adjunctive oxcarbazepine.

Outcomes with no evidence
There were no studies that reported:

• at least 50% reduction in seizure frequency
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• quality of life outcomes

10.3.6.6 Levetiracetam versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis

Levetiracetam and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

One economic evaluation of AEDs, including levetiracetam and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy - statistically significant results

- Significantly more participants on levetiracetam adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)
- Significantly more participants on levetiracetam adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)
- Significantly more participants on levetiracetam adjunctive therapy than placebo experienced seizure freedom. (LOW QUALITY)

Efficacy - statistically non-significant results

- No significant difference between levetiracetam adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events - statistically significant

- Significantly more participants on levetiracetam adjunctive therapy than placebo withdrew due to adverse events (NCGC network meta-analysis).
- Significantly more participants on levetiracetam adjunctive therapy than the placebo had higher incidence of:
  - Infection (MODERATE QUALITY)
  - Somnolence (MODERATE QUALITY)
  - Asthenia (MODERATE QUALITY)

Adverse events - statistically non-significant results

- No significant difference between levetiracetam adjunctive therapy and placebo for withdrawal due to adverse events (VERY LOW QUALITY)
- No significant difference between levetiracetam adjunctive therapy and placebo for incidence of:
  - Alanine aminotransferase (VERY LOW QUALITY)
• Aspartate aminotransferase (VERY LOW QUALITY)
• Decreases in platelets (VERY LOW QUALITY)
• Decreases in white blood cells (VERY LOW QUALITY)
• Dizziness (VERY LOW QUALITY)
• Agitation (VERY LOW QUALITY)
• Nasopharyngitis (VERY LOW QUALITY)
• Asthenia (VERY LOW QUALITY)
• Accidental injury (VERY LOW QUALITY)
• Diarrhea (VERY LOW QUALITY)
• Flu (VERY LOW QUALITY)
• Headache (VERY LOW QUALITY)
• Pain (VERY LOW QUALITY)
• Rhinitis (VERY LOW QUALITY)
• Death (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results
Participants in levetiracetam (1000mg and 3000mg) adjunctive group had significant improvement in mean scores compared to placebo on the following QOLIE-31 measures:
• seizure worry
• overall QOL
• cognitive functioning
• total score
• social function

Cognitive outcomes – statistically non-significant results
Participants in levetiracetam (1000mg and 3000mg) adjunctive group had no significant improvement in mean scores compared to placebo on the following QOLIE-31 measures:
• Emotional well-being
• Energy-fatigue
• Medication effects
• Health status

Cost-effectiveness
Two economic evaluations based on decision analytic models showed adjunctive levetiracetam to be more costly and more effective than placebo, with incremental cost-effectiveness ratios of £32,487 per QALY (directly applicable and potentially serious limitations) and £26,211 per QALY (directly applicable and minor limitations). In both of these analyses adjunctive levetiracetam was more costly and less effective than adjunctive oxcarbazepine.

10.3.6.7 Levetiracetam extended release versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Levetiracetam extended release and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.
Health Economic Evidence

No studies were identified in the economic literature search. Levetiracetam extended release was not included in the original economic model as it is not currently available in the UK.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on levetiracetam adjunctive therapy (extended release) than placebo experienced seizure freedom although there is uncertainty in the magnitude of clinical effect. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for:

- Proportion of participants experiencing at least a 50% reduction in seizure frequency. (MODERATE QUALITY)
- Proportion of participants having treatment withdrawn due to efficacy. (LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for proportion of participants experiencing at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Adverse events – statistically non-significant

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for the proportion of participants having treatment withdrawn due to adverse event. (LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for the proportion of participants withdrawing due to adverse events. (NCGC network meta-analysis)

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for incidence of headache. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing levetiracetam extended release adjunctive therapy to placebo was identified.

10.3.6.8 Topiramate versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Topiramate and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.
Health Economic Evidence

One economic evaluation of AEDs, including topiramate and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on topiramate adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (VERY LOW QUALITY)

Significantly more participants on topiramate adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Significantly more participants on topiramate adjunctive therapy than placebo experienced seizure freedom. (LOW QUALITY)

Adverse events - statistically significant

Significantly more participants on topiramate adjunctive therapy than placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on topiramate adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

Significantly more participants on topiramate adjunctive therapy than placebo experienced:

- Anorexia (MODERATE QUALITY)
- Abdominal discomfort/pain although there is uncertainty in the magnitude of effect (LOW QUALITY)
- Dizziness (LOW QUALITY)
- Somnolence (LOW QUALITY)
- Confusion (VERY LOW QUALITY)
- Weight decrease (VERY LOW QUALITY)
- Fatigue (LOW QUALITY)
- Impaired concentration (VERY LOW QUALITY)
- Abnormal thinking (VERY LOW QUALITY)
- Ataxia (LOW QUALITY)
- Paresthesia (VERY LOW QUALITY)

Adverse events - statistically non-significant

No significant difference between topiramate adjunctive therapy and placebo for:
• Incidence of nausea/vomiting (VERY LOW)
• Incidence of headache (VERY LOW)
• Incidence of amblyopia (VERY LOW)
• Incidence of dizziness/somnolence (VERY LOW)
• Incidence of speech disorder (VERY LOW)
• Incidence of aphasia (VERY LOW)
• Incidence of abnormal vision (VERY LOW)
• Incidence of anxiety (VERY LOW)
• Incidence of depression (VERY LOW)
• Incidence of nervousness (VERY LOW)
• Incidence of amnesia (VERY LOW)
• Incidence of emotional lability (VERY LOW)
• Incidence of upper respiratory tract infection (VERY LOW)
• Incidence of pharyngitis (VERY LOW)
• Incidence of asthenia (VERY LOW)
• Incidence of injury (VERY LOW)
• Incidence of nystagmus (VERY LOW)
• Incidence of diplopia (VERY LOW)
• Incidence of diarrhea (VERY LOW)
• Incidence of nausea (VERY LOW)
• Incidence of memory difficulty (VERY LOW)
• Incidence of speech difficulty (VERY LOW)
• Aggravation of seizures (LOW QUALITY)

**Cognitive outcomes – statistically significant**

Participants in topiramate adjunctive group had significantly worse scores for the following tests compared to placebo group:

- SDMT
- COWA
- Stroop-word
- Stroop-colour

**Cost-effectiveness**

Two economic evaluations based on decision analytic models showed adjunctive topiramate to be more costly and more effective than placebo, with incremental cost-effectiveness ratios of £32,164 per QALY (directly applicable and potentially serious limitations) and £18,824 per QALY (directly
applicable and minor limitations). In both of these analyses adjunctive topiramate was more costly and less effective than adjunctive oxcarbazepine.

10.3.6.9 Topiramate versus sodium valproate

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Topiramate and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

No studies were identified in the economic literature search. Adjunctive sodium valproate was not included in the original economic model as it is not commonly used as adjunctive treatment.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically non-significant

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to adverse events. (LOW QUALITY)

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for incidence of:

- Memory difficulty
- Speech difficulty
- Depression

Cognitive outcomes – statistically significant

Significant worse scores compared to baseline for immediate recall for topiramate adjunctive therapy and significant improvement compared to baseline for sodium valproate adjunctive therapy.

Cognitive outcomes – statistically non-significant

No significant change in scores of cognitive or quality of life on the following measures:

- Motor speed/motor fluency
- Alertness/reaction speed
- Information processing speed
- Memory
- POMS scale
Cost-effectiveness
No economic evidence comparing adjunctive topiramate to adjunctive sodium valproate was identified.

10.3.6.10 Gabapentin versus Placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Gabapentin and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
One economic evaluation of AEDs, including gabapentin and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements
Efficacy – statistically significant results
Significantly more participants on gabapentin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)
Significantly more participants on gabapentin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Efficacy – statistically non-significant results
No significant difference between gabapentin adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant
Significantly more participants on gabapentin adjunctive therapy than placebo withdrew due to adverse events. (MODERATE QUALITY)
Significantly more participants on gabapentin adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

Significantly more participants on gabapentin adjunctive therapy than placebo experienced:
  • Somnolence (MODERATE QUALITY)
  • Dizziness (MODERATE QUALITY)
  • Ataxia (MODERATE QUALITY)
Significantly more participants on placebo than gabapentin adjunctive therapy experienced aggravation of seizures.

Adverse events – statistically non-significant
No significant difference between gabapentin adjunctive therapy and placebo for:

- Incidence of nystagmus (VERY LOW QUALITY)
- Incidence of headache (VERY LOW QUALITY)
- Incidence of tremor (VERY LOW QUALITY)
- Incidence of fatigue (VERY LOW QUALITY)
- Incidence of rhinitis (VERY LOW QUALITY)
- Incidence of drowsiness (VERY LOW QUALITY)
- Incidence of blurred vision (VERY LOW QUALITY)
- Incidence of death (VERY LOW QUALITY)

Cost-effectiveness
Two economic evaluations based on decision analytic models showed adjunctive gabapentin to be more costly and more effective than placebo, with incremental cost-effectiveness ratios of £25,709 per QALY (directly applicable and potentially serious limitations) and £5,162 per QALY (directly applicable and minor limitations).

10.3.6.11 Gabapentin versus sodium valproate

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Gabapentin and sodium valproate were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. Adjunctive sodium valproate was not included in the original economic model as it is not commonly used as adjunctive treatment.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between gabapentin adjunctive therapy and sodium valproate adjunctive therapy for:

- At least a 50% reduction in seizure frequency (VERY LOW QUALITY)
- Seizure freedom (VERY LOW QUALITY)
**Adverse events – statistically non-significant results**

No significant difference between gabapentin adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

**Cost-effectiveness**

No economic evidence comparing adjunctive gabapentin to adjunctive sodium valproate was identified.

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10.3.6.12 Gabapentin versus vigabatrin

**Direct clinical evidence**

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Network meta-analysis**

Gabapentin and vigabatrin were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

**Health Economic Evidence**

No studies were identified in the economic literature search. As there were gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of these studies and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

**Evidence statements**

**Efficacy – statistically non-significant results**

No significant difference between gabapentin adjunctive therapy and vigabatrin adjunctive therapy for:

- At least a 50% reduction in seizure frequency (VERY LOW QUALITY)
- Seizure freedom (VERY LOW QUALITY)

**Adverse events – statistically non-significant results**

No significant difference between gabapentin adjunctive therapy and vigabatrin adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

**Cost-effectiveness**

One economic evaluation based on a decision analytic model showed adjunctive vigabatrin to be more costly and more effective than adjunctive gabapentin with an incremental cost-effectiveness ratio of £10,405 per QALY (directly applicable and very serious limitations). The economic analysis did not take account of the potential long term adverse effects associated with vigabatrin.

10.3.6.13 Gabapentin versus lamotrigine

**Direct clinical evidence**

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis

Gabapentin and lamotrigine were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

One economic evaluation of AEDs, including gabapentin and lamotrigine, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events – statistically non-significant

No significant difference gabapentin adjunctive therapy and lamotrigine adjunctive therapy for any adverse events. (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed adjunctive lamotrigine to be more costly and less effective than adjunctive gabapentin (directly applicable and very serious limitations). Another economic evaluation based on a decision analytic model showed adjunctive lamotrigine to be more costly and more effective than adjunctive gabapentin, with an incremental cost-effectiveness ratio of £9,643 per QALY (directly applicable and minor limitations).

10.3.6.14 Tiagabine versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Tiagabine and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

One economic evaluation of AEDs, including tiagabine and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The
complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

**Evidence statements**

**Efficacy—statistically significant results**

Significantly more participants on tiagabine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Significantly more participants on tiagabine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (NCGC network meta-analysis)

**Efficacy—statistically non-significant results**

No significant difference between tiagabine adjunctive therapy and placebo for seizure freedom and withdrawal due to lack of efficacy. (VERY LOW QUALITY)

**Adverse events—statistically significant**

Significantly more participants on tiagabine adjunctive therapy than placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on tiagabine adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

Significantly more participants on tiagabine adjunctive therapy than the placebo experienced:

- Dizziness (LOW QUALITY)
- Tremor (LOW QUALITY)

**Adverse events—statistically non-significant**

No significant difference between tiagabine adjunctive therapy and placebo for incidence of:

- Abnormal thinking (VERY LOW QUALITY)
- Nervousness (VERY LOW QUALITY)
- Asthenia (VERY LOW QUALITY)
- Headache (VERY LOW QUALITY)
- Somnolence (VERY LOW QUALITY)
- Infection (VERY LOW QUALITY)
- Nausea (VERY LOW QUALITY)
- Injury (VERY LOW QUALITY)
- Flu syndrome (VERY LOW QUALITY)

**Cognitive outcomes—statistically non-significant**

No significant association between cognitive and quality of life tests for tiagabine adjunctive therapy and placebo.

**Cost-effectiveness**
Two economic evaluations based on decision analytic models showed adjunctive tiagabine to be more costly and more effective than placebo with incremental cost-effectiveness ratios of £25,452 per QALY (directly applicable and potentially serious limitations) and £34,117 per QALY (directly applicable and minor limitations). In one analysis, adjunctive tiagabine was ruled out through extended dominance and in the other adjunctive tiagabine was dominated by adjunctive oxcarbazepine.

10.3.6.15 Tiagabine versus phenytoin

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Tiagabine and phenytoin were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. Tiagabine was included in the model, but phenytoin was not owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between tiagabine adjunctive therapy and phenytoin for proportion of participants experiencing at least a 50% reduction in seizure frequency.

Cognitive outcomes – non-statistically significant
No significant association between cognitive and quality of life tests for tiagabine adjunctive therapy and phenytoin adjunctive therapy.

Cost-effectiveness
No economic evidence comparing adjunctive tiagabine to adjunctive phenytoin was identified.

10.3.6.16 Tiagabine versus carbamazepine

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Tiagabine and carbamazepine were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as...
adjunctive therapy in adults with refractory focal epilepsy. Tiagabine was included in the model, but carbamazepine was not as it is most often used as monotherapy.

Evidence statements

Efficacy – statistically significant results
Significantly more participants on carbamazepine adjunctive therapy than tiagabine adjunctive therapy experienced at least 50% reduction in seizure frequency. (MODERATE QUALITY)

Cognitive outcomes – statistically significant results
Significant improvement for tiagabine mean scores compared to carbamazepine on the following tests:

- Financial status
- Mood rating scale
- Digit cancellation correct test

Cognitive outcomes – statistically non-significant results
No significant difference difference between tiagabine and carbamazepine on mean scores of:

- the QOLIE scale
- WPSI subtests
- Ability tests

Cost-effectiveness
No economic evidence comparing adjunctive tiagabine to adjunctive carbamazepine was identified.

10.3.6.17 Vigabatrin versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Vigabatrin and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. Vigabatrin was excluded from one study owing to its potential toxicity. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.
Evidence statements

Efficacy – statistically significant results
Significantly more participants on vigabatrin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency (MODERATE QUALITY)
Significantly more participants on vigabatrin adjunctive therapy than placebo experienced seizure freedom although there is uncertainty in the magnitude of effect (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between vigabatrin adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants on vigabatrin adjunctive therapy than placebo experienced withdrawal due to adverse events (MODERATE QUALITY)
Significantly more participants on vigabatrin adjunctive therapy than the placebo experienced:
- drowsiness (MODERATE QUALITY)
- dizziness (MODERATE QUALITY)

Significantly more participants on placebo than vigabatrin adjunctive therapy experienced aggravation of seizures. (MODERATE QUALITY)

Adverse events – statistically non-significant results
No significant difference between vigabatrin adjunctive therapy and placebo for:
- fatigue (VERY LOW QUALITY)
- nystagmus (VERY LOW QUALITY)
- agitation (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- amnesia (VERY LOW QUALITY)
- abnormal vision (VERY LOW QUALITY)
- weight gain (VERY LOW QUALITY)
- constipation (VERY LOW QUALITY)
- mild depression (VERY LOW QUALITY)
- double vision (VERY LOW QUALITY)
- Irritability (VERY LOW QUALITY)
- Confusion (VERY LOW QUALITY)
- Suicide (VERY LOW QUALITY)
- Attempted suicide (VERY LOW QUALITY)
Cognitive events—statistically significant

Significant improvement for vigabatrin adjunctive therapy mean scores for the following measures compared to placebo:

- Motor speed
- Flexibility
- Design learning task

Significantly worse scores for vigabatrin adjunctive therapy mean scores for the following measures compared to placebo:

- digit cancellation scale
- Stroop tests

Cost-effectiveness

One economic evaluation based on a decision analytic model showed adjunctive vigabatrin to be more costly and more effective than placebo, with an incremental cost-effectiveness ratio of £8,059 per QALY (directly applicable and very serious limitations). The economic analysis did not take account of the potential long term adverse effects associated with vigabatrin.

10.3.6.18 Pregabalin versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Pregabalin and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy—statistically significant results

Significantly more participants on pregabalin adjunctive therapy than placebo experienced:

- At least 50% reduction in seizure frequency (LOW QUALITY)
- Seizure freedom (LOW QUALITY)
Significantly more participants on pregabalin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Significantly more participants on placebo than pregabalin adjunctive therapy experienced:
- Withdrawal due to lack of efficacy (MODERATE QUALITY)

**Adverse events – statistically significant**

Significantly more participants on pregabalin adjunctive therapy than placebo withdrew due to adverse events. (MODERATE QUALITY)

Significantly more participants on pregabalin adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

Significantly more participants on pregabalin adjunctive therapy than the placebo experienced:
- Dizziness (MODERATE QUALITY)
- Somnolence (MODERATE QUALITY)
- Ataxia (LOW QUALITY)
- Weight gain (MODERATE QUALITY)
- Vertigo (VERY LOW QUALITY)
- Tremor (MODERATE QUALITY)
- Amblyopia (MODERATE QUALITY)
- Diplopia (MODERATE QUALITY)

**Adverse events – statistically non-significant**

No significant difference between pregabalin adjunctive therapy and placebo for:
- Incidence of asthenia (LOW QUALITY)
- Incidence of headache (LOW QUALITY)

**Cost-effectiveness**

One economic evaluation based on a decision analytic model showed adjunctive pregabalin to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £55,431 per QALY (directly applicable and minor limitations). Adjunctive pregabalin was more costly and less effective than adjunctive oxcarbazepine.

**Outcomes with no evidence**

There were no studies that reported:
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes.
10.3.6.19  Clobazam versus placebo

**Direct clinical evidence**
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Network meta-analysis**
Clobazam and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

**Health Economic Evidence**
No studies were identified in the economic literature search. Clobazam was not included in the original economic model owing to its sedative side effects and the fact that their effectiveness may wane with long term and continuous use.

**Evidence statements**

**Efficacy - statistically significant results**
Significantly more participants on clobazam adjunctive therapy than placebo experienced seizure freedom although there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

**Efficacy – statistically non-significant results**
No significant difference between clobazam adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

**Adverse effects – statistically significant results**
Significantly more participants on clobazam adjunctive therapy than placebo had withdrawal due to adverse events although there is uncertainty in the magnitude of clinical effect (VERY LOW QUALITY)

Significantly more participants on clobazam adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

**Cost-effectiveness**
No economic evidence comparing adjunctive clobazam to placebo was identified.

**Outcomes with no evidence**
There were no studies that reported:
- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes
10.3.6.20 Lacosamide versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Lacosamide and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy—statistically significant results
Significantly more participants on lacosamide adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency (LOW QUALITY)
Significantly more participants on lacosamide adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Efficacy—statistically non-significant results
No significant difference between lacosamide adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)
No significant difference between lacosamide adjunctive therapy and placebo for withdrawal due to lack of efficacy (VERY LOW QUALITY)

Adverse events—statistically significant
Significantly more participants on lacosamide adjunctive therapy than placebo withdrew due to adverse events (LOW QUALITY)
Significantly more participants on lacosamide adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)
Significantly more participants on lacosamide adjunctive therapy than the placebo experienced:
- Dizziness (LOW QUALITY)
- Vomiting (VERY LOW QUALITY)

Adverse events—statistically non-significant
No significant difference between lacosamide adjunctive therapy and placebo for:
- Incidence of headache (VERY LOW QUALITY)
- Incidence of nausea (VERY LOW QUALITY)
- Incidence of fatigue (VERY LOW QUALITY)
Incidence of URI (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed adjunctive lacosamide to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £66,257 per QALY (directly applicable and minor limitations). Adjunctive lacosamide was more costly and less effective than adjunctive oxcarbazepine.

Outcomes with no evidence
There were no studies that reported:
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.21 Zonisamide versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Zonisamide and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy - statistically significant results
Significantly more participants on zonisamide adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (MODERATE QUALITY)

Significantly more participants on zonisamide adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (NCGC network meta-analysis)

Efficacy – statistically non-significant results
No significant difference between zonisamide adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)
No significant difference between zonisamide adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)
Adverse events – statistically significant results

Significantly more participants on zonisamide adjunctive therapy than placebo withdrew due to adverse events (MODERATE QUALITY).

Significantly more participants on zonisamide adjunctive therapy than placebo withdrew due to adverse events (NCGC network meta-analysis).

Significantly more participants on zonisamide adjunctive therapy than the placebo experienced dizziness and somnolence (in the titration period) although there is uncertainty in the magnitude of effect. (VERY LOW QUALITY)

Significantly more participants on placebo than zonisamide adjunctive therapy experienced aggravation of seizures. (MODERATE QUALITY)

Adverse events – statistically non-significant

No significant difference between zonisamide adjunctive therapy and placebo for incidence of:

- Somnolence (VERY LOW QUALITY)
- Fatigue (VERY LOW QUALITY)
- Dizziness (VERY LOW QUALITY)
- Anorexia (VERY LOW QUALITY)
- Abnormal thinking (VERY LOW QUALITY)
- Ataxia (VERY LOW QUALITY)
- Rhinitis (VERY LOW QUALITY)
- Nausea or vomiting (VERY LOW QUALITY)
- Death (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation from a decision analytic model showed adjunctive zonisamide to be more costly and more effective than placebo, with an incremental cost-effectiveness of £71,656 per QALY (directly applicable and minor limitations). However, in this analysis, adjunctive zonisamide was more costly and less effective than several other AEDs including levetiracetam, topiramate, tiagabine, oxcarbazepine and lamotrigine.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.22 Eslicarbazepine versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Network meta-analysis

Eslicarbazepine and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on eslicarbazepine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Significantly more participants on eslicarbazepine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (NCGC network meta-analysis)

Significantly more participants on eslicarbazepine adjunctive therapy than placebo experienced seizure freedom. (LOW QUALITY)

Efficacy - statistically non-significant results

No significant difference between eslicarbazepine adjunctive therapy and placebo for withdrawal due to lack of efficacy although there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Adverse events - statistically significant

Significantly more participants on eslicarbazepine adjunctive therapy than placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on eslicarbazepine adjunctive therapy than placebo had:

- Incidence of dizziness (LOW QUALITY)
- Incidence of nausea (LOW QUALITY)
- Incidence of diplopia although there is uncertainty in the magnitude of clinical effect (VERY LOW QUALITY)

Adverse events - statistically non-significant

No significant difference between eslicarbazepine adjunctive therapy and placebo for participants withdrawing due to adverse events (NCGC network meta-analysis).

No significant difference between eslicarbazepine adjunctive therapy and placebo for:

- Aggravation of seizures (VERY LOW QUALITY)
- Incidence of death (VERY LOW QUALITY)
- Incidence of somnolence (VERY LOW QUALITY)
- Incidence of headache (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation from a decision analytic model showed adjunctive eslicarbazepine to be more costly and more effective than placebo, with an incremental cost-effectiveness of £43,333 per QALY (directly applicable and minor limitations). However, in this analysis, adjunctive zonisamide was more costly and less effective than several other AEDs including levetiracetam, topiramate, tiagabine, oxcarbazepine, lamotrigine and gabapentin.

Outcomes with no evidence
There were no studies that reported:
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.23 Felbamate versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Felbamate and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. Because there was only data for this comparison on the outcome of withdrawal due to adverse events, it was only included in the network meta-analysis for that outcome. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
No studies were identified in the economic literature search. Felbamate was not included among comparators in the NCGC economic model for adjunctive AED treatment for refractory focal epilepsy due to its potential for serious adverse effects and its limited use on a ‘named patient’ basis.

Evidence statements
Adverse events – statistically significant results
Significantly more participants on felbamate adjunctive therapy than the placebo experienced:
- Headache (MODERATE QUALITY)
- Insomnia although there is uncertainty in the magnitude of effect. (LOW QUALITY)
- Nausea although there is uncertainty in the magnitude of effect. (VERY LOW QUALITY)

Adverse events – statistically non-significant
No significant difference between felbamate adjunctive therapy and placebo for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between felbamate adjunctive therapy and placebo for:
- Incidence of dyspepsia (VERY LOW QUALITY)

The epilepsies: full guideline DRAFT (July 2010)
Incidence of dizziness (VERY LOW QUALITY)
Incidence of fatigue (VERY LOW QUALITY)
Incidence of constipation (VERY LOW QUALITY)
Incidence of somnolence (VERY LOW QUALITY)
Incidence of anorexia (VERY LOW QUALITY)
Incidence of anxiety (VERY LOW QUALITY)
Incidence of vomiting (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing adjunctive felbamate to placebo was identified.

Outcomes with no evidence
There were no studies that reported:
- seizure freedom
- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.24 Oxcarbazepine versus placebo

Direct clinical evidence
For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis
Oxcarbazepine and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence
One economic evaluation of AEDs, including oxcarbazepine and placebo, used as adjunctive therapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.3.8.

Evidence statements

Efficacy- statistically significant results
Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (NCGC network meta-analysis)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on oxcarbazepine adjunctive therapy than the placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo withdrew due to adverse events. (NCGC network meta-analysis)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced:

- Dizziness (LOW QUALITY)
- Somnolence (LOW QUALITY)
- Ataxia (LOW QUALITY)
- Nystagmus (LOW QUALITY)
- Abnormal gait (VERY LOW QUALITY)
- Vomiting although there is uncertainty in the magnitude of clinical effect. (LOW QUALITY)
- Vertigo (VERY LOW QUALITY)
- Nausea (LOW QUALITY)
- Abnormal vision (LOW QUALITY)
- Fatigue (LOW QUALITY)

Adverse events – statistically non-significant

No significant difference between oxcarbazepine adjunctive therapy and placebo for incidence of headache. (VERY LOW QUALITY)

Cost-effectiveness

Two economic evaluations based on decision analytic models showed adjunctive oxcarbazepine to be more costly and more effective than placebo with incremental cost-effectiveness ratios of £17,095 per QALY (directly applicable and potentially serious limitations) and £10,226 per QALY (directly applicable and minor limitations). In both analyses, oxcarbazepine was the most cost-effective of included adjunctive AEDs.
Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.3.6.25  Sodium valproate versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

Sodium valproate and placebo were among AEDs included in a network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The complete results of this analysis are presented in section 10.3.7.

Health Economic Evidence

No studies were identified in the economic literature search. Sodium valproate was not included among comparators in the NCGC economic model for adjunctive treatment for refractory focal epilepsy because it is most commonly used as a first line monotherapy and was less effective than placebo in the NCGC network meta-analysis.

Evidence statements

Efficacy - statistically non significant results

No significant difference between sodium valproate adjunctive therapy and placebo for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (NCGC network meta-analysis)

Adverse events - statistically non significant results

No significant difference between sodium valproate adjunctive therapy and placebo for the proportion of participants withdrawing due to adverse events. (VERY LOW QUALITY)

No significant difference between sodium valproate adjunctive therapy and placebo for the proportion of participants withdrawing due to adverse events. (NCGC network meta-analysis)

Cost-effectiveness

No economic evidence comparing adjunctive sodium valproate to placebo was identified.
Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.3.6.26 Primidone versus sodium valproate

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Network meta-analysis

The evidence for this comparison was identified too late in the development of the guideline to incorporate it into the network meta-analysis of AEDs used as adjunctive therapy in adults with refractory focal epilepsy. The addition of this evidence is not expected to change the conclusions of the network meta-analysis. However, for completeness, this evidence will be added to the network meta-analysis during the consultation.

Health Economic Evidence

No studies were identified in the economic literature search. Neither sodium valproate nor primidone were included in the NCGC economic model of adjunctive AEDs used in the treatment of refractory focal epilepsy as sodium valproate is most commonly used as first line monotherapy and primidone is currently being withdrawn from the UK market.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on primidone than sodium valproate had at least 50% reduction in seizure frequency although there is uncertainty in the magnitude of clinical effect.

Efficacy - statistically non-significant results

No significant difference between primidone and sodium valproate for seizure freedom. (VERY LOW QUALITY)

Adverse events - statistically non-significant results

No significant difference between primidone and sodium valproate for withdrawal due to adverse events. (VERY LOW QUALITY)
Cost-effectiveness

No economic evidence comparing adjunctive sodium valproate to adjunctive primidone was identified.

Outcomes with no evidence

There were no studies that reported:
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.3.7 Network meta-analysis of AEDs used as adjunctive therapy for refractory focal epilepsy

Our analyses were based on a total of 56 studies, randomised to 17 different interventions used as adjunctive treatment. These studies formed the third and the fourth networks of evidence; the third was based on proportion of participants achieving at least 50% reduction in seizure frequency and the fourth on proportion of participants withdrawn due to adverse events. For details on these networks, please see pages 33-46 of Appendix O. The baseline risk for these two networks was calculated by aggregating the number of people achieving at least 50% reduction in seizure frequency and withdrawing due to adverse events across the placebo arms included in the adjunctive treatment networks and dividing by the aggregate sample size from the same arms.

The results of the network meta-analysis showed that most AEDs were significantly more effective in reducing at least 50% seizure frequency compared to placebo in refractory focal seizures. Based on point estimates, distribution of rank and proportion of simulations in which they are the most effective adjunctive AEDs for refractory focal seizures, carbamazepine, valproate, phenytoin, oxcarbazepine and phenytoin were the five most effective AEDs in achieving a reduction of at least 50% seizure frequency.

The results from the fourth network showed that most of the AEDs were less tolerable compared to placebo, with sodium valproate found to be the most tolerable AED with a probability of 66.7%.

For detailed explanation on methodology and results of NMA refer to Appendix O.

10.3.8 Health economic evidence of AEDs used as adjunctive therapy for adults with refractory focal epilepsy

11 studies published since the systematic review of economic studies undertaken to inform TA76 and TA79 were identified in the economic literature search. Nine of these studies were excluded from the economic evidence review due to poor applicability or very serious limitations. Full details of exclusion are included in appendix M.

Two studies assessing the cost-effectiveness of AEDs used as adjunctive therapy in adults with refractory focal epilepsy were included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adult patients with refractory focal epilepsy. This was based on clinical evidence from the network meta-analysis (see section 10.3.7). See appendix P for full details and results of modelling.
**Economic study characteristics**

**Table 10-11: Adjunctive therapy for adults with refractory focal epilepsy - Economic study characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC Model – adults adjunctive therapy (see Appendix P for details)</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; comparators included placebo, lamotrigine, oxcarbazepine, gabapentin, topiramate, levetiracetam, tiagabine, pregabalin, lacosamide, eslicarbazepine, zonisamide and vigabatrin; time horizon 15 years; clinical data based on NCGC network meta-analysis (see appendix O for details)</td>
</tr>
<tr>
<td>Hawkins (2005)150</td>
<td>Potentially serious limitations (a)</td>
<td>Partially applicable (b)</td>
<td>Decision analytic model; comparators included placebo, lamotrigine, gabapentin, tiagabine, oxcarbazepine, topiramate, levetiracetam; time horizon 15 years; clinical data based on network meta-analysis that included some studies with mixed focal and generalised epilepsy populations</td>
</tr>
<tr>
<td>Spackman (2007)252</td>
<td>Potentially serious limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; comparators included zonisamide and levetiracetam; time horizon 15 years</td>
</tr>
</tbody>
</table>

(a) Unit costs of interventions are from 2002/03 and since publication, lamotrigine has come off patent and the non-proprietary price is dramatically lower

(b) Costs and effects discounted at 6% and 1.5% per annum, respectively.

**Economic study results**

**NCGC adults adjunctive therapy model (directly applicable, minor limitations)**

For full details of base case and all sensitivity analyses, see appendix P.
Table 10-12: Adjunctive therapy for adults with refractory focal epilepsy – Summary of NCGC model findings

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£8,457</td>
<td>7.655</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0.36% Excluding LTG and OXC: 1.85% At £30K per QALY threshold: 0.03%</td>
</tr>
<tr>
<td>GBP</td>
<td>£8,808</td>
<td>7.723</td>
<td>£5,162</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 12.69% Excluding LTG and OXC: 75.42% At £30K per QALY threshold: 4.95%</td>
</tr>
<tr>
<td>LTG</td>
<td>£9,348</td>
<td>7.779</td>
<td>£9,643</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 40.07% Excluding LTG and OXC: 53.77%</td>
</tr>
<tr>
<td>OXC</td>
<td>£10,083</td>
<td>7.814</td>
<td>£21,000</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 42.94% At £30K per QALY threshold: 53.77%</td>
</tr>
<tr>
<td>LAC</td>
<td>£10,776</td>
<td>7.690</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0% Excluding LTG and OXC: 0.01% At £30K per QALY threshold: 0%</td>
</tr>
<tr>
<td>TGB</td>
<td>£11,084</td>
<td>7.732</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0.01% Excluding LTG and OXC: 0.21% At £30K per QALY threshold: 0.04%</td>
</tr>
<tr>
<td>TPM</td>
<td>£11,243</td>
<td>7.803</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 3.85% Excluding LTG and OXC: 20.76% At £30K per QALY threshold: 7.11%</td>
</tr>
<tr>
<td>LEV</td>
<td>£11,445</td>
<td>7.769</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0.08% Excluding LTG and OXC: 1.75% At £30K per QALY threshold: 0.2%</td>
</tr>
<tr>
<td>ESL</td>
<td>£12,877</td>
<td>7.757</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0% Excluding LTG and OXC: 0% At £30K per QALY threshold: 0.04%</td>
</tr>
<tr>
<td>ZON</td>
<td>£13,043</td>
<td>7.719</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0% Excluding LTG and OXC: 0% At £30K per QALY threshold: 0.02%</td>
</tr>
<tr>
<td>PGB</td>
<td>£14,887</td>
<td>7.771</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective. Base case: 0% Excluding LTG and OXC: 0% At £30K per QALY threshold: 0%</td>
</tr>
</tbody>
</table>

(a) VGB was included in an analysis, and was found to be very cost-effective (£8,059 compared to placebo). This finding is not presented here as the model does not adequately capture the potential harms of vision defect that have been associated with long term use of VGB.
Evidence statements

Adjunctive oxcarbazepine is the most effective and most cost-effective AED among evaluated adjunctive AEDs (directly applicable and minor limitations).

Adjunctive lamotrigine is also likely to be cost-effective with an acceptable incremental cost-effectiveness over adjunctive gabapentin and was the optimal AED in nearly 40% of simulations given a threshold willingness to pay of £20,000 per QALY (directly applicable and minor limitations).

Adjunctive gabapentin is among the less effective AEDs, but is cost-effective compared to placebo and is less costly and more effective than both adjunctive lacosamide and adjunctive eslicarbazepine (directly applicable and minor limitations).

If lamotrigine and oxcarbazepine were excluded because they had been previously tried and failed as monotherapy, adjunctive gabapentin is the most likely to be cost-effective, but topiramate may also be cost-effective (directly applicable and minor limitations).

Eslicarbazepine, lacosamide, levetiracetam, pregabalin, tiagabine and zonisamide were more costly and less effective than other adjunctive AED options including topiramate and oxcarbazepine (directly applicable and minor limitations).

Hawkins 2005 (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.
Table 10-13: Adjunctive therapy for adults with refractory focal epilepsy – Summary of Hawkins 2005\textsuperscript{150} findings

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£5,064</td>
<td>8.716</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Base case: 40% Excluding LTG and OXC: 58%</td>
</tr>
<tr>
<td>GBP</td>
<td>£5,861</td>
<td>8.747</td>
<td>Extended</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dominance</td>
<td>Base case: 2% Excluding LTG and OXC: 12%</td>
</tr>
<tr>
<td>LTG</td>
<td>£5,926</td>
<td>8.746</td>
<td>Extended</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dominance</td>
<td>Base case: 2% Excluding LTG and OXC: 12%</td>
</tr>
<tr>
<td>TGB</td>
<td>£6,133</td>
<td>8.758</td>
<td>Extended</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dominance</td>
<td>Base case: 2% Excluding LTG and OXC: 12%</td>
</tr>
<tr>
<td>OXC</td>
<td>£6,400</td>
<td>8.794</td>
<td>£17,095</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td>LEV</td>
<td>£6,984</td>
<td>8.775</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
<tr>
<td>TPM</td>
<td>£7,026</td>
<td>8.777</td>
<td>Dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective</td>
</tr>
</tbody>
</table>

Evidence statements

Adjunctive oxcarbazepine is the most effective and most cost-effective AED among evaluated adjunctive AEDs (partially applicable and potentially serious limitations).

Adjunctive gabapentin, adjunctive lamotrigine and adjunctive tiagabine are ruled out through extended dominance by adjunctive oxcarbazepine and placebo (monotherapy) (partially applicable and potentially serious limitations).

Adjunctive levetiracetam and adjunctive topiramate are more costly and less effective than adjunctive oxcarbazepine (partially applicable and potentially serious limitations).

Spackman 2007\textsuperscript{252} (directly applicable, potentially serious limitations)

See economic evidence table in appendix M for details.
Table 10-14: Adjunctive therapy for adults with refractory focal epilepsy – Summary of Spackman 2007

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEV</td>
<td>£15,610</td>
<td>7.897</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZON</td>
<td>£15,630</td>
<td>7.923</td>
<td>£761</td>
<td>No probabilistic sensitivity analysis was performed. The results did not change dramatically in one-way sensitivity analyses of discounting rates, shorter time horizon, variation to proportion of responders, variation in utility weights. Annual cost of each AED did impact results: cost of LEV halved or cost of ZON doubled makes ICER of ZON £45K+.</td>
</tr>
</tbody>
</table>

Evidence statements

Adjunctive zonisamide is cost-effective compared to adjunctive levetiracetam (directly applicable and potentially serious limitations). However, other economic evaluations showed both levetiracetam and zonisamide to be more costly and less effective than other adjunctive AEDs.

10.3.9 Adjunctive therapy for children with refractory focal epilepsy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. The complete results of this study and the NCGC children adjunctive therapy model are presented in section 10.3.10.

Evidence statements

Efficacy – statistically significant results

Significantly more children on the lamotrigine adjunctive therapy than the placebo experienced at least a 50% reduction in seizure frequency. (HIGH QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for withdrawal due to lack of efficacy (LOW QUALITY)

Adverse events – statistically significant

Significantly more children on lamotrigine adjunctive therapy compared to placebo had:

- Higher incidence of dizziness although there is uncertainty in the magnitude of effect. (MODERATE QUALITY)
- Higher incidence of tremor (MODERATE QUALITY)
• Higher incidence of nausea (MODERATE QUALITY)
• Incidence of ataxia although there is uncertainty in the magnitude of effect. (MODERATE QUALITY)

Adverse events – statistically non-significant
No significant difference between lamotrigine adjunctive therapy and placebo for withdrawal due to adverse events. (LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and placebo for:

• Incidence of vomiting (LOW QUALITY)
• Incidence of somnolence (LOW QUALITY)
• Incidence of infection (LOW QUALITY)
• Incidence of rash (LOW QUALITY)
• Incidence of headache (LOW QUALITY)
• Incidence of rhinitis (LOW QUALITY)
• Incidence of accidental injury (LOW QUALITY)
• Incidence of diarrhea (LOW QUALITY)
• Incidence of fever (LOW QUALITY)
• Incidence of abdominal pain (LOW QUALITY)
• Incidence of otitis media (LOW QUALITY)
• Incidence of pharyngitis (LOW QUALITY)
• Incidence of asthenia (LOW QUALITY)

Cognitive outcomes – statistically non-significant results
No significant difference between lamotrigine adjunctive therapy and placebo in children for all cognitive tests.

Quality of life outcomes – statistically significant results
Significantly higher scores acquired when on lamotrigine adjunctive therapy than placebo for happiness and mastery domains.

Cost-effectiveness
One economic evaluation based on a decision analytic model showed considerable uncertainty into the cost-effectiveness of adjunctive lamotrigine and did not produce a point estimate of its incremental cost-effectiveness over placebo. In 77% of simulations, placebo came out as optimal given a £20,000 per QALY willingness to pay threshold (partially applicable and potentially serious limitations).
One economic evaluation based on a decision analytic model showed adjunctive lamotrigine to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £8,157 per QALY. However, in this analysis, adjunctive lamotrigine was extendedly dominated by adjunctive oxcarbazepine and adjunctive gabapentin. (directly applicable and potentially serious limitations).

10.3.9.1 Levetiracetam versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. The complete results of the NCGC children adjunctive therapy model are presented in section 10.3.10.

Evidence statements
Efficacy - statistically significant results
Significantly more participants on levetiracetam adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (HIGH QUALITY)

Efficacy – statistically non-significant results
No significant difference between levetiracetam adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically significant
Significantly more participants on levetiracetam adjunctive therapy than the placebo experienced somnolence. (MODERATE QUALITY)

Adverse events – statistically non-significant
No significant difference between levetiracetam adjunctive therapy and placebo for withdrawal due to adverse events. (LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy and placebo for:

- Incidence of accidental injury (LOW QUALITY)
- Incidence of vomiting (LOW QUALITY)
- Incidence of anorexia (LOW QUALITY)
- Incidence of rhinitis (LOW QUALITY)
- Incidence of hostility (LOW QUALITY)
- Incidence of increased cough (LOW QUALITY)
Cost-effectiveness

One economic evaluation based on a decision analytic model showed adjunctive levetiracetam to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £10,741 per QALY. In this analysis, levetiracetam was shown to be the most costly and most effective and most cost-effective of AEDs evaluated (directly applicable and potentially serious limitations).

10.3.9.2 Topiramate versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
One economic evaluation of AEDs, including topiramate and placebo, used as adjunctive therapy in the treatment of children with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. The complete results of this study and the NCGC children adjunctive therapy model are presented in section 10.3.10.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between topiramate adjunctive therapy and placebo for proportion of participants experiencing at least a 50% reduction in seizure frequency. (LOW QUALITY)
No significant difference between topiramate adjunctive therapy and placebo for proportion of seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant
No significant difference between topiramate adjunctive therapy and placebo for proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between topiramate adjunctive therapy and placebo for:
  - Incidence of upper respiratory tract infection (VERY LOW QUALITY)
  - Incidence of sinusitis (VERY LOW QUALITY)
  - Incidence of coughing (VERY LOW QUALITY)
  - Incidence of diarrhea (VERY LOW QUALITY)
  - Incidence of somnolence (VERY LOW QUALITY)
  - Incidence of anorexia (VERY LOW QUALITY)
  - Incidence of emotional lability (VERY LOW QUALITY)
  - Incidence of difficulty with concentration or attention (VERY LOW QUALITY)
  - Incidence of mood problems (VERY LOW QUALITY)
• Incidence of viral infection (VERY LOW QUALITY)
• Incidence of otitis media (VERY LOW QUALITY)
• Incidence of rash (VERY LOW QUALITY)
• Incidence of purpura (VERY LOW QUALITY)
• Incidence of fever (VERY LOW QUALITY)
• Incidence of injury (VERY LOW QUALITY)
• Incidence of fatigue (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed considerable uncertainty into the cost-effectiveness of adjunctive topiramate and did not produce a point estimate of its incremental cost-effectiveness over placebo. In 70% of simulations, placebo came out as optimal given a £20,000 per QALY willingness to pay threshold (partially applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed adjunctive topiramate to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £11,614 per QALY. However, in this analysis, adjunctive topiramate was extendedly dominated by adjunctive levetiracetam and adjunctive oxcarbazepine (directly applicable and potentially serious limitations).

10.3.9.3 Gabapentin versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation of AEDs, including gabapentin and placebo, used as adjunctive therapy in the treatment of children with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. The complete results of this study and the NCGC children adjunctive therapy model are presented in section 10.3.10.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and placebo for at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and placebo for withdrawal due to adverse events. (VERY LOW QUALITY)
Cost-effectiveness

One economic evaluation based on a decision analytic model showed considerable uncertainty into the cost-effectiveness of adjunctive gabapentin and did not produce a point estimate of its incremental cost-effectiveness over placebo. In 82% of simulations, placebo came out as optimal given a £20,000 per QALY willingness to pay threshold (partially applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed adjunctive gabapentin to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £2,370 per QALY. In this analysis, adjunctive oxcarbazepine and adjunctive levetiracetam were more costly and more effective than adjunctive gabapentin, with acceptable incremental cost-effectiveness ratios (directly applicable and potentially serious limitations).

10.3.9.4 Oxcarbazepine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation of AEDs, including oxcarbazepine and placebo, used as adjunctive therapy in the treatment of children with refractory focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. The complete results of this study and the NCGC children adjunctive therapy model are presented in section 10.3.10.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on oxcarbazepine adjunctive therapy (in children) than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine adjunctive therapy and placebo for seizure freedom. (LOW QUALITY)

No significant difference between oxcarbazepine adjunctive therapy and placebo for withdrawal due to lack of efficacy (VERY LOW QUALITY)

Adverse events – statistically significant

Significantly more participants on oxcarbazepine adjunctive therapy than the placebo experienced withdrawal due to adverse events. (VERY LOW QUALITY)

Significantly more participants on oxcarbazepine adjunctive therapy than the placebo experienced:

- Somnolence (LOW QUALITY)
- Headache (LOW QUALITY)
- Dizziness (LOW QUALITY)
- Ataxia (LOW QUALITY)
• Abnormal gait (LOW QUALITY)
• Nystagmus (VERY LOW QUALITY)
• Vomiting (LOW QUALITY)
• Nausea (LOW QUALITY)
• Diplopia (LOW QUALITY)
• Abnormal vision (LOW QUALITY)

**Adverse events – statistically non-significant**

No significant difference between oxcarbazepine adjunctive therapy and placebo for:

• Incidence of abdominal pain (VERY LOW QUALITY)
• Incidence of anorexia (VERY LOW QUALITY)
• Incidence of fever (VERY LOW QUALITY)
• Incidence of fatigue (VERY LOW QUALITY)
• Incidence of rhinitis (VERY LOW QUALITY)
• Incidence of pharyngitis (VERY LOW QUALITY)
• Incidence of upper respiratory tract syndrome (VERY LOW QUALITY)
• Incidence of viral infection (VERY LOW QUALITY)

**Cost-effectiveness**

One economic evaluation based on a decision analytic model showed considerable uncertainty into the cost-effectiveness of adjunctive oxcarbazepine and did not produce a point estimate of its incremental cost-effectiveness over placebo. In 70% of simulations, placebo came out as optimal given a £20,000 per QALY willingness to pay threshold (partially applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed adjunctive oxcarbazepine to be more costly and more effective than placebo with an incremental cost-effectiveness ratio of £7,448 per QALY. However, in this analysis, adjunctive levetiracetam was more costly and more effective than adjunctive oxcarbazepine, with an acceptable incremental cost-effectiveness ratio (directly applicable and potentially serious limitations).

### 10.3.9.5 Topiramate versus placebo (infants)

**Clinical evidence**

For details on the direct clinical evidence please refer to Appendix N.

**Health Economic Evidence**

No studies were identified in the economic literature search.
Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo for at least 50% reduction in seizure frequency. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo for withdrawal due to adverse events. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive topiramate to placebo in infants was identified.

10.3.10 Health economic evidence of AEDs used as adjunctive therapy for children with refractory focal epilepsy

One study\textsuperscript{155} assessing the cost-effectiveness of AEDs used as adjunctive therapy in children with refractory focal epilepsy was identified in the economic literature search and included in the economic evidence review. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. This was based on evidence included in the clinical review\textsuperscript{233,234,236,238}. See appendix P for full details and results of modelling.

Economic study characteristics

Table 10-15: Adjunctive therapy for children with refractory focal epilepsy - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC Model – children adjunctive therapy (see Appendix P for details)</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; comparators included carbamazepine, carbamazepine controlled release, oxcarbazepine, sodium valproate, lamotrigine, topiramate and levetiracetam; time horizon 15 years; clinical data based on systematic review detailed above.</td>
</tr>
<tr>
<td>Frew (2007)\textsuperscript{155}</td>
<td>Potentially serious limitations (a)</td>
<td>Partially applicable (b)</td>
<td>Decision analytic model; comparators were treatment sequences including gabapentin, lamotrigine, oxcarbazepine and topiramate as possible adjunctive therapy all compared to a baseline of only older AEDs (carbamazepine, sodium valproate and phenytoin); time horizon up to 15 years; clinical data based on Nieto-Barrera 2001\textsuperscript{152}, Zamponi 1999\textsuperscript{154};</td>
</tr>
</tbody>
</table>

(a) 2002/03 UK pounds
(b) costs discounted at 6% per annum; Effects discounted at 1.5% per annum

Updated 2011
Economic study results

NCGC Model – children adjunctive therapy (directly applicable, minor limitations)
For full details of base case and all sensitivity analyses, see appendix P.

Table 10-16: Adjunctive therapy for children with refractory focal epilepsy – Results from NCGC 2010

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£16,149</td>
<td>9.471</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>£16,204</td>
<td>9.494</td>
<td>£2,370</td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>£16,720</td>
<td>9.541</td>
<td>£10,981 (Extended Dominance)</td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>£16,864</td>
<td>9.567</td>
<td>£9,045</td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>£17,362</td>
<td>9.575</td>
<td>£62,300 (Extended Dominance)</td>
<td></td>
</tr>
<tr>
<td>LEV</td>
<td>£17,642</td>
<td>9.610</td>
<td>£18,088</td>
<td></td>
</tr>
</tbody>
</table>

Evidence statements

Adjunctive levetiracetam is the most effective and most costly AED, and is likely to be considered cost-effective with an acceptable incremental cost-effectiveness ratio compared to all other AEDs included in the analysis (directly applicable and minor limitations). However, its likelihood of being optimal decreases as the age (and therefore weight and daily dose) of the hypothetical cohort increases.

Adjunctive gabapentin has the greatest probability of being considered cost-effective at a threshold willingness to pay of £20,000 per QALY and in all sensitivity analyses conducted (directly applicable and minor limitations).
Adjunctive oxcarbazepine is very likely to be cost-effective compared to placebo, adjunctive gabapentin, adjunctive lamotrigine and adjunctive topiramate (directly applicable and minor limitations).

Adjunctive lamotrigine and adjunctive topiramate are ruled out through extended dominance by combinations of other adjunctive AEDs evaluated (directly applicable and minor limitations).

*Frew 2007*  **(directly applicable, potentially serious limitations)**  
See economic evidence table in appendix M for details.

**Table 10-17: Adjunctive therapy for children with refractory focal epilepsy – Results from Frew 2007**

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs)</th>
<th>ICER (£ / QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (no new AEDs)</td>
<td>Point estimates cannot be determined from the data provided</td>
<td></td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 0%</td>
<td></td>
</tr>
<tr>
<td><strong>TPM (adjunctive therapy)</strong></td>
<td>Point estimates cannot be determined from the data provided</td>
<td>More costly and possibly more effective, but ICER cannot be determined from the data provided.</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 30%</td>
<td></td>
</tr>
<tr>
<td><strong>OXC (adjunctive therapy)</strong></td>
<td>Point estimates cannot be determined from the data provided</td>
<td>Likely dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 30%</td>
<td></td>
</tr>
<tr>
<td><strong>LTG (second line monotherapy)</strong></td>
<td>Point estimates cannot be determined from the data provided</td>
<td>Likely dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 23%</td>
<td></td>
</tr>
<tr>
<td><strong>LTG (adjunctive therapy)</strong></td>
<td>Point estimates cannot be determined from the data provided</td>
<td>Likely dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 23%</td>
<td></td>
</tr>
<tr>
<td><strong>GBP (adjunctive therapy)</strong></td>
<td>Point estimates cannot be determined from the data provided</td>
<td>Likely dominated</td>
<td>At £20K per QALY threshold, probability most cost-effective Base case: 18%</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence statements**

Cost-effectiveness of adjunctive AEDs including gabapentin, lamotrigine, oxcarbazepine and topiramate compared to a baseline strategy of only older AEDs is highly uncertain. No definitive conclusion about relative cost-effectiveness can be determined.
10.3.11 Recommendations and link to evidence

Adjunctive treatment in adults and children with refractory focal seizures

**Recommendation**
Offer clobazam*, gabapentin*, lamotrigine, oxcarbazepine, or topiramate as adjunctive treatment to adults and children with focal seizures if first-line treatments (see recommendations 4.10.3.1 and 4.10.3.2) are ineffective or not tolerated. [new 2011]

**Relative values of different outcomes**
In adults and children, the achievement of seizure freedom or at least a 50% reduction in seizure frequency were the most clinically relevant outcomes. Tolerability, as measured by withdrawals due to adverse events, was also considered important.

**Trade off between clinical benefits and harms**
From the direct comparative evidence for adults, significantly more participants receiving clobazam, oxcarbazepine and topiramate achieved seizure freedom than placebo. Significantly more on gabapentin, oxcarbazepine, lamotrigine and topiramate experienced at least a 50% reduction in seizure frequency when compared to placebo. From the direct evidence for children, significantly more participants on lamotrigine and oxcarbazepine compared to placebo experienced at least a 50% reduction in seizure frequency. More people on oxcarbazepine (adults and children) achieved seizure freedom than those on placebo in a refractory population on monotherapy.

Also from the direct evidence, the drugs recommended above had unfavourable adverse events profiles, but the GDG found this unsurprising given that they were being evaluated as combination treatment in a refractory population. Many of the adverse events observed in the trials were dose related and in clinical practice these can be mitigated through careful dose titration. Significantly more participants receiving clobazam and gabapentin withdrew due to adverse events compared to placebo. Gabapentin had higher incidence of somnolence, dizziness and ataxia and aggravation of seizures when compared to placebo. No specific adverse events were reported in the trial for clobazam, but GDG considered its tendency to have sedative side effects and its efficacy can wane over extended use. Oxcarbazepine and lamotrigine had a less favourable adverse events profile compared to placebo. Topiramate had higher incidence of headache when compared with lamotrigine. In children taking lamotrigine the incidence of dizziness, tremor, nausea and ataxia were higher compared to to placebo.

The network meta-analysis findings showed almost all AEDs to be more effective than placebo on the outcome of reducing seizure frequency by at least 50%, but none were demonstrably more effective than another (all had overlapping 95% credible intervals). On considering

* Please see appendix K for licensing details.
adjunctive therapy it is presumed sodium valproate and/or carbamazepine will already have been trialled as monotherapy and hence why not listed as a therapy here. Almost all AEDs were less tolerable than placebo, but none were demonstrably more or less tolerable than another (all had overlapping 95% credible intervals). Oxcarbazepine and topiramate were the 4th and 5th most effective AEDs in reducing at least 50% seizure frequency but they were within the five least tolerable among the 17 AEDs compared in the network meta-analysis for refractory focal seizures. Lamotrigine ranked the 6th most effective and the 7th most tolerable AED among the 17 AEDs. Gabapentin ranked among the least tolerable and the least tolerated. Lamotrigine extended release was less effective and less well tolerated than normal release lamotrigine. Owing to a lack of data, clobazam was not evaluated in the effectiveness network, but it was shown to be the 6th least tolerated in the network evaluating withdrawal due to adverse events.

A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. For the drugs recommended here, the treatment benefits outweighed the harms for the average patient and the QALYs gained justified the additional costs over placebo (no adjunctive AED).
Economic considerations

Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. Oxcarbazepine was consistently among the most cost-effective AEDs used as adjunctive therapy in adults and children with focal epilepsy. Lamotrigine was just ruled out through extended dominance in both original economic analyses for adults and children, but as it was still optimal in a non-negligible number of simulations and in various sensitivity analyses, the GDG considered its benefits very likely to be worth the additional cost. In the original economic analyses, gabapentin, whilst not being the most effective AED, was shown to be cost-effective compared to alternatives, even dominating some of the newer AEDs such as lacosamide and eslicarbazepine. Although not cost-effective in the base case when all other AEDs were evaluated, adjunctive topiramate is cost-effective if lamotrigine and oxcarbazepine have already been trialed as first-line monotherapy.

Adjunctive levetiracetam was shown to be cost-effective in the original analysis undertaken for children, but its cost-effectiveness is sensitive to the starting age of the hypothetical cohort. The older the starting age, the less likely adjunctive levetiracetam is to be cost-effective. The cost-effectiveness of AEDs, particularly the newer AEDs, is closely linked to the daily dose required as drug cost is the largest contributor to total costs. Therefore, in the model, the sooner children reach adult doses, the less cost-effective levetiracetam becomes. In the economic analysis for adults only, levetiracetam was more costly and less effective than topiramate and had a less than 1% probability of being optimal at a willingness to pay of £20,000 or £30,000 per QALY gained in the base case and all but one sensitivity analysis where it had a 4.5% probability at a £20K threshold.

Quality of evidence

For adults, the majority of evidence was placebo controlled and there were few head to head comparisons. All of the studies were randomised controlled trials, the majority of which were double-blind. Most of the studies gave unclear details of their methods of randomisation, allocation concealment and blinding. The statistically significant results for 50% reduction in seizure frequency were from the placebo-controlled studies. None of the evidence comparing drugs was statistically significant. The evidence for children was of higher quality with less chance of bias. The quality overall was generally low or very low.

The economic evidence varied in methodological quality, but was all directly applicable. Some had out of date costs that could change the study’s conclusions or had did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Limitations of the
original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.

**Other considerations**

The drugs recommended above are older and therefore there is long-term experience with them. Eslicarbazepine, lacosamide, pregabalin, and zonisamide showed efficacy but were not included for first-line adjunctive treatment as they are newer drugs and the GDG felt that there needed to be more long-term evidence of their efficacy and cost-effectiveness for adjunctive treatment. There is limited evidence for tiagabine being effective.

Gabapentin was included as first-line adjunctive drug option, but based on the clinical experience of the GDG was regarded as less effective than the other AEDs.

The GDG considered the addition of oxcarbazepine without trying carbamazepine as unusual but may be considered, as it is less enzyme inducing.

In clinical practice a second AED is added to the first. If the latter helps the first may be taken away if the patient agrees.\textsuperscript{253}

Care should be taken with clobazam when withdrawing and a slow withdrawal of clobazam over/up to 4-6m in view of the risk of withdrawal seizures. Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in the lamotrigine dose. Topiramate may affect phenytoin levels.
Recommendation
Discuss management with, or offer referral to, a tertiary epilepsy specialist if adjunctive treatment with AEDs listed in recommendation 4.12.3 is ineffective or not tolerated in adults and children with focal seizures. Other AEDs that may be considered are: eslicarbazepine*, lacosamide, levetiracetam, phenobarbital, phenytoin, pregabalin*, tiagabine and zonisamide*. [new 2011]

Relative values of different outcomes
In adults and children, achievement of at least a 50% reduction in seizure frequency was an important outcome. These AEDs have evidence of efficacy in some patients, and may benefit patients who have not responded to and/or who have experienced adverse effects with other AEDs.

Trade off between clinical benefits and harms
The balance of benefit and adverse effects needs to be carefully monitored in all patients, and it must be recognised that different individuals may have different responses to various AEDs. From the direct evidence for adults, lacosamide, zonisamide, eslicarbazepine, levetiracetam and pregabalin had more participants with at least 50% reduction in seizure frequency when compared to placebo. Eslicarbazepine, levetiracetam, levetiracetam extended-release and pregabalin also had more seizure freedom than placebo. Phenobarbital was added by the GDG based on their professional opinion. Tiagabine was not significantly different when compared with placebo and was found to have no difference when compared to lamotrigine, levetiracetam or phenytoin. In children, significantly more participants on levetiracetam compared to placebo experienced at least a 50% reduction in seizure frequency.

Also from the direct evidence pregabalin was shown to have a less favourable adverse events profile, causing greater withdrawal due to adverse events than placebo. Eslicarbazepine, lacosamide, zonisamide and tiagabine had more withdrawal due to adverse events and more adverse events than placebo arm. There was no difference between phenytoin and tiagabine or lamotrigine and tiagabine for withdrawal due to adverse events. There was no significant difference between levetiracetam and placebo for withdrawal due to adverse events although incidence of adverse events was significantly higher in the levetiracetam arm.

The network meta-analysis findings showed almost all AEDs to be more effective than placebo on the outcome of reducing seizure frequency by at least 50%, but none were demonstrably more effective than another (all had overlapping 95% credible intervals). Almost all AEDs were less tolerable than placebo, but none were demonstrably more or less tolerable than another (all had overlapping 95% credible intervals). Pregabalin was ranked among the five least effective AEDs in terms of reducing at least 50% seizure

* Please see appendix K for licensing details.
frequency, and was also the least tolerable. Levetiracetam ranked the 8th most effective and the 8th most tolerable AED among the 17 AEDs compared in the network meta-analysis. Tiagabine, zonisamide and lacosamide ranked in the five least effective and tolerable places. Eslicarbazepine was on the fourth least effective AED but was shown to be the fourth most tolerable AED among the 17 AEDs compared. Finally, owing to a lack of data, phenytoin was not evaluated in the tolerability network, but it was shown to be of the third most effective AED in the network meta-analysis of 17 AEDs.

A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. The drugs recommended for consideration here were effective to varying degrees, but the treatment benefits, in terms of QALYs gained, or in some cases lost, did not justify the additional costs over drugs recommended in the previous recommendation (gabapentin, lamotrigine, oxcarbazepine, topiramate).

**Economic considerations**

Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. One published study showed adjunctive zonisamide to be cost-effective compared to adjunctive levetiracetam, but in all other studies and/or in the original modelling work undertaken for the guideline, neither levetiracetam nor zonisamide were shown to be cost-effective compared to alternative AEDs. In the economic analysis undertaken for the guideline, eslicarbazepine, lacosamide, levetiracetam, pregabalin, tiagabine and zonisamide were all more costly and less effective than either oxcarbazepine or topiramate. Therefore, the GDG considered that these drugs were more costly with no extra benefit for the average patient and should therefore be reserved for cases where previously recommended drugs are contraindicated or have been tried and were either not effective or not tolerated.

The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome.

**Quality of evidence**

Overall the quality of evidence was low and most of the studies had unclear or no details of randomisation, allocation concealment or blinding and higher drop-out in the treatment arms. There was no evidence found for phenobarbital but this recommendation is based on GDG expertise.

The economic evidence varied in methodological quality, but was all directly applicable. Some had out of date costs that
could change the study’s conclusions or had did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.

**Other considerations**

GDG consensus opinion was that management should be discussed with patients or they should be offered referral to, a tertiary epilepsy specialist if adjunctive treatment with AEDs listed in recommendation 1.13.2.1 is ineffective or not tolerated because achieving successful treatment may be complex.

Long term experience with some of these drugs (pregabalin, lacosamide, zonisamide and eslicarbazepine) is limited. There is limited evidence for tiagabine being effective.

Care should be taken when withdrawing phenobarbitone and should be slowly withdrawn in view of the risk of withdrawal seizures.
**Recommendation**

Only offer vigabatrin to adults and children who are receiving tertiary epilepsy specialist care, because of the potential for serious adverse effects. [new 2011]

**Relative values of different outcomes**

In adults, at least 50% reduction in seizure frequency was an important outcome, as was tolerability in the short and longer term.

**Trade off between clinical benefits and harms**

From the direct evidence, more participants on vigabatrin experienced seizure freedom or at least a 50% reduction in seizure frequency than participants taking placebo. Also, in terms of efficacy, there was no significant difference between vigabatrin and gabapentin.

The results of the network meta-analysis showed that vigabatrin was the seventh most effective and the fourth least tolerable AED among the 17 AEDs compared in the network meta-analysis for refractory focal seizures. However, withdrawals due to adverse events were also higher with vigabatrin than placebo.

Vigabatrin has a harmful and irreversible side effects profile with retinal toxicity causing visual impairment, according to the GDG expertise and epilepsy literature. These side effects occur over the longer term and would not be observed in any of the short term trials combined in the direct and indirect evidence presented above. The short term trial evidence did show that significantly more participants on vigabatrin had drowsiness, dizziness and withdrawal due to adverse events than placebo.

**Economic considerations**

Vigabatrin was specifically excluded from various published economic evaluations due to its potential for long term toxicity and adverse effects. It was included in the original economic analysis undertaken for this guideline and was shown to be very effective and cost-effective. However, a very serious limitation of the model was that it did not account for vigabatrin’s potential for long term toxicity and development of visual field defects. Vigabatrin’s cost-effectiveness in the model was driven by its efficacy and relatively low rates of withdrawal due to adverse events from short term trial data. Had the model accounted for long term, irreversible effects to vision, it is unlikely to have performed quite as well. The GDG recognised its relative effectiveness over other AEDs, and considered the risk of long term visual field defect to outweigh its clinical benefit.

**Quality of evidence**

The majority of evidence was placebo controlled and there were few head to head comparisons. All of the studies were randomised controlled trials, the majority of which were double-blind. Most of the studies gave unclear details of their methods of randomisation, allocation concealment and blinding. The statistically significant results for 50% reduction in seizure frequency were from the placebo-controlled studies. None of the evidence comparing drugs directly was
statistically significant.

The original decision model undertaken for the guideline aimed to overcome the limitations of previous analyses, but in terms of modelling the long term costs and outcomes associated with vigabatrin, the model fell short. Due to this limitation, results concerning vigabatrin’s cost-effectiveness were of limited value to GDG decision-making.

Other considerations

Careful evaluation of risk/benefit for each individual needs to be undertaken for each individual and the GDG consensus opinion was that vigabatrin should only be prescribed in tertiary epilepsy specialist care.
10.4 Idiopathic Generalised Epilepsy (IGE)

10.4.1 Introduction

The idiopathic generalised epilepsies are a group of epilepsies characterised by typical absences, myoclonic jerks and generalised tonic clonic seizures, alone or in varying combinations in otherwise normal individuals. They probably constitute up to one third of all the epilepsies and are genetically determined. The EEG is characteristic, demonstrating a distinct pattern of generalised polyspike wave discharges and/or generalised spike wave which may be provoked by hyperventilation or sleep deprivation. Some IGEs are associated with photosensitivity.

Depending on the relative prevalence of individual seizure types, the age of onset and frequency of spike wave activity, IGE may be further categorised into individual syndromes. The predominant characteristics of those to be considered in this review are outlined in the table.

This section contains studies that look at idiopathic generalised epilepsies (IGE) (including all) and looking separately on the following subgroups:

- Epilepsy with Tonic-Clonic Seizures only
- Absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes)
- Juvenile Myoclonic Epilepsy.

### Table 10-18: Characteristics of the individual syndromes

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Age of onset</th>
<th>Predominant seizure types/frequency</th>
<th>EEG</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Absence Epilepsy</td>
<td>4-10 years</td>
<td>Absence, many/day GTCS infrequent</td>
<td>3Hz generalised spike and wave</td>
<td>80% remit by adulthood</td>
</tr>
<tr>
<td>Juvenile Absence Epilepsy</td>
<td>9-13 years</td>
<td>Absence GTCS in 80% Myoclonic jerks infrequent</td>
<td>3-4Hz generalised spike and wave Photosensitivity 8%</td>
<td>Lifelong; seizure control in 70-80%</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>5-16 years</td>
<td>Myoclonic jerks on awakening in all GTCS in most Absence in &gt;30% (may be initial seizure type)</td>
<td>3-6 Hz generalised polyspike and wave Photosensitivity in &gt;30%</td>
<td>Lifelong; seizure control in up to 90% patients</td>
</tr>
<tr>
<td>Epilepsy with GTCS only</td>
<td>6-30 years</td>
<td>GTCS 1-2 hours after waking</td>
<td>Generalised polyspike wave in up to 50% patients</td>
<td>Lifelong; seizure control in 90%</td>
</tr>
</tbody>
</table>
10.4.2 Methods of the evidence review of IGE

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with the following syndromes: Absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes), Juvenile Myoclonic Epilepsy and Epilepsy with Tonic-Clonic Seizures only.

10.4.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for IGE. The following interventions were included in our search; clobazam, clonazepam, ethosuximide, lamotrigine, levetiracetam, sodium valproate topiramate and zonisamide. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below are the matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
### Matrix of the evidence for IGE

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Oxcarbazepine</th>
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</table>

Updated 2011
Matrix of the evidence for Generalised Tonic-Clonic Seizures only

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Oxcarbazepine</th>
<th>Phenytoin</th>
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<td>ACT</td>
<td>VPA</td>
<td>ZNS</td>
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</tr>
</tbody>
</table>
Matrix of the evidence for Absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Ethosuximide</th>
<th>Zonisamide</th>
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<th>Clonazepam</th>
<th>Sodium valproate</th>
</tr>
</thead>
</table>

Matrix of the evidence for Juvenile Myoclonic Epilepsy

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Clobazam</th>
<th>Clonazepam</th>
<th>Zonisamide</th>
<th>Sodium valproate</th>
</tr>
</thead>
</table>
10.4.4 AEDs for the treatment of IGE

10.4.4.1 Lamotrigine monotherapy versus sodium valproate monotherapy in newly diagnosed patients

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
Two economic evaluations \(^{134,150}\) of AEDs, including lamotrigine and sodium valproate, used as monotherapy in the treatment of people with newly diagnosed IGE were identified and included in the economic literature search. The complete results of these studies are presented in section 10.4.5.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking sodium valproate monotherapy compared to lamotrigine had seizure freedom. (VERY LOW QUALITY)

Significantly fewer participants taking sodium valproate monotherapy compared to lamotrigine monotherapy withdrew due to lack of efficacy (VERY LOW QUALITY)

Sodium valproate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to first seizure and time to exit/withdrawal (LOW QUALITY).

Sodium valproate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to exit/withdrawal (LOW QUALITY).

Adverse events - statistically non-significant results

No significant difference between lamotrigine monotherapy versus sodium valproate monotherapy in the proportion of participants withdrawn due to adverse events (VERY LOW QUALITY).

There is no significant difference between lamotrigine monotherapy versus sodium valproate monotherapy in the incidence of:

- Tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY).
- Incidence of other side-effects (please see extraction for full list) (VERY LOW QUALITY).
Quality of Life - statistically significant results

Significantly more participants taking lamotrigine monotherapy compared to sodium valproate monotherapy had higher scores at 2 years on the GQoL questionnaire (LOW QUALITY).

Quality of Life - statistically non-significant results

There is no significant difference between lamotrigine and sodium valproate monotherapy in:

- Two year anxiety scores (VERY LOW QUALITY)
- Two year depression scores (VERY LOW QUALITY)
- Two year AEP scores (VERY LOW QUALITY)
- Two year neurotoxicity scale scores (VERY LOW QUALITY)
- Two year EQ-5D scores (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:

- At least a 50% reduction in seizure frequency
- Any outcomes relating to cognitive effects.

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, lamotrigine monotherapy is more effective than sodium valproate in terms of total QALYs gained and also less costly when using 2010 drug costs. This evidence is directly applicable but has potentially serious limitations.

Evidence from another cost-effectiveness analysis indicates that lamotrigine monotherapy is more costly and less effective than sodium valproate in terms of total QALYs gained. The evidence is directly applicable but as it uses costs from 2001-02, it has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, sodium valproate monotherapy is more costly and more effective at preventing seizures than lamotrigine monotherapy (ICER=£5 per seizure avoided). This evidence is partially applicable and has potentially serious limitations.

10.4.4.2 Topiramate monotherapy versus sodium valproate monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation of AEDs, including topiramate and sodium valproate, used as monotherapy in the treatment of people with newly diagnosed IGE was identified and included in the economic literature search. The complete results of this study are presented in section 10.4.5.

Evidence statements

Efficacy – statistically significant results

Valproate monotherapy is significantly more effective than topiramate monotherapy in prolonging time to exit/withdrawal of allocated treatment (LOW QUALITY).
Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the proportion of participants having treatment withdrawn due to lack of efficacy (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure (VERY LOW QUALITY).

Adverse events-statistically significant results

Significantly more participants in topiramate monotherapy had treatment withdrawn due to adverse events than participants in sodium valproate monotherapy (VERY LOW QUALITY).

Adverse events-statistically non-significant results

No significant difference between topiramate monotherapy versus sodium valproate monotherapy in the incidence of:

- Tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY).
- Incidence of other side-effects (please see extraction for full list) (VERY LOW QUALITY).

Quality of Life -statistically significant results

Significantly more participants taking topiramate monotherapy compared to sodium valproate monotherapy had higher scores at 2 years on the GQoL questionnaire (VERY LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:

- At least 50% reduction in seizure frequency
- Cognitive outcomes.

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is very likely to be cost-effective compared with sodium valproate when using 2010 drug costs (ICER=£944 per QALY gained). This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is more costly, but less effective at preventing seizures than sodium valproate monotherapy. This evidence is partially applicable but has potentially serious limitations.
10.4.4.3 Lamotrigine monotherapy versus topiramate monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
One economic evaluation of AEDs, including lamotrigine and topiramate, used as monotherapy in the treatment of people with newly diagnosed IGE was identified and included in the economic literature search. The complete results of this study are presented in section 10.4.5.

Evidence statements

Efficacy – statistically significant results
Significantly fewer participants receiving topiramate monotherapy compared to lamotrigine monotherapy withdrew due to lack of efficacy (VERY LOW QUALITY).
Topiramate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging the time to first seizure (VERY LOW QUALITY).

Efficacy – statistically non-significant results
No significant difference between lamotrigine monotherapy and topiramate monotherapy in the proportion of seizure free participants (VERY LOW QUALITY).
No significant difference between lamotrigine monotherapy and topiramate monotherapy in the time to exit/withdrawal of allocated treatment (VERY LOW QUALITY).

Adverse events – statistically significant results
Significantly fewer participants receiving lamotrigine monotherapy compared to topiramate monotherapy withdrew due to adverse events (VERY LOW QUALITY).

Adverse events – statistically non-significant results
There is no significant difference between lamotrigine monotherapy versus topiramate monotherapy in the incidence of:

- Tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY).
- Other side-effects (please see evidence extraction Appendix L) (VERY LOW QUALITY).

Quality of Life – statistically significant results
Significantly more participants taking lamotrigine monotherapy compared to topiramate monotherapy had higher scores on the GQoL questionnaire (VERY LOW QUALITY).

Quality of Life – statistically non-significant results
There is no significant difference between lamotrigine monotherapy and topiramate monotherapy in:

- Two year anxiety scores (VERY LOW)
- Two year depression scores (VERY LOW QUALITY)
- Two year AEP scores (VERY LOW QUALITY)
• Two year neurotoxicity scale scores (VERY LOW QUALITY)
• Two year EQ-5D scores (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:
• At least 50% reduction in seizure frequency.
• Cognitive outcomes.

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is very likely to be cost-effective when compared with lamotrigine monotherapy when using 2010 drug costs (ICER=£4,982). This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is more costly and more effective at preventing seizures than lamotrigine monotherapy (ICER=£11 per seizure avoided). However, sodium valproate monotherapy is most cost-effective in this analysis. This evidence is partially applicable but has potentially serious limitations.

10.4.4.4 Levetiracetam adjunctive therapy versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search, however the NCGC model evaluating adjunctive AEDs in the treatment of adults with refractory generalised tonic-clonic seizures used clinical evidence from this comparison. For results of this analysis, see section 10.6.7.

Evidence statements

Efficacy – statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy were seizure free during the titration and evaluation period and the evaluation period alone compared to placebo. (MODERATE QUALITY)

Significantly more participants receiving levetiracetam adjunctive therapy had at least a 50% reduction in seizure frequency compared to placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy versus placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

There is no significant difference between levetiracetam adjunctive therapy and placebo for the incidence of:
• nasopharyngitis (VERY LOW QUALITY)
• headache (VERY LOW QUALITY)
• fatigue (VERY LOW QUALITY).

**Quality of life – statistically non-significant results**

No significant difference between levetiracetam adjunctive therapy and placebo in achieving a greater improvement in the quality of life (VERY LOW QUALITY).

**Outcomes with no evidence**

There were no studies that reported:

• withdrawal due to lack of efficacy,
• time to first seizure,
• time to exit/withdrawal of allocated treatment
• cognitive outcomes.

**Cost-effectiveness**

No economic evidence comparing levetiracetam adjunctive therapy to placebo was identified. However, adjunctive levetiracetam was found to be cost-effective in the treatment of adults with refractory generalized tonic-clonic seizures if adjunctive lamotrigine was not an appropriate clinical option. For details on this evidence, see section 10.6.7.

10.4.5 Health economic evidence for AEDs used as monotherapy in the treatment of patients with newly diagnosed IGE

Two economic evaluations assessing the cost-effectiveness of AEDs used as monotherapy in patients with newly diagnosed IGE were identified in the economic literature search and included in the economic evidence review. See appendix M for full study details and assessments of limitations and applicability. These studies were considered sufficient to inform recommendations in this population, therefore no original economic modelling was undertaken.

**Economic study characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marson (2007)134</td>
<td>Potentially serious limitations (a, b)</td>
<td>Directly applicable (c)</td>
<td>Economic evaluation conducted alongside RCT; comparators included sodium valproate, lamotrigine and topiramate; 2-year time horizon; effect measured as QALYs gained</td>
</tr>
<tr>
<td>Marson (2007)134</td>
<td>Potentially serious limitations (a, b)</td>
<td>Partially applicable (c, d)</td>
<td>Economic evaluation conducted alongside RCT; comparators included sodium valproate, lamotrigine and topiramate; 2-year time horizon; effect measured as seizures avoided</td>
</tr>
<tr>
<td>Hawkins (2005)150</td>
<td>Potentially serious limitations (e, f, g)</td>
<td>Directly applicable</td>
<td>Decision analytic model; 15-year time horizon; effectiveness data based on an unpublished study240</td>
</tr>
</tbody>
</table>
(a) Sensitivity analysis incomplete in that it only presents comparisons of VPA v LTG and VPA v TPM but fails to present comparison of LTG v TPM.
(b) Unit costs estimates are from 2005.
(c) Study population included patients with IGE (63%) and some patients with an unclassified epilepsy (27%).
(d) Analysis of cost per seizures avoided, not QALYs.
(e) Costs discounted at 3.5% per annum; QALYs discounted 1.5% per annum.
(f) Unit cost estimates are from 2001-2002.
(g) Treatment effects based on results of an unpublished study that was not included in NCGC systematic review.

### Economic study results

#### Table 10-20: Monotherapy for patients with IGE – Results of Marson 2007

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects per patient</th>
<th>ICER</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(QALYs)</td>
<td>(£ / QALY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>£1,390</td>
<td>1.648</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, VPA has a 5% and 37% probability of being cost-effective compared to TPM and LTG respectively. At a willingness to pay threshold of £30,000/QALY, this figure is 97%.
| TPM | £1,568                    | 1.809                    | £1,606|             |
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, TPM has a 95% probability of being cost-effective compared to VPA. At a willingness to pay threshold of £30,000/QALY, this figure is 97%.
| LTG | £1,906 (a)                | 1.701                    | Dominated |             |
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, LTG has a 63% probability of being cost-effective compared to VPA. At a willingness to pay threshold of £30,000/QALY, this figure is 68%.

#### Cost per seizure avoided analysis

<table>
<thead>
<tr>
<th>AED</th>
<th>Cost per seizure avoided analysis</th>
<th>(total seizures)</th>
<th>(£/seizure avoided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>£1,136</td>
<td>44.1</td>
<td></td>
</tr>
</tbody>
</table>
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, VPA has an 84% and 99% probability of being cost-effective compared to TPM and LTG, respectively.
| TPM | £1,568                            | 75.1            | Dominated           |
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, TPM has a 16% probability of being cost-effective compared to VPA.
| LTG | £1,761 (a)                        | 120.9           | Dominated           |
|     | Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, LTG has a 1% probability of being cost-effective compared to VPA.

(a) Unit costs estimates are from 2005, and since then, unit cost of lamotrigine has reduced and may change conclusions of the cost-effectiveness analysis.

As the unit costs of anti-epileptic drugs used in the SANAD trial were from 2005 and the unit cost of lamotrigine had changed dramatically since then, it was considered appropriate to update these and perform an incremental analysis based on current AED costs. Current unit costs for lamotrigine and sodium valproate were taken from the BNF and a weighted average cost per milligram was calculated based on relative quantities prescribed from the Prescription Cost Analysis 2008.
Total drug costs were then combined with the hospitalisation and other costs published in SANAD to calculate a more current average cost per patient. The updated results are presented in Table X.

Table 10-21: Monotherapy for patients with IGE – Results of Marson 2007134

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient (a)</th>
<th>Total effects per patient</th>
<th>ICER (£/QALY)</th>
<th>Uncertainty (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTG</td>
<td>£1,090</td>
<td>1.701</td>
<td>Dominated</td>
<td>No analysis of uncertainty could be recreated in the update of drug unit costs.</td>
</tr>
<tr>
<td>VPA</td>
<td>£1,476</td>
<td>1.648</td>
<td>Dominated</td>
<td>No analysis of uncertainty could be recreated in the update of drug unit costs.</td>
</tr>
<tr>
<td>TPM</td>
<td>£1,628</td>
<td>1.809</td>
<td>£4,982</td>
<td>No analysis of uncertainty could be recreated in the update of drug unit costs.</td>
</tr>
</tbody>
</table>

(a) In the published analyses, estimates of total cost were slightly different due to different numbers of patients being included in the cost per QALY and cost per seizure avoided analyses. In this recalculation, they’re assumed to have been the same.

(b) Uncertainty is not reflected in these new estimates, as bootstrapped estimates could not be recalculated or cost-effectiveness acceptability curves re-plotted.

(c) Sodium valproate is more costly and more effective in preventing seizures. No explicit willingness to pay per seizure avoided threshold exists to assess the cost-effectiveness of interventions on this measure.

Table 10-22: Monotherapy for patients with IGE – Results of Hawkins 2005150

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (QALYs) per patient</th>
<th>ICER (£/QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>£4,288</td>
<td>9.814</td>
<td></td>
<td>At a threshold of £30,000 per QALY, VPA has a 95% probability of being optimal.</td>
</tr>
<tr>
<td>LTG</td>
<td>£6,675 (a)</td>
<td>9.748</td>
<td>Dominated</td>
<td>At a threshold of £30,000 per QALY, LTG has a</td>
</tr>
</tbody>
</table>

Evidence statements

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, lamotrigine monotherapy is more effective than sodium valproate in terms of total QALYs gained. Using study costs from 2005, lamotrigine is more costly than sodium valproate, but using costs from 2010, lamotrigine is less costly than sodium valproate. This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, sodium valproate monotherapy is more effective at preventing seizures than lamotrigine monotherapy. Using study costs from 2005, lamotrigine is more costly than sodium valproate and was thus dominated; using costs from 2010, lamotrigine is less costly than sodium valproate and the ICER for sodium valproate is £5 per seizure avoided. Without an explicit willingness to pay threshold for seizures avoided, the cost-effectiveness of sodium valproate from this analysis is indeterminable. This evidence is partially applicable and has potentially serious limitations.
Evidence statements

Evidence from a cost-effectiveness analysis indicates that lamotrigine monotherapy is more costly and less effective than sodium valproate in terms of total QALYs gained. The evidence is directly applicable but as it uses costs from 2001-02, it has potentially serious limitations.

10.4.6 AEDs for the treatment of Generalised Tonic-Clonic Seizures only
10.4.6.1 Lamotrigine monotherapy versus sodium valproate monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
Economic evidence could not be extracted from the unpublished data for this subgroup of patients.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (LOW QUALITY).

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to exit/withdrawal of allocated treatment at 12 months follow-up (VERY LOW QUALITY).

Adverse events – statistically non-significant results
No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of other adverse events (for full list please see extractions) at 12 months follow-up (VERY LOW QUALITY).

Outcomes with no evidence
There were no studies that reported:
- Seizure freedom
- At least 50% reduction in seizure frequency
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Incidence of other side effects (please see evidence review Appendix XX)
- Cognitive outcomes
• Outcomes relating to quality of life.

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients.

10.4.6.2 Topiramate monotherapy versus sodium valproate monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

Economic evidence could not be extracted from the unpublished data for this subgroup of patients.

Evidence statements

Efficacy – statistically non significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (VERY LOW QUALITY).

No significant difference between sodium valproate monotherapy and topiramate monotherapy for time to exit/withdrawal of allocated treatment at 12 months follow-up (VERY LOW QUALITY).

Adverse events - statistically non significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy at 12 months follow-up in the incidence of:

• Tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY)

• Other adverse events (for full list please see evidence extractions Appendix L) (VERY LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:

• Seizure freedom
• At least 50% reduction in seizure frequency
• Withdrawal due to adverse events
• Withdrawal due to lack of efficacy
• Cognitive outcomes
• Outcomes relating to quality of life.

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients.
10.4.7 AEDs for the treatment of absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes)

10.4.7.1 Lamotrigine monotherapy versus sodium valproate monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified.

Evidence statements

Efficacy – statistically significant results
Significantly more participants in sodium valproate monotherapy were seizure free compared to lamotrigine monotherapy (MODERATE QUALITY).

Efficacy – statistically non-significant results
No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to first seizure at 12months follow-up (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and valproate monotherapy in the time to exit/withdrawal of allocated treatment at 12months follow-up (VERY LOW QUALITY).

Adverse events – statistically significant results
Significantly more participants in sodium valproate monotherapy had an incidence of sleep problem compared to lamotrigine monotherapy, however there is an uncertainty over the clinical importance of its effect (LOW QUALITY).

Adverse events – statistically non-significant results
No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of other adverse events (for full list please see evidence extractions Appendix L) at 12months follow-up (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- Fatigue (VERY LOW QUALITY)
- Hyperactivity (VERY LOW QUALITY)
- Hostility (VERY LOW QUALITY)
- Personality change (VERY LOW QUALITY)

Cognitive effect- statistically significant results
Significantly more patients in sodium valproate monotherapy had attentional dysfunction compared to lamotrigine monotherapy at 16-20 weeks follow up (MODERATE QUALITY).
Outcomes with no evidence

There were no studies that reported:

- At least 50% reduction in seizure frequency
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Outcomes relating to quality of life.

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients and no other economic studies comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with CAE or JAE were identified.

10.4.7.2 Topiramate monotherapy versus sodium valproate monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Sodium valproate monotherapy is significantly more effective than topiramate monotherapy in prolonging time to exit/withdrawal of allocated treatment at 12months follow-up (VERY LOW QUALITY).

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure at 12months follow-up (VERY LOW QUALITY).

Adverse events – statistically non-significant

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the incidence of tiredness, drowsiness, fatigue and lethargy at 12months follow-up (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the incidence of other adverse events (for full list please see extractions in Appendix L) at 12months follow-up (VERY LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:

- Seizure freedom
- At least 50% reduction in seizure frequency
- Withdrawal due to adverse events
Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients and no other economic studies comparing topiramate monotherapy to sodium valproate monotherapy in a population of patients with CAE or JAE were identified.

10.4.7.3 Valproic acid monotherapy versus ethosuximide monotherapy (newly diagnosed patients)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non significant results

No statistically significant difference between ethosuximide monotherapy and valproate monotherapy on the proportion of seizure free participants (LOW QUALITY).

Adverse events – statistically significant results

Significantly more patients on ethosuximide monotherapy had an incidence of nausea, vomiting or both compared to valproic acid monotherapy at 16-20 weeks follow-up (HIGH QUALITY).

Significantly more patients on valproic acid monotherapy had an incidence of hostility compared to ethosuximide monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (MODERATE QUALITY).

Significantly more patients on valproic acid monotherapy had an incidence of personality change compared to ethosuximide monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (MODERATE QUALITY).

Adverse events – statistically non significant results

No statistically significant difference between ethosuximide monotherapy and valproic acid monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- fatigue (LOW QUALITY)
- headache (LOW QUALITY)
- sleep problem (LOW QUALITY)
- stomach upset (LOW QUALITY)
- hyperactivity (LOW QUALITY)
Cognitive effect - statistically significant results

Significantly more patients on valproic acid monotherapy had attentional dysfunction compared to ethosuximide monotherapy at 16-20 weeks follow up (HIGH QUALITY).

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- outcomes relating to quality of life

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to ethosuximide monotherapy in a population of patients with CAE or JAE was identified.

10.4.7.4 Ethosuximide monotherapy versus lamotrigine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy - statistically significant results

Significantly more participants in ethosuximide monotherapy were seizure free compared to lamotrigine monotherapy (MODERATE QUALITY).

Adverse events - statistically significant results

Significantly more patients in ethosuximide monotherapy had an incidence of nausea, vomiting or both compared to lamotrigine monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (LOW QUALITY).

Significantly more patients in ethosuximide monotherapy had an incidence of stomach upset compared to lamotrigine monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (LOW QUALITY).
Adverse events – statistically non-significant results

No significant difference between ethosuximide monotherapy and lamotrigine monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- Fatigue (VERY LOW QUALITY)
- Headache (VERY LOW QUALITY).

Cognitive effect – statistically non-significant results

No significant difference between ethosuximide monotherapy and lamotrigine monotherapy in attentional dysfunction at 16-20 weeks follow up (VERY LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:

- At least 50% reduction in seizure frequency
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Time to first seizure
- Time to exit/withdrawal of allocated treatment
- Outcomes relating to quality of life.

Cost-effectiveness

No economic evidence comparing ethosuximide monotherapy to lamotrigine monotherapy in a population of patients with CAE or JAE was identified.

10.4.7.5 Lamotrigine monotherapy versus placebo (newly diagnosed population)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on lamotrigine monotherapy were seizure free compared to participants on placebo. However, there is uncertainty in the magnitude of clinical effect (LOW QUALITY).

Adverse events – statistically non significant results

No significant difference between lamotrigine monotherapy and placebo on the proportion of participants withdrawn due to adverse events (LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• cognitive outcomes
• outcomes relating to quality of life

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to placebo in a population of patients with CAE or JAE was identified.

10.4.7.6 Valproic acid adjunctive versus ethosuximide adjunctive (refractory patients)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between valproic acid adjunctive and ethosuximide adjunctive for the proportion of participants with at least 80% reduction in seizure frequency (VERY LOW QUALITY).

Outcomes with no evidence

There were no studies that reported:
• seizure frequency
• withdrawal due to adverse events
• withdrawal due to lack of efficacy
• time to first seizure
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• outcomes relating to cognitive effects
• outcomes relating to quality of life.

Cost-effectiveness

No economic evidence comparing adjunctive valproic acid to adjunctive ethosuximide in a population of patients with CAE or JAE was identified.

10.4.8 AEDs for the treatment of Juvenile Myoclonic Epilepsy (JME)

10.4.8.1 Topiramate monotherapy/adjunctive therapy versus sodium valproate monotherapy/adjunctive therapy)
Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy on the proportion of seizure-free participants (VERY LOW QUALITY)

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy on the proportion of participants experiencing at least a 50% reduction in seizure frequency (50 to <100%) (VERY LOW QUALITY).

Adverse events – statistically non-significant results
No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for the incidence of the following adverse events:

- Headache (VERY LOW QUALITY)
- Concentration/attention difficulty (VERY LOW QUALITY)
- Fatigue (VERY LOW QUALITY)
- Alopecia (VERY LOW QUALITY)
- Dizziness (VERY LOW QUALITY)
- Weight loss (VERY LOW QUALITY)
- Paresthesia (VERY LOW QUALITY)
- Psychomotor slowing (VERY LOW QUALITY)
- Somnolence (VERY LOW QUALITY)
- Nausea (VERY LOW QUALITY)
- Weight gain (VERY LOW QUALITY)
- Appetite increase (VERY LOW QUALITY)
- Insomnia (VERY LOW QUALITY)
- Abnormal vision (VERY LOW QUALITY)
- Rash (VERY LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- outcomes relating to quality of life
Cost-effectiveness

No economic evidence comparing topiramate monotherapy/adjunctive therapy to sodium valproate monotherapy/adjunctive therapy in a population of patients with JME was identified.

10.4.8.2 Levetiracetam versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants receiving levetiracetam adjunctive were myoclonic seizure-free compared to placebo in the titration and evaluation periods combined and the evaluation period alone. However, there is uncertainty on the magnitude of the clinical effect (LOW QUALITY).

Significantly more participants receiving levetiracetam adjunctive achieved 50% or above reduction in myoclonic seizure frequency compared to placebo in the titration and evaluation period (MODERATE QUALITY).

Adverse events – statistically non significant results

There is no significant difference between the levetiracetam adjunctive group and the placebo group on the incidence of:

- somnolence (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

Quality of life - statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy had experienced improvement in health related quality of life compared to placebo (MODERATE QUALITY).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive effects.

Cost-effectiveness

No economic evidence comparing levetiracetam adjunctive therapy to placebo in a population of patients with JME was identified.
10.4.9 Recommendations and link to evidence

**Idiopathic Generalised Epilepsy (use for unclassified IGE - for specific syndromes see below)**

**First-Line treatment in adults and children with IGE**

| Recommendation | Offer sodium valproate as first-line treatment to adults and children with newly diagnosed IGE. Offer lamotrigine or topiramate if sodium valproate is contraindicated or not tolerated. Be aware that lamotrigine can exacerbate myoclonic seizures. [new 2011] |

**Relative values of different outcomes**

The GDG placed greater importance on efficacy as measured by withdrawal due to lack of efficacy, time to withdrawal and cost-effectiveness in the trials than the quality of life (measured by EQ5D). EQ5D was undertaken on a small subgroup of individuals and excluded children.

**Trade off between clinical benefits and harms**

Sodium valproate is the most effective drug for IGE but has disadvantages. The risk of teratogenicity associated with valproate's use is significant, particularly at higher doses, so caution is advised in the use of sodium valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of sodium valproate should be reviewed and options discussed.

Lamotrigine was less effective but better tolerated than topiramate. Lamotrigine had longer time to withdrawal due to side–effects, whereas topiramate had a longer time to first seizure. Lamotrigine may be used in PGCTS but may exacerbate myoclonic seizures. Lamotrigine in high dose (>400mg/day) is associated with increased risk of teratogenicity. There are limited data on the safety of topiramate in pregnancy. At present the risk appears overall similar to lamotrigine.

Topiramate particularly at higher doses may reduce the efficacy of the combined oral contraceptive.

Lamotrigine may reduce the concentration of progesterone component of oral contraceptives, so the efficacy of systemic progesterone only methods is reduced. Oestrogens may significantly reduce the concentration of lamotrigine.

**Economic considerations**

Sodium valproate emerged as the drug most likely to be cost-effective in the cost per seizure avoided analysis conducted as part of SANAD. Greater weight was given to this analysis as the reduction in seizure frequency is considered to be the most important clinical outcome. The GDG considered the seemingly inconsistent results between the cost per seizure avoided analysis and the cost per QALY gained analysis and concluded that some of the difference may be attributable to the QALY capturing elements of health-related quality of life other than those associated with seizures. Lamotrigine did have a lower rate of withdrawal due to adverse events compared to sodium valproate but this was not statistically significant. Another
possible reason for the contradictory result may stem from the fact that QALYs were only measured in adults and total number of seizures was counted for both adults and children. The majority of the patient population in these study arms was under the age of 20, thus the cost per QALY analysis may not be based upon a truly representative sample. Given GDG emphasis on outcomes of effect such as the achievement of seizure freedom/reduction and treatment retention (i.e. avoidance of withdrawal for any reason), sodium valproate is considered to be a drug that produces favourable outcomes to patients and represents good value to the NHS.

The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, lamotrigine or topiramate may be cost-effective alternatives. The published economic evidence for the cost effectiveness of lamotrigine and topiramate was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and topiramate has the highest. Patients taking topiramate were reported to enjoy more QALYs and experience fewer seizures than patients taking lamotrigine. Although results would point to topiramate as the most cost-effective drug between the two, other clinical outcomes were also taken into account. In the subgroup of patients with IGE, no statistically significant differences were demonstrated between topiramate and lamotrigine for withdrawal due to adverse events or remission of seizures at 12 months. Both drugs are likely to be considered cost-effective and a decision between the two should be based on clinical judgement and patient preference.

Quality of evidence

Evidence was of low quality. There were methodological limitations with the evidence as the comparisons of sodium valproate, lamotrigine and topiramate were included in an unblinded study, with no detail on randomisation and allocation concealment.

Other considerations

For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Clinicians should consider that VPA may inhibit the hepatic metabolism of other drugs and enzyme inducing drugs may enhance the metabolism of VPA.
## Adjunctive treatment in adults and children with IGE

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th>Offer levetiracetam as adjunctive treatment to adults and children with IGE if first-line treatments (see recommendation 4.10.4.1) are ineffective or not tolerated. [new 2011]</th>
</tr>
</thead>
</table>

### Relative values of different outcomes

The GDG based greater importance for this recommendation on seizure freedom and 50% reduction in seizure frequency when levetiracetam used as adjunctive therapy in IGE.

### Trade off between clinical benefits and harms

Levetiracetam as add on treatment is an effective adjunctive therapy in IGE and has the advantage of no significant interactions with other medications. There is insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline.

### Economic considerations

No economic evaluations were available to inform the GDG on the cost-effectiveness of levetiracetam as a treatment specifically in patients with IGE. However, the GDG considered the evidence of cost-effectiveness for levetiracetam as adjunctive treatment for primary generalised tonic-clonic seizures from the NCGC cost-effectiveness analysis summarised in section 10.6.7 and detailed in appendix P. Many of the studies used in the NCGC economic model included patients with IGE therefore the GDG considered its conclusions applicable to this population as well.

### Quality of evidence

Evidence for levetiracetam comes from the data on adjunctive treatment because no monotherapy studies in IGE were identified. Evidence was of moderate quality. The methodological limitation with the evidence was including a wide age range (4-65 years).

### Other considerations

For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Clinicians should be aware that there may be potential problems from withdrawal from these drugs.

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3

4
Absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes)

First-line treatment in adults and children with absence seizures

**Recommendation**  Offer ethosuximide or sodium valproate as first-line treatment to adults and children with absence seizures, unless they have also experienced generalised tonic-clonic seizures when sodium valproate should be offered first. [new 2011]

**Relative values of different outcomes**  The GDG considered seizure freedom to be the most important outcome for this recommendation.

**Trade off between clinical benefits and harms**  The GDG considered that the different side effect profiles of sodium valproate and ethosuximide could not determine which one of these drugs be used first, although there may be individual factors that may determine the choice of one drug over the other. Significantly more patients on valproate showed difficulties in attention. Caution should be used with sodium valproate in girls of child bearing potential.

**Economic considerations**  No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. At the time the GDG considered the evidence, there were significant cost differences between ethosuximide capsules (£0.68 per 250 mg) and ethosuximide syrup (£0.108 to £0.165 per 250 mg). According to the Prescription Cost Analysis of 2008, 99.7% of ethosuximide prescriptions were for syrup. When ethosuximide syrup is prescribed, the daily unit costs of ethosuximide and sodium valproate are very comparable. On this basis the GDG considered that clinical judgement and patient choice should guide the decision for which of the likely cost-effective drugs to offer.

**Quality of evidence**  The evidence base for this recommendation was retrieved from a double blinded study of a very good quality and from a low quality unblinded study with no details on randomisation and allocation concealment.

**Other considerations**  The GDG considered that the data available for childhood absence epilepsy can be extrapolated to those individuals with juvenile absence epilepsy, and also to those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.
**Recommendation**

Offer lamotrigine* to adults and children with absence seizures if ethosuximide and sodium valproate have been ineffective or not tolerated. [New 2011]

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>The GDG considered seizure freedom to be the most important outcome for this recommendation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>The GDG considered that the side effect profile of lamotrigine was more favourable, but its efficacy was less favourable, when compared with ethosuximide and sodium valproate.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. The GDG considered that at recommended daily doses lamotrigine, sodium valproate and ethosuximide syrup have broadly similar unit costs, but that lamotrigine was less effective than sodium valproate and ethosuximide in this population. But if sodium valproate and/or ethosuximide do not produce the clinical benefit desired, the GDG felt that lamotrigine was a potentially cost-effective alternative.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The evidence base was retrieved from a double blinded study of a very good quality and from a low quality unblinded study with no details on randomisation and allocation concealment.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The GDG considered that the data available for CAE can be extrapolated to those individuals with JAE, and those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.</td>
</tr>
</tbody>
</table>

* Please see appendix K for licensing details.
**Recommendation**

**Do not offer carbamazepine, oxcarbazepine, phenytoin, tiagabine or vigabatrin to adults and children with absence seizures. [new 2011]**

**Relative values of different outcomes**
Seizure freedom and adverse effects were considered to be the most important outcomes.

**Trade off between clinical benefits and harms**
Clinical practice suggests that absence seizures can be aggravated by these medications, and can compromise cognition with risk of nonconvulsive status epilepticus. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.

**Economic considerations**
No economic evidence was available to inform the cost-effectiveness of these AEDs in this population, however their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.

**Quality of evidence**
This recommendation was based on GDG consensus.

**Other considerations**
There is no evidence of benefit on use of these medications.

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**Juvenile Myoclonic Epilepsy (JME)**

**First-line treatment in adults and children with JME**

**Recommendation**

**Offer sodium valproate as first-line treatment to adults and children with newly diagnosed JME. Offer lamotrigine* or topiramate* if sodium valproate is contraindicated or not tolerated. Offer topiramate if sodium valproate is ineffective. Be aware that lamotrigine can exacerbate myoclonic seizures. [new 2011]**

**Relative values of different outcomes**
The GDG placed greater importance on efficacy as measured by treatment failure and time to withdrawal in JME.

**Trade off between clinical benefits and harms**
Valproate is the most effective drug for JME but has disadvantages. In high dose the risk of teratogenicity is significant thus caution is advised in the use of sodium valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of sodium valproate should be reviewed and options discussed.

Lamotrigine was less effective but better tolerated than topiramate. Lamotrigine had longer time to withdrawal due to side-effects, whereas topiramate had a longer time to first

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*Please see appendix K for licensing details.
seizure. Lamotrigine may be used in GCTS but may exacerbate myoclonic seizures. Lamotrigine in high doses (>400mg/day) is associated with increased risk of teratogenicity. There are limited data on the safety of topiramate in pregnancy. At present the risk appears overall similar to lamotrigine.

Topiramate particularly at higher doses may reduce the efficacy of the combined oral contraceptive.

Lamotrigine may reduce the concentration of progesterone component of oral contraceptives, so the efficacy of systemic progesterone only methods is reduced. Oestrogens may significantly reduce the concentration of lamotrigine.

Lamotrigine may reduce the concentration of progesterone a component of oral contraceptives, so the efficacy of systemic progesterone only methods is reduced. Oestrogens may significantly reduce the concentration of lamotrigine.

Economic considerations

No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat patients with JME. However, the GDG drew from the cost-effectiveness evidence for sodium valproate in idiopathic generalised epilepsy as a whole. On this basis, they put greater emphasis on the cost per seizure avoided analysis from SANAD because reduction of seizure frequency is considered to be the most important clinical outcome.

The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, lamotrigine or topiramate may be cost-effective alternatives. The published economic evidence for the cost effectiveness of lamotrigine and topiramate in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and topiramate has the highest. Both drugs are likely to be considered cost-effective and a decision between the two should be based on clinical judgement and patient preference.

GDG experience was that lamotrigine is unlikely to be effective (and thus not cost-effective) in patients with JME who have not responded to sodium valproate, and thus topiramate should be the next alternative offered. Additionally, lamotrigine’s potential to exacerbate myoclonic seizures in some patients may make it less cost-effective or not cost-effective as aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use. However, lamotrigine should not be ignored as a possible treatment option as it can be helpful in controlling other seizure types commonly experienced by patients with JME.
Quality of evidence
There is no specific data for monotherapy in Juvenile Myoclonic Epilepsy. Thus, data has been extrapolated from the IGE population. The evidence was of low quality. The evidence had methodological limitations with the evidence as it was based on an unblinded study, with no detail on concealment allocation.

Other considerations
Health care professionals should consider that sodium valproate may inhibit the hepatic metabolism of other drugs and enzyme inducing drugs may enhance the metabolism of sodium valproate.

For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

1. **Adjunctive treatment in adults and children with JME**

   **Recommendation**
   Offer levetiracetam as adjunctive treatment to adults and children with JME if first-line treatments (see recommendation 4.10.6.1) are ineffective or not tolerated. [new 2011]

   **Relative values of different outcomes**
   50% seizure reduction and adverse effects were considered the most important outcomes.

   **Trade off between clinical benefits and harms**
   LEV is effective as adjunctive therapy in myoclonic seizures and has the advantage of no significant interactions with other medications. There are insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline.

   **Economic considerations**
   No economic evaluations were available to inform the GDG on the cost-effectiveness of levetiracetam as a treatment specifically in patients with JME. The clinical evidence for adjunctive levetiracetam in a population with JME shows it to be even more effective compared to placebo than in a population with primary generalised tonic-clonic seizures. On that basis, the GDG felt that the cost-effectiveness of adjunctive levetiracetam was likely to be the same or better than in the analysis conducted for patients with primary generalised tonic-clonic seizures, summarised in section 10.6.7 and detailed in appendix P.

   **Quality of evidence**
   Evidence was of low quality. There were methodological limitations with the evidence as it was an unblinded study, with no detail on concealment allocation.

   **Other considerations**
   For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.
10.4.10 Research Recommendations (for full list see section 2.11)

10.4.10.1 Newly diagnosed seizures (focal and generalised) - monotherapy

How do the newer AEDs compare in efficacy to the standard AEDs in the treatment of newly diagnosed epilepsy?

a. Focal seizures: carbamazepine, eslicarbazepine, lamotrigine, lacosamide, levetiracetam, pregabalin and zonisamide.

b. Generalised seizures: lamotrigine, levetiracetam, sodium valproate and zonisamide.

Why is this important?

Levetiracetam and other AEDS licensed for the treatment of focal and generalised seizures since publication of the original guideline in 2004 have not been evaluated as first line monotherapy. Research should include:

- A prospective randomised controlled trial.
- All ages.
- Primary outcome of seizure freedom
- Secondary outcomes should include seizure-reduction, quality of life and cognitive outcome.
- An attempt to obtain some data on pharmaco-resistance.

10.5 Myoclonic Seizures

10.5.1 Introduction

Myoclonic seizures are defined as sudden, brief involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable limb location. Myoclonic seizures are seen as part of several epilepsy syndromes eg juvenile myoclonic epilepsy, Dravets syndrome. In these circumstances treatment should be considered in the context of the diagnosed syndrome rather than individual seizure types. However there are a variety of static encephalopathies not fulfilling criteria for specific epilepsy syndromes, where myoclonic seizures are the major if not only seizure type. Further there are a number of progressive myoclonic epilepsies for which specific treatment of myoclonus may require consideration.

10.5.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people with myoclonic seizures.

10.5.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for myoclonic seizures. The following interventions were included in our search: clobazam, clonazepam, lamotrigine, levetiracetam, piracetam, sodium valproate, topiramate and zonisamide.

We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).
Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Clobazam</th>
<th>Clonazepam</th>
<th>Piracetam</th>
<th>Zonisamide</th>
<th>Sodium Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla</td>
<td>LTG</td>
<td>LEV</td>
<td>LCS</td>
<td>CLB</td>
<td>CLN</td>
<td>PRC</td>
<td>ZNS</td>
<td>VPA</td>
</tr>
</tbody>
</table>

1 Placebo (Pla)  Zonisamide (ZNS) Lamotrigine (LTG) Levetiracetam (LEV)
2 Topiramate (TPM) Clobazam (CLB) Clonazepam (CLN) Sodium valproate (VPA)
3 Piracetam (PRC)
10.5.4 AEDs for the treatment of Myoclonic Seizures

10.5.4.1 Lamotrigine monotherapy versus sodium valproate monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
There was no significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of seizure free participants (VERY LOW QUALITY).
There was no significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to lack of efficacy (VERY LOW QUALITY).

Adverse events – statistically non-significant results
No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to adverse events (VERY LOW QUALITY).
No statistically significant difference between lamotrigine and sodium valproate for incidence of the following adverse events:

- Erythematous rash (VERY LOW QUALITY)
- Weight increase (VERY LOW QUALITY).

Cost-effectiveness
No economic evidence comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with myoclonic seizures was identified.
### 10.5.5 Recommendations and link to evidence

#### First-line treatment in adults and children with myoclonic seizures

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer sodium valproate as first-line treatment to adults and children with newly diagnosed myoclonic seizures. Offer topiramate* if sodium valproate is contraindicated, not tolerated or ineffective. [new 2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative values of different outcomes</strong></td>
<td>Seizure freedom and adverse effects were considered to be the most important outcomes.</td>
</tr>
<tr>
<td><strong>Trade off between clinical benefits and harms</strong></td>
<td>Reduction in seizures needs to be balanced against adverse effects. The evidence from patients with JME is limited and shows no difference between lamotrigine and sodium valproate. The GDG used evidence extrapolated from idiopathic generalised epilepsy to make this recommendation. Sodium valproate is the most effective drug for treating IGE but has disadvantages. The risk of teratogenicity associated with sodium valproate's use is significant, particularly at higher doses, so caution is advised in the use of valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of valproate should be reviewed and options discussed. There is also a tendency for other drugs, such as lamotrigine, to exacerbate certain seizures types.</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat patients experiencing myoclonic seizures. However, as in the formulation of recommendations for the treatment of juvenile myoclonic epilepsy (JME), the GDG drew from the cost-effectiveness evidence for sodium valproate in idiopathic generalised epilepsy as a whole. On this basis, they put greater emphasis on the cost per seizure avoided analysis from SANAD because reduction of seizure frequency is considered to be the most important clinical outcome. The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, topiramate may be cost-effective alternatives. The published economic evidence for the cost effectiveness of topiramate in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that topiramate has the highest total cost but that it is likely to be considered cost-effective. The GDG recommended lamotrigine as a possible alternative monotherapy for patients with JME, but did not consider it to be an appropriate or likely cost-effective option in patients experiencing myoclonic seizures only. Lamotrigine has the potential to exacerbate myoclonic seizures in some patients and</td>
</tr>
</tbody>
</table>

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*Please see appendix K for licensing details.*
may therefore negatively impact health-related quality of life and increase NHS resource use and make it less or not cost-effective in this group. Unlike in JME, where lamotrigine may help to control other seizure types associated with the syndrome, it is unlikely to offer any advantage in the treatment myoclonic seizures only.

Quality of evidence

One unblinded study of very low quality evidence was included with no details on randomisation and no allocation concealment. This recommendation was based on evidence extrapolated from IGE populations and GDG clinical expertise as there was a limited availability of evidence regarding myoclonic seizures.

Other considerations

For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.
## Adjunctive treatment in adults and children with myoclonic seizures

### Recommendation

Offer levetiracetam as adjunctive treatment to adults and children with myoclonic seizures if first-line treatments (see recommendation 4.10.7.1) are ineffective or not tolerated. If treatment is ineffective or not tolerated discuss with, or refer to, a tertiary epilepsy specialist, and consider offering clobazam*, clonazepam, piracetam or zonisamide*. [new 2011]

### Relative values of different outcomes

The GDG considered seizure freedom and tolerance as the most important outcomes.

### Trade off between clinical benefits and harms

Reduction in seizures needs to be balanced against adverse effects. The evidence from patients with JME is limited and shows no difference between lamotrigine and sodium valproate for first line treatment and there is no specific evidence for adjunctive treatment.

The GDG decided to extrapolate evidence from IGE population. Levetiracetam as add on treatment is effective in IGE and has the advantage of no significant interactions with other medications. There are insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline.

Presentation with isolated myoclonic seizures outside IGE requires further specialist care because it may be a first presentation of complex neurologic disorder.

### Economic considerations

No economic evaluations were available to inform the GDG on the cost-effectiveness of levetiracetam as a treatment specifically in patients experiencing refractory myoclonic seizures. The GDG considered the clinical evidence for adjunctive levetiracetam in a population with JME which shows it to be even more effective compared to placebo than in a population with primary generalised tonic-clonic seizures. On that basis, the GDG felt that the cost-effectiveness of adjunctive levetiracetam was likely to be the same or better than in the analysis conducted for patients with primary generalised tonic-clonic seizures, summarised in section 10.6.7 and detailed in appendix P.

### Quality of evidence

This recommendation is based on evidence extrapolated from IGE populations and on GDG clinical expertise as there was a limited availability of evidence regarding myoclonic seizures.

### Other considerations

Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6m in view of the risk of withdrawal seizures.

For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* Please see appendix K for licensing details.
10.6 Primary Generalised Tonic-Clonic Seizures

10.6.1 Introduction
Tonic clonic seizures are defined as those where individuals have sudden onset, tonic stiffening, followed by rhythmic, clonic jerking of the limbs. It is the most common presenting seizure type, and an individual may manifest with such a seizure type prior to any underlying syndrome or aetiology being determined. It is classified as a generalised seizure type, although these seizures may be seen in many syndromes. Further such an apparent manifestation may be seen of there has been rapid spread of the seizure from a focal source.

10.6.2 Methods of the evidence review
Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people with Primary-Generalised Tonic-Clonic Seizures.

10.6.3 Matrix of the evidence
We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy in a primary generalized tonic-clonic population. The interventions we included in our search were lamotrigine, levetiracetam, topiramate, oxcarbazepine, phenytoin, clobazam, clonazepam, phenobarbitone, primidone, acetazolamide, sodium valproate, zonisamide and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Matrix of the evidence for monotherapy – adults

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Carbamazepine</th>
<th>Phenytoin</th>
<th>Sodium valproate</th>
<th>Oxcarbazepine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1136</td>
<td></td>
<td>1140</td>
<td>2142,264</td>
<td>1141</td>
<td>PCB LTG CBZ PHT VPA OXC TPM</td>
</tr>
</tbody>
</table>

Updated 2011
Matrix of the evidence for monotherapy – children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Oxcarbazepine</th>
<th>Phenytoin</th>
<th>Sodium valproate</th>
<th>Carbamazepine</th>
<th>PCB</th>
<th>OXC</th>
<th>PHT</th>
<th>VPA</th>
<th>CBZ</th>
</tr>
</thead>
</table>

Matrix of the evidence for Adjunctive therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Clobazam</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate (unpublished in HTA)</th>
<th>PCB</th>
<th>CLB</th>
<th>LTG</th>
<th>LEV</th>
<th>TPM</th>
</tr>
</thead>
</table>

Updated 2011
10.6.4 Monotherapy for the treatment of Primary Generalised Tonic-Clonic Seizures

10.6.4.1 Lamotrigine monotherapy versus carbamazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between lamotrigine monotherapy and carbamazepine monotherapy in the proportion of seizure free participants. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing lamotrigine monotherapy to carbamazepine monotherapy in patients with primary generalised tonic-clonic seizures was identified.

10.6.4.2 Lamotrigine monotherapy versus phenytoin monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy in the proportion of seizure free participants. (VERY LOW QUALITY)

There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy in the proportion of patients withdrawing due to adverse events. (VERY LOW QUALITY)

There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to first seizure. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants taking phenytoin monotherapy compared to lamotrigine monotherapy had incidence of the following adverse events:

• Somnolence (VERY LOW QUALITY)
• Ataxia (VERY LOW QUALITY)
1. **Cost-effectiveness**

No economic evidence comparing lamotrigine monotherapy to phenytoin monotherapy in patients with primary generalised tonic-clonic seizures was identified.

2. **10.6.4.3 Oxcarbazepine monotherapy versus phenytoin monotherapy**

   **Clinical evidence**

   For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

   **Health economic evidence**

   No studies were identified in the economic literature search.

   **Evidence statements**

   **Efficacy – statistically significant results**

   No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants.

   **Cost-effectiveness**

   No economic evidence comparing oxcarbazepine monotherapy to phenytoin monotherapy in patients with primary generalised tonic-clonic seizures was identified.

3. **10.6.4.4 Oxcarbazepine monotherapy versus sodium valproate monotherapy**

   **Clinical evidence**

   For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

   **Health economic evidence**

   No studies were identified in the economic literature search.

   **Evidence statements**

   **Efficacy – statistically significant results**

   No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants.

   **Cost-effectiveness**

   No economic evidence comparing oxcarbazepine monotherapy to sodium valproate monotherapy in patients with primary generalised tonic-clonic seizures was identified.
10.6.4.5 Phenytoin monotherapy versus carbamazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Phenytoin monotherapy is more effective than carbamazepine monotherapy in achieving a greater proportion of seizure-free participants.

Cost-effectiveness
No economic evidence comparing phenytoin monotherapy to carbamazepine monotherapy in patients with primary generalised tonic-clonic seizures was identified.

10.6.4.6 Phenytoin monotherapy versus sodium valproate monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
Significantly more participants taking phenytoin monotherapy compared to sodium valproate monotherapy withdrew due to adverse events. (VERY LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to lack of efficacy. (VERY LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the incidence of the following adverse events:

• Gastrointestinal disturbances (VERY LOW QUALITY)
• Drowsiness (VERY LOW QUALITY)
• Nausea (VERY LOW QUALITY)
• Somnolence (VERY LOW QUALITY)
• Death (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenytoin monotherapy to sodium valproate monotherapy in patients with primary generalised tonic-clonic seizures was identified.

10.6.4.7 Sodium valproate monotherapy versus carbamazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing sodium valproate monotherapy to carbamazepine monotherapy in patients with primary generalised tonic-clonic seizures was identified.
10.6.5 Monotherapy for the treatment of Primary Generalised Tonic-Clonic Seizures in children

10.6.5.1 Oxcarbazepine monotherapy versus phenytoin monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants.

Cost-effectiveness
No economic evidence comparing oxcarbazepine monotherapy to phenytoin monotherapy in children with primary generalised tonic-clonic seizures was identified.

10.6.5.2 Sodium valproate monotherapy versus carbamazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of children withdrawn due to adverse events. (VERY LOW QUALITY)
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of children withdrawn due to lack of efficacy. (VERY LOW QUALITY)
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy in children for the incidence of the following adverse events:
  • Somnolence (LOW QUALITY)
  • Fatigue (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing sodium valproate monotherapy to carbamazepine monotherapy in children with primary generalised tonic-clonic seizures was identified.
10.6.6 Adjunctive therapy for the treatment of Primary Generalised Tonic-Clonic Seizures

10.6.6.1 Clobazam adjunctive versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically significant results
Significantly more participants in clobazam adjunctive therapy were seizure free compared to placebo. However, there is uncertainty about the magnitude of the clinical effect. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing clobazam adjunctive therapy to placebo was identified.

10.6.6.2 Lamotrigine adjunctive therapy versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search. As there were gaps in the economic evidence base, original economic modelling was undertaken to evaluate AEDs, including lamotrigine, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of the NCGC GTC model are presented in section 10.6.7

Evidence statements
Efficacy – statistically significant results
Significantly more participants in lamotrigine adjunctive therapy achieved at least 50% reduction in seizure frequency compared to placebo. (VERY LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of participants having their treatment withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed that lamotrigine adjunctive therapy is cost-effective compared to placebo in the treatment of primary generalised tonic-clonic seizures. This evidence is directly applicable and has minor limitations.
10.6.6.3 Levetiracetam adjunctive therapy versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search. As there were gaps in the economic evidence base, original economic modelling was undertaken to evaluate AEDs, including levetiracetam, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of the NCGC GTC model are presented in section 10.6.7

Evidence statements

Efficacy – statistically significant results
Significantly more participants taking levetiracetam adjunctive therapy were seizure free compared to participants taking placebo. (MODERATE QUALITY)
Significantly more participants taking levetiracetam adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to participants taking placebo. (MODERATE QUALITY)

Efficacy – statistically non-significant results
No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)
No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between levetiracetam adjunctive therapy and placebo for the incidence of the following adverse events:
- nasopharyngitis. (LOW QUALITY)
- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- aggravation of seizures (VERY LOW QUALITY)

Quality of life – statistically non-significant results
No statistically significant difference between levetiracetam adjunctive therapy and placebo in achieving a greater improvement in the quality of life.

Cost-effectiveness
One economic evaluation based on a decision analytic model showed that levetiracetam adjunctive therapy is cost-effective compared to placebo in the treatment of primary generalised tonic-clonic seizures. However, lamotrigine adjunctive therapy is less costly and more effective than levetiracetam adjunctive therapy. This evidence is directly applicable and has minor limitations.
10.6.6.4 Topiramate adjunctive therapy versus placebo

**Clinical evidence**
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Health Economic Evidence**
One economic evaluation was identified in the economic literature search and included in the evidence review. As there were still gaps in the economic evidence base, original economic modelling was undertaken to evaluate AEDs, including topiramate, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of this study and the NCGC GTC model are presented in section 10.6.7

**Evidence statements**

**Efficacy – statistically significant results**
Significantly more participants taking topiramate adjunctive therapy compared to placebo achieved at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

**Efficacy – statistically non-significant results**
No significant difference between topiramate adjunctive therapy and placebo in achieving a greater proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between topiramate adjunctive therapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events (VERY LOW QUALITY)

**Adverse events – statistically non-significant**
No statistically significant difference between topiramate adjunctive therapy and placebo for the incidence of the following adverse events:

- somnolence (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- difficulty with memory (VERY LOW QUALITY)
- nervousness (VERY LOW QUALITY)
- psychomotor slowing (VERY LOW QUALITY)
- upper respiratory tract infection (VERY LOW QUALITY)
- pharyngitis (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- speech disorders and related speech problems (VERY LOW QUALITY)
- abdominal pain (VERY LOW QUALITY)
• ataxia (VERY LOW QUALITY)
• insomnia (VERY LOW QUALITY)
• aggressive reaction (VERY LOW QUALITY)
• confusion (VERY LOW QUALITY)

Cost-effectiveness
Two economic evaluations based on cost-utility analyses show that topiramate adjunctive therapy is more effective and more costly than placebo, with incremental cost-effectiveness ratios of £34,417 and £82,816 per QALY gained, respectively. In the second analysis, topiramate adjunctive therapy was dominated by lamotrigine adjunctive therapy and extendedly dominated by levetiracetam adjunctive therapy. This evidence is directly applicable and has minor limitations.

10.6.7 Health economic evidence for AEDs used as adjunctive therapy in adults with refractory generalised tonic-clonic seizures
One study\(^{150}\) assessing the cost-effectiveness of topiramate used as adjunctive therapy in patients with refractory generalised tonic-clonic seizures was identified in the economic literature search and included in the economic evidence review. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in patients with refractory generalised tonic-clonic seizures. This was based on evidence included in the clinical review\(^ {254,268,269}\). See appendix P for full details and results of modelling.

Economic study characteristics
Table 10-23: Monotherapy for patients with IGE - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC GTC model</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
<td>Decision analytic model; 15-year time horizon; comparators included monotherapy (placebo), lamotrigine, topiramate and levetiracetam; effectiveness data from studies included in clinical review(^ {254,268,269}).</td>
</tr>
<tr>
<td>Hawkins 2005(^{150})</td>
<td>Minor limitations</td>
<td>Partially applicable (a)</td>
<td>Decision analytic model; 15-year time horizon; effectiveness data from Barret 1998(^ {270}) and Biton 1999(^ {269}).</td>
</tr>
</tbody>
</table>

(a) Costs discounted 6% per annum; effects discounted 1.5% per annum
**Economic study results – NCGC GTC model**

### Table 10-24: Monotherapy for patients with IGE – Results of NCGC GTC model

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effect (QALYs) per patient</th>
<th>ICER (£/QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£6,239</td>
<td>7.523</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>£6,605</td>
<td>7.770</td>
<td>£1,482</td>
<td>At thresholds of £20K and £30K/QALY, LTG has a 99% and 98% probability of being optimal, respectively.</td>
</tr>
<tr>
<td>TPM</td>
<td>£10,020</td>
<td>7.571</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>LEV</td>
<td>£10,665</td>
<td>7.748</td>
<td>Dominated</td>
<td>At thresholds of £20K and £30K/QALY, LEV has a 0.44% and 1.86% probability of being optimal, respectively.</td>
</tr>
</tbody>
</table>

**Evidence statements**

Evidence from one cost-effectiveness analysis indicates that lamotrigine is the most cost-effective adjunctive AED for the treatment of refractory generalized tonic-clonic seizures. This evidence is directly applicable and has minor limitations.

Evidence from one cost-effectiveness analysis indicates that levetiracetam is more costly and less effective than lamotrigine in the treatment of refractory generalized tonic-clonic seizures. However, if lamotrigine is not a clinically appropriate option, levetiracetam is very likely to be considered cost-effective given a threshold of £20,000 per QALY. This evidence is directly applicable and has minor limitations.

Evidence from one cost-effectiveness analysis indicates that topiramate is more costly and less effective than lamotrigine and is extendedly dominated by levetiracetam when lamotrigine is not a clinically appropriate drug option. This evidence is directly applicable and has minor limitations.
Economic study results – Hawkins 2005150

Table 10-25: Monotherapy for patients with IGE – Results of Hawkins 2005150

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effect (QALYs) per patient</th>
<th>ICER (£/QALY)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£5,064</td>
<td>8.737</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>£7,471</td>
<td>8.807</td>
<td>£34,417</td>
<td></td>
</tr>
</tbody>
</table>

At threshold of £30K /QALY, monotherapy (placebo) has 59% probability of being optimal.
At threshold of £30K/QALY, topiramate has a 41% probability of being optimal.

Evidence statements
Evidence from one cost-effectiveness analysis indicates that topiramate is more costly and more effective than continued monotherapy, but with an incremental cost-effectiveness ratio greater than £20,000 and £30,000 per QALY gained, it is unlikely to be considered cost-effective in this patient group. This evidence is partially applicable and has minor limitations.
10.6.8 Recommendations and link to evidence

First-line treatment in adults and children with newly diagnosed PGTC seizures

**Recommendation**

Offer carbamazepine, lamotrigine, oxcarbazepine* or sodium valproate as first-line treatment to adults and children with PGTC seizures, unless they have also had myoclonic and/or absence seizures, when sodium valproate should be offered first. [new 2011]

**Relative values of different outcomes**

In adults and children seizure-freedom and adverse effects were considered to be the most important outcomes.

**Trade off between clinical benefits and harms**

In adults, there was no significant difference in seizure freedom between sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. In children there was no difference between sodium valproate and carbamazepine.

The GDG consensus opinion was that there is a tendency for drugs such as carbamazepine and oxcarbazepine to exacerbate certain seizures types such as myoclonic and absence seizures. Carbamazepine, lamotrigine, oxcarbazepine, and sodium valproate are associated with an increased risk of neural tube and other defects and so the women of child-bearing age should be informed of such risks.

The GDG considered that the benefits of reduction of seizures outweighed the adverse effects.

**Economic considerations**

No economic evidence was identified in the literature and no economic evaluation was undertaken to inform the cost-effectiveness of first line AEDs used to treat newly diagnosed patients experiencing primary generalised tonic-clonic seizures. The GDG felt that an extrapolation from the SANAD study population with generalised epilepsies to a population with primary generalised tonic-clonic seizures was not unreasonable and that the relative cost-effectiveness of sodium valproate was unlikely to be different between these groups.

Sodium valproate emerged as the drug most likely to be cost-effective in the cost per seizure avoided analysis conducted as part of the SANAD trial\(^1\). Greater weight was given to this analysis as the reduction in seizure frequency, particularly of primary generalised tonic-clonic seizures, is considered to be the most important clinical outcome. The published economic evidence for the cost effectiveness of lamotrigine in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and is also likely to be considered cost-effective.

No economic evidence for carbamazepine or oxcarbazepine in a population with generalised epilepsy was available, but their relative cost-effectiveness to sodium valproate and lamotrigine in populations with focal epilepsy was considered.

\(^*\) Please see appendix K for licensing details.
when including them in this recommendation. However, the GDG considered that carbamazepine and oxcarbazepine may aggravate other seizure types, thus negatively impacting patient quality of life and potentially increasing NHS resource use.

**Quality of evidence**

Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power of studies particularly with regard to adverse events. The overall quality of studies was very low with poor reporting of randomisation methods, allocation concealment and many studies were unblinded. There was a high drop-out rate in the majority of studies.

**Other considerations**

Phenytoin was shown to have efficacy but the GDG considered it to have a very high adverse events profile.

Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in the lamotrigine dose.
### Adjunctive treatment for people with newly diagnosed PGTC seizures

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer clobazam*, lamotrigine, levetiracetam or topiramate as adjunctive treatment to adults and children with PGTC seizures if first-line treatments (see recommendation 4.10.8.1) are ineffective or not tolerated. [new 2011]</th>
</tr>
</thead>
</table>

#### Relative values of different outcomes

The most important outcomes were adverse effects and 50% reduction in seizure frequency.

#### Trade off between clinical benefits and harms

Lamotrigine, levetiracetam and topiramate adjunctive therapies all significantly reduced seizure frequency by at least 50% when compared to placebo. There was significantly more seizure freedom with clobazam and levetiracetam compared to placebo but lamotrigine and topiramate showed no difference compared to placebo.

There was no significant difference for any adverse event, withdrawal due to adverse events or lack of efficacy for lamotrigine, levetiracetam and topiramate adjunctive therapies when compared to placebo.

#### Economic considerations

The GDG considered the evidence from the economic evaluation undertaken for the guideline in which lamotrigine emerged as a very cost-effective adjunctive therapy in patients experiencing refractory primary generalised tonic-clonic seizures. If lamotrigine had been tried previously, levetiracetam was also likely to be a cost-effective adjunctive AED. Topiramate was not shown to be cost-effective, but in the event that other alternatives fail to produce the desired reduction in seizure frequency, the GDG felt that it should be considered. Clobazam was not evaluated as part of the cost-effectiveness analysis because the clinical studies did not report all outcomes necessary for inclusion. However, the GDG felt that its effectiveness compared to placebo and its small unit cost were likely to make it cost-effective.

#### Quality of evidence

Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power in the studies particularly with regard to side-effects. The overall quality of studies was low, some had no details of randomisation or allocation concealment, high drop-out rate or a very small sample size.

* Please see appendix K for licensing details.
Other considerations

There is a pharmacodynamic interaction between levetiracetam and carbamazepine and between lamotrigine and carbamamzepine so side effects may be enhanced.

Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose. Care should be taken when withdrawing clobazam with a slow withdrawal up to 4-6m in view of the risk of withdrawal seizures. Topiramate may affect phenytoin levels.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not offer tiagabine and vigabatrin to adults and children with PGTC seizures. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**
Reduction in seizures and adverse effects were considered to be the most important outcomes.

**Trade off between clinical benefits and harms**
Vigabatrin and tiagabine have the potential to exacerbate myoclonic seizures and absences. According to the GDG expertise, and the BNF, vigabatrin is associated with visual field defects. These drugs are used as adjunctive treatment of partial seizures with or without secondary generalisation. The GDG suggested that these two drugs be avoided in a population with primary generalised tonic-clonic seizures.

**Economic considerations**
No economic evidence was available to inform the cost-effectiveness of these AEDs in this population, however their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.

**Quality of evidence**
We found no evidence for these drugs in relation to primary generalised tonic-clonic seizures.

**Other considerations**
None.
Infantile spasms are a specific seizure type presenting in the first year of life, most commonly between 3 and 7 months of age. Spasms are brief axial movements lasting 0.2-2 seconds, most commonly flexor in nature, involving flexion of the trunk with extension of the upper and lower limbs. They typically occur in clusters, and most commonly on awakening. The EEG characteristically shows random high voltage slow waves and spikes, so called hypsarrhythmia, and together with the developmental plateau typically seen at the onset of spasms, form the triad of ‘West’ syndrome. However full criteria of hypsarrhythmia are not always seen with spasms, especially at the onset, and in these circumstances management should be the same. Spasms may be seen with many underlying causes, whether genetic (eg mutation on CDKL5 gene), structural/metabolic (eg tuberous sclerosis) or unknown.

Long term prognosis is poor for neurodevelopmental progress, impaired in the long term in 85%. Many respond to first line therapy; long term neurodevelopmental progress is thought to be improved should there be a short lag to treatment, as well as prompt response to treatment, although the underlying cause is equally relevant. However 60% go on to develop epilepsy at a later stage even if spasms respond to treatment in the first instance.

Methods of the evidence review

For this review we included adults and children with Infantile Spasms with or without tuberous sclerosis as a cause. The outcomes were the same as other reviews except instead of the proportion of participants with seizure freedom we looked at the proportion of participants with cessation of spasms and the proportion of participants with resolution of hypsarrhythmia.

Matrix of the evidence for Adjunctive therapy

We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy (name the specific group). The interventions we included in our search were nitrazepam, pyridoxine, adrenocorticotropic hormone, hydrocortisone, prednisolone, prednisone, vigabatrin, topiramate, clobazam, clonazepam, zonisamide and sodium valproate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
10.7.3.1 Vigabatrin versus placebo (in a population without tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin and placebo for cessation of spasms in a population without tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and placebo for resolution of hypsarrhythmia in a population without tuberous sclerosis. (MODERATE QUALITY)

No significant difference between vigabatrin and placebo for at least 70% reduction in seizure frequency in a population without tuberous sclerosis. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and placebo in a population without tuberous sclerosis for:

- Incidence of drowsiness (LOW QUALITY)
- Incidence of irritability (LOW QUALITY)
- Incidence of death (LOW QUALITY)
Cost-effectiveness

No economic evidence comparing vigabatrin to placebo was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.7.3.2 Vigabatrin versus ACTH (in a population with tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin and ACTH for cessation of spasms in a population with tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and ACTH for resolution of hypsarrhythmia in a population with tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and ACTH for withdrawal due to adverse events in a population with tuberous sclerosis (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on ACTH than vigabatrin in a population with tuberous sclerosis had:

- incidence of irritability (MODERATE QUALITY)
- incidence of hypertension (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and ACTH in a population with tuberous sclerosis for incidence of death. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin to ACTH was identified in a population with tuberous sclerosis experiencing infantile spasms.
10.7.3.3 Vigabatrin versus ACTH (in a population without tuberous sclerosis)

**Clinical evidence**

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Health economic evidence**

No studies were identified in the economic literature search.

**Evidence statements**

**Efficacy – statistically significant results**

Significantly more participants on ACTH compared to vigabatrin had cessation of spasms in a population without tuberous sclerosis although there is uncertainty in the magnitude of clinical effect. (LOW QUALITY)

Significantly more participants on ACTH compared to vigabatrin had resolution of hypsarrhythmia in a population without tuberous sclerosis. (MODERATE QUALITY)

**Efficacy – statistically non-significant results**

No significant difference between vigabatrin and ACTH for withdrawal due to adverse events in a population without tuberous sclerosis. (LOW QUALITY)

**Adverse events – statistically significant results**

Significantly more participants on ACTH than vigabatrin in a population without tuberous sclerosis had:

- Incidence of irritability (MODERATE QUALITY)

**Adverse events – statistically non-significant results**

No significant difference between vigabatrin and ACTH in a population without tuberous sclerosis for:

- Incidence of gastrointestinal disturbances
- Incidence of drowsiness
- Incidence of increased appetite
- Incidence of dermatological problems

**Cost-effectiveness**

No economic evidence comparing vigabatrin to ACTH was identified in a population without tuberous sclerosis experiencing infantile spasms.
10.7.3.4 Vigabatrin versus hydrocortisone (in a population with only tuberous sclerosis)

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Significantly more participants on vigabatrin compared to hydrocortisone had cessation of spasms in a population with only tuberous sclerosis. (MODERATE QUALITY)

Adverse events – statistically non-significant results
No significant difference between vigabatrin and hydrocortisone in a population with only tuberous sclerosis for:

- Incidence of drowsiness (VERY LOW QUALITY)
- Incidence of hyperexcitability/hyperkinesia (VERY LOW QUALITY)
- Incidence of sleep disorders (VERY LOW QUALITY)
- Incidence of weight gain (VERY LOW QUALITY)
- Incidence of abdominal distension (VERY LOW QUALITY)
- Incidence of hypertension (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing vigabatrin to hydrocortisone was identified in a population with only tuberous sclerosis experiencing infantile spasms.
10.7.3.5 Vigabatrin versus prednisolone (in a population without tuberous sclerosis)

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between vigabatrin and prednisolone for cessation of spasms in a population without tuberous sclerosis. (VERY LOW QUALITY)
No significant difference between vigabatrin and prednisolone for resolution of hypsarrhythmia in a population without tuberous sclerosis. (VERY LOW QUALITY)
No significant difference between vigabatrin and prednisolone for withdrawal due to adverse events in a population without tuberous sclerosis. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants on prednisolone than vigabatrin in a population without tuberous sclerosis had:

- Incidence of irritability (MODERATE QUALITY)

Adverse events – statistically non-significant results
No significant difference between vigabatrin and prednisolone in a population without tuberous sclerosis for:

- Incidence of gastrointestinal disturbances (VERY LOW QUALITY)
- Incidence of drowsiness (VERY LOW QUALITY)
- Incidence of increased appetite (VERY LOW QUALITY)
- Incidence of fluid and electrolyte (including high b.p) (VERY LOW QUALITY)
- Incidence of infection (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing vigabatrin to prednisolone was identified in a population without tuberous sclerosis experiencing infantile spasms.
10.7.3.6 ACTH versus prednisone (in a population with tuberous sclerosis)

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically significant results
Significantly more participants on ACTH compared to prednisone in a population with tuberous sclerosis had cessation of spasms. (MODERATE QUALITY)
Significantly more participants on ACTH compared to prednisone in a population with tuberous sclerosis had resolution of hypsarrhythmia. (MODERATE QUALITY)

Cost-effectiveness
No economic evidence comparing ACTH to prednisone was identified in a population with tuberous sclerosis experiencing infantile spasms.

10.7.3.7 ACTH versus prednisone (in a population with tuberous sclerosis)

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – non-statistically significant results
No significant difference between ACTH and prednisone for response to treatment in a population without tuberous sclerosis. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between ACTH and prednisone for incidence of hypertension in a population without tuberous sclerosis (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing ACTH to prednisone was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.7.3.8 Prednisolone versus ACTH (in a population without tuberous sclerosis)

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.
Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between prednisolone and ACTH for cessation of spasms in a population without tuberous sclerosis. (VERY LOW QUALITY)

No significant difference between prednisolone and ACTH for resolution of hypsarrhythmia in a population without tuberous sclerosis. (VERY LOW QUALITY)

No significant difference between prednisolone and ACTH for withdrawal due to adverse events in a population without tuberous sclerosis (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between prednisolone and ACTH in a population without tuberous sclerosis for:

• Incidence of gastrointestinal disturbances
• Incidence of irritability
• Incidence of drowsiness
• Incidence of increased appetite
• Incidence of fluid and electrolyte (including high b.p)
• Incidence of blood pressure above 110/80mmHg
• Incidence of blood pressure above 120/90mmHg

Cost-effectiveness

No economic evidence comparing prednisolone to ACTH was identified in a population without tuberous sclerosis experiencing infantile spasms.
10.7.3.9 Nitrazepam versus ACTH

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between nitrazepam and ACTH for at least 50% reduction in seizure frequency. (VERY LOW QUALITY)
No significant difference between nitrazepam and ACTH for withdrawal due to adverse events (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between nitrazepam and ACTH for incidence of death. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing nitrazepam to ACTH was identified in a population experiencing infantile spasms.
10.7.4 Recommendations and link to evidence

First-line treatment in children with infantile spasms

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with infantile spasms. [new 2011]</th>
</tr>
</thead>
</table>

Relative values of different outcomes | Reduction in seizures and adverse effects were considered to be the most important outcomes. |

Trade off between clinical benefits and harms | Infantile spasms is a rare seizure type which requires input from specialists with expertise in the area. The adverse events profile of individual drugs needs to be evaluated and fully discussed with parents. This was a recommendation based on the GDG expertise as it is thought important that children with infantile spasms should see, or get advice from, a specialist. Limited evidence suggests early resolution of hypsarrhythmia leads to better prognosis. |

Economic considerations | No economic evidence was available to inform recommendations about the treatment of infantile spasms. However, the GDG considered that discussion with or referral to a tertiary paediatric specialist and early intervention in this group of patients may lead to a better prognosis, preventing long term cognitive deterioration and associated decrements to health related quality of life. |

Quality of evidence | There was no evidence sought for this recommendation. The recommendation was based on GDG expertise. |

Other considerations | The adverse events profile of individual medicines needs to be evaluated and fully discussed with parents. The long term functional risk to visual field defects from vigabatrin is unknown with short term use; the short term side effects of high dose steroids such as high blood pressure and glucose intolerance require monitoring. |
Recommendation: Offer a steroid (prednisolone or tetracosactide*) or vigabatrin as first-line treatment to children with infantile spasms that are not due to tuberous sclerosis. [new 2011]

Relative values of different outcomes: Cessation of spasms, resolution of hypsarrhythmia and side effects are considered important primary outcome measures.

Trade off between clinical benefits and harms: Significantly more participants (without tuberous sclerosis as cause) on ACTH than vigabatrin had cessation of spasms and hypsarrhythmia. No difference was found in efficacy in a study of vigabatrin versus prednisolone or prednisolone versus ACTH or prednisone versus ACTH for those without tuberous sclerosis as cause.

The GDG considered the drugs to have clinically relevant differences in their side-effects profile. The long term functional risk to visual field defects from vigabatrin is unknown with short term use. The GDG suggest monitoring of visual fields, where possible. Short term side effects of high dose steroids such as high blood pressure and glucose intolerance should be monitored. The evidence indicated that hypertension and irritability are worse with steroids. ACTH had a higher incidence of irritability than vigabatrin whether tuberous sclerosis was the cause or not. Prednisolone had higher incidence of irritability than vigabatrin in a population where tuberous sclerosis was excluded.

Economic considerations: No economic evidence was available to inform the GDG of the relative cost-effectiveness of any drugs used in the treatment of infantile spasms. The population of children experiencing infantile spasms is quite small, treatment duration is short and it is difficult to weigh up the benefits and harms of treatment in terms of quality of life in children so young. Early diagnosis and treatment are essential as this may impact on longer term cognitive and social outcomes. The potential side-effects of steroids (hypertension and irritability) pose additional costs in terms of management and monitoring.

Quality of evidence: Overall number and quality of studies was limited. There was heterogeneity of cause of infantile spasms, dosage of interventions, and duration of the treatment and follow-up. All of the studies were of limited power and do not exclude the possibility of significant differences between the treatments.

Other considerations: Compared with the original guideline (2004), one additional RCT was appropriate for consideration.

* Please see appendix K for licensing details.
Recommendation

Offer vigabatrin as first-line treatment to children with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide). [new 2011]

Relative values of different outcomes

Cessation of spasms, resolution of hypsarrhythmia and adverse events are considered important primary outcome measures.

Trade off between clinical benefits and harms

Vigabatrin is significantly more effective at stopping spasms than steroids in patients with infantile spasms caused only by tuberous sclerosis.

Significantly more patients (including those with tuberous sclerosis as cause) on ACTH than prednisolone had cessation of spasms and hypsarrhythmia. There was no significant difference between vigabatrin and ACTH in studies where tuberous sclerosis was the cause.

The GDG considered the drugs to have clinically relevant differences in their adverse events profile. The long term functional risk to visual field defects from vigabatrin is unknown with short term use. The GDG suggest monitoring of visual fields, where possible. Short term side effects of high dose steroids such as high blood pressure and glucose intolerance should be monitored. The evidence found ACTH had higher incidence of irritability and hypertension than vigabatrin for those with tuberous sclerosis as the cause.

The GDG felt that overall the advantages of vigabatrin outweighed the potential adverse effects. Steroids were found to be less effective at stopping seizures but the GDG considered that they are a valuable option if vigabatrin is ineffective.

Economic considerations

No economic evidence was available to inform the GDG of the relative cost-effectiveness of any drugs used in the treatment of infantile spasms associated with tuberous sclerosis. The population of children experiencing infantile spasms is quite small, treatment duration is short and it is difficult to weigh up the benefits and harms of treatment in terms of quality of life in children so young. Early diagnosis and treatment are essential as this may impact on longer term cognitive and social outcomes. The potential side-effects of steroids (hypertension and irritability) pose additional costs in terms of management and monitoring.

Quality of evidence

Overall number and quality of studies was limited. Heterogeneity of cause, dosage of interventions, and duration of the treatment and follow-up. All of the studies were of limited power and do not exclude the possibility of significant differences between the treatments.

Other considerations

No other considerations.
10.7.5 Research recommendations (for full list see section 2.11)

10.7.5.1 Infantile spasms

Does treatment response relate to aetiology in infantile spasms? Does early treatment success in seizure control and resolution of the hypsarrhythmic EEG influence the long-term developmental and cognitive outcome more than the underlying cause of the spasms?

Why is this important

The UK Infantile Spasms Study (UKISS)\textsuperscript{27} study demonstrated 14-day outcome efficacy of steroids over vigabatrin although this excluded children with tuberous sclerosis. This study provided no specific sub-group analysis based on the cause of the spasms. There was no analysis on the effect of treatment lag on the study findings. Further data is available on behavioural outcome at 14 months and 5 years with regard to different treatments but with no analysis based on cause or treatment lag. Further developmental and cognitive outcomes would be useful, including response by specific cause and by treatment lag (delay).

Research should include:
- Prospective randomised design; this must include sub-group analyses based on both cause and treatment lag (delay); this will necessitate large numbers of patients and will need to be multi-centre, possibly involving Western Europe.
- EEG outcomes.
- Developmental status at presentation, and at follow-up.
- An attempt to obtain some data on pharmaco-resistance.

10.7.6 Deleted recommendations from the 2004 guideline

10.7.6.1 Vigabatrin is recommended as a first-line therapy for the management of infantile spasms.

10.8 Lennox-Gastaut Syndrome

10.8.1 Introduction

Lennox Gastaut syndrome is an epilepsy syndrome characterised by multiple seizure types (including atonic, tonic, tonic clonic and atypical absence seizures), cognitive impairment and specific EEG features. Age of onset is typically between 3 and 10 years, usually before 8 years, with 10-30\% having an earlier history of infantile spasms. The characteristic EEG pattern of diffuse slow spike and wave (<2.5Hz) may not be present at onset but may evolve with time; some authors also require the presence of fast (10Hz) rhythms in sleep, with or without tonic seizures, to make the diagnosis. Episodes of non convulsive status epilepticus are common, but may be under recognised. Long term prognosis for both neurocognitive outcome and seizure control is poor, with a high rate of behaviour disorder. Aims of management should be discussed carefully with each family and medication kept to a minimum where possible to avoid toxicity.

10.8.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with Lennox-Gastaut Syndrome.

10.8.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for Lennox-Gastaut syndrome. The following interventions were included in our search; rufinamide, clobazam, clonazepam, felbamate, ethosuximide, lamotrigine, levetiracetam, sodium valproate and topiramate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Rufinamide (RFM)</th>
<th>Lamotrigine (LTG)</th>
<th>Topiramate (TPM)</th>
<th>Levetiracetam (LEV)</th>
<th>Felbamate (FBM)</th>
<th>Ethosuximide (ETX)</th>
<th>Clobazam (CLB)</th>
<th>Clonazepam (CLZ)</th>
<th>Sodium valproate (VPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1 280</td>
<td>2281,282</td>
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<td>1 284</td>
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<td>Rufinamide</td>
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<td>Lamotrigine</td>
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<td>Topiramate</td>
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<td>Levetiracetam</td>
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<td>Felbamate</td>
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<td>Ethosuximide</td>
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<td>Clobazam</td>
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<tr>
<td>Clonazepam</td>
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<tr>
<td>Sodium valproate</td>
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<tr>
<td>Pla</td>
<td>RFM</td>
<td>LTG</td>
<td>TPM</td>
<td>LEV</td>
<td>FBM</td>
<td>ETX</td>
<td>CLB</td>
<td>CLZ</td>
<td>VPA</td>
</tr>
</tbody>
</table>

Updated 2011
1.0.8.3.1 Lamotrigine adjunctive therapy versus placebo

**Clinical evidence**
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Health economic evidence**
One economic evaluation of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.8.4.

**Evidence statements**

**Efficacy – statistically significant results**
Significantly more participants taking lamotrigine adjunctive experienced at least 50% reduction in drop attack seizure frequency compared to placebo. (MODERATE QUALITY)

Significantly more participants taking lamotrigine adjunctive experienced at least 50% reduction in tonic clonic seizure frequency compared to placebo. (MODERATE QUALITY)

**Efficacy – statistically non-significant results**
No significant difference between lamotrigine adjunctive and placebo for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive and placebo for the proportion of participants experienced at least 50% reduction in seizure frequency (VERY LOW QUALITY)

**Adverse events – statistically significant results**
Significantly more participants taking placebo experienced fatigue compared to lamotrigine adjunctive. (LOW QUALITY)

**Adverse events – statistically non-significant results**
No significant difference between lamotrigine adjunctive and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between lamotrigine adjunctive and placebo for the incidence of the following adverse events:

- Pharyngitis (VERY LOW QUALITY)
- Fever (VERY LOW QUALITY)
- More intense seizures (VERY LOW QUALITY)

**Cost-effectiveness**
One economic evaluation based on a decision analytic model showed that adjunctive lamotrigine is less costly and more effective than placebo in the treatment of total seizures and drop attack seizures in people with Lennox-Gastaut syndrome. This evidence is partially applicable and has potentially serious limitations.
Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes.

10.8.3.2 Topiramate adjunctive therapy versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

One economic evaluation of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.8.4.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking topiramate adjunctive therapy experienced at least 50% reduction in frequency of all major seizures compared to placebo, however there is uncertainty over the magnitude of this clinical effect. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo for the proportion of participants free from drop attack seizures. (VERY LOW QUALITY)

No significant difference between topiramate adjunctive therapy and placebo for the proportion of participants experienced at least 50% reduction in drop attack seizure frequency (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking topiramate adjunctive therapy experienced somnolence compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly more participants taking topiramate adjunctive therapy experienced anorexia compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly more participants taking topiramate adjunctive therapy experienced fatigue compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)
Adverse events – statistically non-significant results

No significant difference was found between topiramate adjunctive and placebo for the incidence of the following adverse events:

- Nervousness (VERY LOW QUALITY)
- Behavioural problems (VERY LOW QUALITY)
- More intense seizures (VERY LOW QUALITY)
- Dizziness (VERY LOW QUALITY)
- Weight loss (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that adjunctive topiramate is less costly and more effective than placebo in the treatment of drop attack seizures in people with Lennox-Gastaut syndrome. Adjunctive topiramate is more costly and more effective than placebo in terms of total seizure reduction, with an incremental cost-effectiveness ratio of £58 per additional 1% of successfully treated patients. This evidence is partially applicable and has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes

10.8.3.3 Felbamate adjunctive therapy versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between felbamate adjunctive therapy and placebo for the proportion of participants free from seizures (atonic and tonic-clonic seizure). (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking felbamate adjunctive therapy experienced anorexia compared to placebo. (MODERATE QUALITY)
Significantly more participants taking felbamate adjunctive therapy experienced vomiting compared to placebo. (MODERATE QUALITY)

Significantly more participants taking felbamate adjunctive therapy experienced somnolence compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly fewer participants taking felbamate adjunctive therapy experienced diarrhoea compared to placebo. (MODERATE QUALITY)

**Adverse events – statistically non-significant results**

No significant difference between felbamate adjunctive therapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between felbamate adjunctive and placebo for the incidence of the following adverse events:

- Upper respiratory tract infection (VERY LOW QUALITY)
- Injury (VERY LOW QUALITY)
- Fever (VERY LOW QUALITY)
- Insomnia (VERY LOW QUALITY)
- Nervousness (VERY LOW QUALITY)
- Headache (VERY LOW QUALITY)
- Fatigue (VERY LOW QUALITY)
- Purpura (VERY LOW QUALITY)
- Abnormal gait (VERY LOW QUALITY)
- Rhinitis (VERY LOW QUALITY)
- Ataxia (VERY LOW QUALITY)

**Cost-effectiveness**

No economic evidence comparing felbamate adjunctive therapy to placebo was identified in a population with Lennox-Gastaut syndrome.

**Outcomes with no evidence**

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes
10.8.3.4 Rufinamide adjunctive versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
One economic evaluation of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.8.4.

Evidence statements

Efficacy – statistically significant results
Significantly more participants in rufinamide adjunctive experienced at least 50% reduction in seizure frequency compared to placebo. (LOW QUALITY)
Significantly more participants in rufinamide adjunctive experienced at least 50% reduction in frequency of tonic-atactic seizures compared to placebo. (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between rufinamide adjunctive and placebo for the proportion of participants withdrawn due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants taking rufinamide adjunctive experienced vomiting compared to placebo. (LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between rufinamide adjunctive and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between rufinamide adjunctive and placebo for the incidence of the following adverse events:

- Somnolence (VERY LOW QUALITY)
- Pyrexia (VERY LOW QUALITY)
- Diarrhoea (VERY LOW QUALITY)

Cost-effectiveness
One economic evaluation based on a decision analytic model showed that adjunctive rufinamide is less costly and more effective than placebo in the treatment of drop attack seizures in people with Lennox-Gastaut syndrome. Adjunctive rufinamide is more costly and more effective than placebo in terms of total seizure reduction, with an incremental cost-effectiveness ratio of £85 per additional 1% of successfully treated patients. This evidence is partially applicable and has potentially serious limitations.
Outcomes with no evidence

There were no studies that reported:

- time to first seizure,
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes.

10.8.4 Health economic evidence of AEDs used as adjunctive therapy for children with Lennox-Gastaut syndrome

One study\textsuperscript{285} assessing the cost-effectiveness of AEDs used as adjunctive therapy in children with Lennox-Gastaut syndrome was identified in the economic literature search and included in the economic evidence review. See appendix M for full study details.

Economic study characteristics

Table 10-26: Adjunctive therapy for children with Lennox-Gastaut syndrome - Economic study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Applicability</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedict (2010)</td>
<td>Potentially serious limitations (a, b)</td>
<td>Partially applicable (c, d, e)</td>
<td>Decision analytic model; comparators included monotherapy (placebo), lamotrigine, rufinamide and topiramate; time horizon 3 years; clinical data based on indirect treatment comparison of data presented in clinical review\textsuperscript{280,282,283}; 2 analyses conducted: one on reduction in ‘drop attack’ seizure frequency and other on percent reduction in total seizure frequency</td>
</tr>
</tbody>
</table>

(a) Authors do not detail how non-reported outcomes for lamotrigine and topiramate were handled. Details of how adverse events were costed were not reported.
(b) Potential conflict of interest in terms of funding source
(c) Estimates of resource use based on ‘expert’ opinion of five physicians
(d) Analysis based percent of successfully treated patients, not QALYs
(e) Costs discounted at 3.5% per annum; no discounting applied to estimate of effect
Economic study results

Table 10-27: Adjunctive therapy for children with Lennox-Gastaut syndrome – Results of Benedict 2010

<table>
<thead>
<tr>
<th>AED</th>
<th>Total cost (£) per patient</th>
<th>Total effects (% successfully treated patients)</th>
<th>ICER (£ / 1% increase in successfully treated patients)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPM</td>
<td>£50,728</td>
<td>7.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>£50,975</td>
<td>5.2%</td>
<td>At threshold of £100 per 1% increase in successfully treated patients ('drop attacks'), probability of TPM being optimal is 36%</td>
<td></td>
</tr>
<tr>
<td>RUF</td>
<td>£50,985</td>
<td>11.3%</td>
<td>At threshold of £100 per 1% increase in successfully treated patients ('drop attacks'), probability of LTG being optimal is 10%</td>
<td></td>
</tr>
<tr>
<td>Monotherapy (placebo)</td>
<td>£51,437</td>
<td>3.3%</td>
<td>Dominated</td>
<td></td>
</tr>
</tbody>
</table>

Measured on outcome of reduction in 'drop attack' seizures

TPM: Probability of TPM being optimal is 36%.
LTG: Probability of LTG being optimal is 10%.
RUF: Probability of RUF being optimal is 54%; One-way sensitivity analysis indicates ICER for RUF is sensitive to decrease in rate of hospitalisation for 'drop attack' seizures.
Monotherapy (placebo): Dominated.

Measured on outcome of reduction in total seizures

LTG, Monotherapy (placebo), TPM, RUF: Dominated.

(a) Text states that at threshold of £900 per 1% increase in successfully treated patients RUF has a >80% probability of being optimal; however, the CEAC presented cannot be interpreted to confirm this.

Evidence statements

One economic evaluation based on a decision-analytic model shows that adjunctive rufinamide is more costly and more effective than lamotrigine and topiramate, but its cost-effectiveness is indeterminable as the analysis did not measure effects in terms of QALYs. The cost-effectiveness of rufinamide is sensitive to assumptions about the rate of hospitalisation caused by ‘drop attack’ seizures. The analysis is partially applicable and has potentially serious limitations.

Topiramate is less costly and more effective than lamotrigine when evaluation is based on the reduction in ‘drop attack’ seizures, but lamotrigine is less costly and more effective than topiramate when evaluation is based on the reduction in all seizure types. The analysis is partially applicable and has potentially serious limitations.
### 10.8.5 Recommendations and link to evidence

#### First-line treatment in children with Lennox-Gastaut syndrome

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th><strong>Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. [new 2011]</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Relative values of different outcomes</strong></th>
<th>Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Trade off between clinical benefits and harms</strong></th>
<th>The potential benefits of reducing seizures need to be balanced against the potential for adverse effects. No RCT evidence was retrieved on sodium valproate in this area. There is however evidence that sodium valproate is effective at reducing seizures in idiopathic generalised epilepsy and the GDG opinion was that this evidence could be extrapolated to this group.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Economic considerations</strong></th>
<th>No economic evidence was available to determine the cost-effectiveness of any AEDs used as first-line treatment in a population of patients with newly diagnosed Lennox-Gastaut syndrome. However, the GDG considered that at initial presentation, treatment choice is influenced by the predominant seizure type, and in this case that is typically a generalised seizure type. Therefore, the GDG extrapolated the evidence of cost-effectiveness for sodium valproate from the results of SANAD, presented in section 10.4.5.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Quality of evidence</strong></th>
<th>We found no RCTs in newly diagnosed patients or that compared sodium valproate with another antiepileptic drug. We also found no RCTs that compared two drugs as add-on treatment. The recommendation is based on extrapolated evidence from idiopathic generalised epilepsy and GDG consensus opinion.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Other considerations</strong></th>
<th>The GDG considered that there is no new evidence to challenge first-line treatment (from original guideline). At initial presentation, exact syndromic diagnosis may be unclear and therefore treatment choice influenced by predominant seizure type. Low rates of seizure freedom can be expected in this syndrome as verified by results of clinical trials.</th>
</tr>
</thead>
</table>
**Adjunctive treatment in adults and children with Lennox-Gastaut syndrome**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer lamotrigine as adjunctive treatment to adults and children with Lennox-Gastaut syndrome if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**  
Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.

**Trade off between clinical benefits and harms**  
Lamotrigine adjunctive treatment is more effective in reducing at least 50% the seizure frequency and has a similar side effects profile when compared to placebo.

**Economic considerations**  
The treatment of Lennox-Gastaut syndrome generally requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. The GDG considered the results of one cost-effectiveness analysis, wherein lamotrigine was less costly and more effective than standard treatment in terms of reducing the frequency of all seizures and drop attack seizures and less costly and more effective than topiramate in reduction of all seizures. The analysis had some serious limitations, but the GDG considered that lamotrigine is a relatively inexpensive AED and was shown to be effective in terms of reducing the number of drop attack and tonic-clonic seizures. It was also associated with fewer side effects than topiramate and rufinamide. On this basis, the GDG judged it the AED most likely to be considered cost-effective.

**Quality of evidence**  
The two studies included for the comparison of lamotrigine adjunctive versus placebo were of low quality due to serious limitations in the study design as both of them had no information on randomisation and no allocation concealment.

**Other considerations**  
None.
**Recommendation**

Discuss with a tertiary epilepsy specialist if adjunctive treatment in adults and children with Lennox-Gastaut syndrome is ineffective or not tolerated. Other AEDs that may be considered are rufinamide or topiramate. [new 2011]

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>If adjunctive treatment is not tolerated or ineffective further treatment may be successful but the GDG felt that this should be discussed with a tertiary epilepsy specialist. The balance between reducing seizures (which may be debilitating) and adverse effects needs to be considered when choosing drug treatment. Rufinamide adjunctive treatment was more effective in reducing at least 50% the seizure frequency. Both and topiramate treatments had worst side-effect profile compared to placebo.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>The treatment of Lennox-Gastaut syndrome generally requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. Drop-attack seizures, common in people with Lennox-Gastaut can be debilitating and dangerous, therefore achieving adequate seizure control with adjunctive AEDs can potentially improve quality of life and reduce accidents requiring emergency and/or routine care. The GDG considered the results of one cost-effectiveness analysis, wherein topiramate and rufinamide were less costly and more effective than standard treatment in the reduction of drop attack seizures. However, in the reduction of all seizure types, topiramate and rufinamide were more effective than standard treatment, but lamotrigine dominated topiramate and was more likely to be cost-effective than rufinamide. Although there is no threshold willingness to pay for an additional 1% of successfully treated patients, the ICER for rufinamide over lamotrigine was £2,205 which the GDG judged to be very high and left them uncertain as to its cost-effectiveness in terms of a cost per QALY measure. Also, the cost-effectiveness of rufinamide was very sensitive to the proportion of drop attacks requiring hospitalisation. The analysis had some serious limitations, but the GDG considered that with the estimated daily cost of rufinamide is nearly 10 times that of lamotrigine, it is highly unlikely that the extra benefit observed with rufinamide compared to lamotrigine justifies the substantial additional cost.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The evidence for both topiramate and rufinamide was of low quality. There were no head-to-head comparisons of rufinamide and topiramate with any other antiepileptic drug in Lennox Gastaut Syndrome.</td>
</tr>
</tbody>
</table>
### Other considerations

Clinical experience with rufinamide is considerably less than with lamotrigine which was shown to be effective.

### Recommendation

**Do not offer carbamazepine or oxcarbazepine to adults and children with Lennox-Gastaut syndrome. [new 2011]**

### Relative values of different outcomes

Seizure freedom and adverse effects were considered to be the most important outcomes.

### Trade off between clinical benefit and harms

Clinical practice suggests that seizures can be aggravated by these medications, and can compromise cognition with risk of nonconvulsive status epilepticus. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.

### Economic considerations

No economic evidence was available to inform the cost-effectiveness of these AEDs in this population, however their potential to aggravate seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.

### Quality of evidence

This recommendation was based on GDG expertise.

### Other considerations

There is no evidence of benefit on use of these medications.

### Recommendation

**Only offer felbamate\* to adults and children with Lennox-Gastaut syndrome in centres providing tertiary epilepsy specialist care when treatment with all the above AEDs listed in recommendations 4.10.10.2 and 4.10.10.3 have proved ineffective or not tolerated. [new 2011]**

### Relative values of different outcomes

Reduction in seizures and adverse effects were considered to be the most important outcomes.

### Trade off between clinical benefit and harms

Felbamate adjunctive was not found to be more effective compared to placebo and demonstrated a serious side-effect burden.

### Economic considerations

No economic evidence is available to evaluate the relative cost-effectiveness of felbamate in the treatment of people with Lennox-Gastaut syndrome. However, the potential for serious adverse events, such as aplastic anaemia, and the need for ongoing monitoring make it unlikely to be a cost-effective AED for the average patient.

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* Please see appendix K for licensing details.
Quality of evidence

One RCT was identified which had serious limitations.

Other considerations

The GDG considered felbamate to be a last-line therapy, reserved for patients who have not responded to alternative, cost-effective treatment options. It is only available on a named patient basis. Use of felbamate should be accompanied by monitoring of liver and bone marrow function.

10.9 Severe myoclonic epilepsy in infancy (SMEI)

10.9.1 Introduction

Severe myoclonic epilepsy of infancy, now specifically referred to as Dravets syndrome (as first described by Charlotte Dravet) is a syndrome within the GEFS+ (genetic epilepsy with febrile seizures) spectrum. Typically children will present within the first year of life with lateralized often prolonged febrile seizures, with appearance in the second year (or up to four years of life) of other seizure types including focal seizures and myoclonus. Development is often normal over the first year, but subsequently over the second year may appear to slow. 80% of children with this electroclinical syndrome have a mutation in the sodium channel gene, SCN1A. Although referred to as an epileptic encephalopathy, the degree to which the epilepsy contributes to the neurodevelopmental compromise is unclear, and there may be a contribution from the genetic background. There are also other individuals who do not develop myoclonus but otherwise fulfill the clinical picture, and therefore are known as severe myoclonic epilepsy borderline (SMEB). The aim of treatment remains to control seizures and minimize the occurrence of status epilepticus where possible, remembering some medications may aggravate this condition eg lamotrigine. Long term prognosis both for neurodevelopmental outcome and seizure control in SMEI remains poor.

10.9.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with SMEI.
10.9.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy in a population with severe myoclonic epilepsy of infancy. The interventions we included in our search were stiripentol, levetiracetam, topiramate, clobazam, clonazepam, phenobarbitone and sodium valproate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
10.9.3.1 Stiripentol adjunctive therapy versus Placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically significant results
For people with SMEI, significantly more patients on stiripentol adjunctive therapy were seizure free compared to placebo, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

For people with SMEI, significantly more patients on stiripentol adjunctive therapy experienced at least a 50% reduction in seizure frequency compared to placebo, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically significant results
For people with SMEI, significantly more patients on stiripentol adjunctive therapy experienced drowsiness compared to patients taking placebo, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results
For people with SMEI, there was no significant difference between stiripentol adjunctive therapy and placebo on the incidence of the following adverse events:

- hyperexcitability (VERY LOW QUALITY)
- aggressiveness (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- loss of appetite (VERY LOW QUALITY)
- loss of weight (VERY LOW QUALITY)
- weight gain (VERY LOW QUALITY)
- neutropenia (1000-1500/Ml) (VERY LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:

- withdrawal due to adverse events,
- withdrawal due to lack of efficacy,
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes.
Cost-effectiveness

No economic evidence comparing adjunctive stiripentol to placebo in a population of patients with SMEI was identified.

10.9.4 Recommendations and link to evidence

First-line treatment in children with SMEI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Consider sodium valproate or topiramate* as first-line treatment in children with SMEI. [new 2011]</th>
</tr>
</thead>
</table>

Relative values of different outcomes  
Seizure freedom and withdrawal due to adverse events were considered to be the most important outcomes.

Trade off between clinical benefits and harms  
No evidence was found for monotherapy treatment of SMEI. On first presentation exact syndromic diagnosis may be unclear and therefore treatment choice will be influenced by the predominant seizure type, typically generalised epilepsy. Sodium valproate and topiramate have been shown to be effective in other epilepsy populations. The drugs recommended above are also likely to stop status epilepticus, whereas other drugs such as lamotrigine exacerbate myoclonic seizures (BNF).

Economic considerations  
No economic evidence was available to inform the GDG on the cost-effectiveness of any AEDs used in the treatment of children with SMEI. Sodium valproate was shown to be a cost-effective monotherapy in other epilepsy populations and the GDG considered it likely to be cost-effective in this population as well. Based on clinical experience, the GDG considered topiramate to be another effective and possibly cost-effective AED for patients with SMEI.

Quality of evidence  
No RCT was found in newly diagnosed patients which compared sodium valproate or topiramate with another antiepileptic drug. The recommendation was based on GDG consensus opinion and extrapolated evidence from other epilepsy populations.

Other considerations  
Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose.

* Please see appendix K for licensing details.
Adjunctive treatment in children with SMEI

**Recommendation**
Refer children with SMEI in whom first-line treatment has proved ineffective or not tolerated to a tertiary paediatric epilepsy specialist for consideration of the use of stiripentol as adjunctive treatment. [new 2011]

**Relative values of different outcomes**
The GDG considered that the most important outcomes were a greater than 50% reduction in seizures and seizure freedom for this recommendation, as well as reduction in episodes of status epilepticus (SE).

**Trade off between clinical benefits and harms**
Only one study was found which compared stiripentol to placebo and this showed a significant difference in favour of stiripentol for seizure freedom and at least a 50% reduction in seizure frequency. The GDG considered the benefits to outweigh the risks of using stiripentol. Patients on stiripentol experience drowsiness and appropriate manipulation of the drug may alleviate this side effect. Caution should be given with any drugs that are metabolised by the liver. Stiripentol impairs the breakdown of VPA and CLB and other AEDs metabolised by the liver.

**Economic considerations**
No economic evidence was available to inform the GDG on the cost-effectiveness of any AEDs in the treatment of children with SMEI. Stiripentol is a very expensive drug relative to other first line AEDs currently available in the NHS that are used to treat SMEI. The GDG considered that at an average cost of £0.016 per mg, the annual cost of 30 mg per kilogram per day for a 3-year old child of average weight (16.5 kg) is almost £3000. A dose of 30 mg per kilogram is only the average dose of stiripentol and the annual cost would rise with an increased dose and also increased age and weight of the child. The GDG considered that patients with SMEI whose seizures are poorly controlled are at risk of developing status epilepticus which carries with it increased risks of mortality and morbidity and in some cases can require hospitalisation. Although the clinical evidence shows adjunctive stiripentol to be more effective than placebo, there is considerable uncertainty as to whether associated health gains, measured in terms of seizure reduction, are worth this substantial extra cost.

**Quality of evidence**
Low quality evidence. There was only one trial in SMEI, and it included a small number of patients and provided no details of concealment of allocation.

**Other considerations**
This AED has orphan status. SMEI is a life-long condition which usually has an onset in the first year of life and is associated with severe learning difficulties.
**Recommendation**

Do not offer carbamazepine, lamotrigine, oxcarbazepine, phenytoin or vigabatrin to children with SMEI. [new 2011]

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>Withdrawal due to adverse events and incidence of adverse events were considered to be the most important outcomes for this recommendation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>No other RCTs of AEDs used in SMEI were identified. Therefore this recommendation is based on the consensus opinion of the GDG. These drugs have the potential to exacerbate seizures in SMEI.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic evidence was available to inform the cost-effectiveness of any AEDs in the treatment of children with SMEI, however the potential for these drugs to aggravate seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use, particularly as these patients are at a higher risk for developing convulsive status epilepticus which is associated with increased risks of mortality, morbidity and possible hospitalisation.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>No RCT evidence was found for any of these AEDs therefore the recommendation is based on GDG consensus opinion.</td>
</tr>
</tbody>
</table>
| Other considerations | The GDG considered that there is no new evidence to challenge drugs to be avoided (from original guideline) but decided to add phenytoin.  
  
  Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose. |
10.9.5 Research recommendations (for full list see section 2.11)

10.9.5.1 Epilepsy Syndromes

What is the initial and add-on AEDs of choice in the treatment of the epilepsy syndromes with onset in childhood, for example, myoclonic-astatic epilepsy and SMEI?

Why is this important

Despite the need to diagnose individual epilepsy syndromes, there is little evidence base for the most appropriate initial or add-on AEDs in the treatment of the rarer epilepsies.

Research should include:

- Multicentre randomised controlled comparative trials with centralized national data collection.
- The ketogenic diet as one of the randomised treatments.
- Primary outcome seizure freedom.
- Secondary outcome measures including seizure-reduction, quality of life and cognitive outcome.
- An attempt to obtain some data on pharmaco-resistance.
- The possibility to include all children with specific epilepsy syndromes to be considered for trial.

10.10 Other epilepsy syndromes

10.10.1 Introduction

There remain further epilepsy syndromes with recognizable characteristic electroclinical features where natural history and prognosis is known. However, many of these syndromes are rare and evidence base with regard to their management lacking. In view of this in many management may be continued under tertiary paediatric neurology care.

Clinical evidence

No evidence was retrieved for other epilepsy syndromes

Health Economic Evidence

No studies were identified in the economic literature search.
10.10.2 Recommendations and link to evidence

**Recommendation**

Refer to a tertiary paediatric epilepsy specialist all children with continuous spike and wave during slow sleep (CSWSS), Landau-Kleffner syndrome (LKS) or myoclonic-astatic epilepsy (MAE).

[new 2011]

**Relative values of different outcomes**

Children with these syndromes are very unlikely to achieve seizure freedom. The children usually have additional learning difficulties. Optimal seizure control without unacceptable side effects was therefore the most important outcome for this recommendation.

**Trade off between clinical benefits and harms**

No RCT studies were found and therefore this recommendation is based on the consensus opinion of the GDG. These syndromes, if untreated, can lead to significant cognitive impairment and reduced educational potential, with a high risk of co-morbidities. The GDG felt that it was important that these children are referred to a tertiary epilepsy specialist to manage their care.

**Economic considerations**

No economic evidence was available to inform recommendations in groups with CSWSS, LKS or MAE.

**Quality of evidence**

No RCT data was available for any of these syndromes. This recommendation is based on GDG consensus opinion.

**Other considerations**

None.

10.10.3 Research recommendations (for full list see section 2.11)

10.10.3.1 Epilepsy Syndromes

**Question:** What is the initial and add-on AEDs of choice in the treatment of the epilepsy syndromes with onset in childhood eg: myoclonic-astatic epilepsy, SMEI?

**Why is this important?**

Despite the need to diagnose individual epilepsy syndromes, there is little evidence base for the most appropriate initial or add-on AEDs in the treatment of the rarer epilepsies.

Research should include:

- Multicentre randomised controlled comparative trials with centralized national data collection
- To include the ketogenic diet as one of the randomised treatments
- Primary outcome seizure freedom
- Secondary outcome measures including seizure-reduction, quality of life and cognitive outcome
- Attempt to obtain some data on pharmaco-resistance

**Possibility to include all children with specific epilepsy syndromes to be considered for trial**

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10.11 Benign partial epilepsies of childhood (benign epilepsy with centrotemporal spikes (BECTS) or benign epilepsy with occipital paroxysms (BEOP))

10.11.1 Introduction
Benign epilepsy with centrotemporal spikes (or benign rolandic epilepsy) is one of the most common epilepsies in childhood. It is characterised by focal motor seizures in the majority from sleep, in an otherwise normal individual. An EEG characteristically shows focal spikes in the centrotemporal regions, unilateral or bilateral, enhanced by sleep. The majority of children present between 5 and 8 years, with all resolving by the age of 14 years. Seizure frequency is highly variable; in some seizures will be infrequent. At onset therefore, there may be some discussion as to whether treatment is necessary, remembering the term benign refers to the prognosis rather than the seizures themselves. Some families prefer to avoid treatment where possible. Some authors have reported associated verbal deficits on detailed testing at the time of the active epilepsy; whether treatment impacts on the occurrence of this is unknown.

10.11.2 Methods of the evidence review
Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with BECTS and BEOPs.

10.11.3 Matrix of the evidence
We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy in a population with benign partial epilepsies of childhood. The interventions we included in our search were lamotrigine, levetiracetam, topiramate, gabapentin, oxcarbazepine, sulthiame, sodium valproate and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Gabapentin</th>
<th>Oxcarbazepine</th>
<th>Sulthiame</th>
<th>Sodium valproate</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (287)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLA</td>
<td>CBZ</td>
<td>VPA</td>
<td>GBP</td>
<td>LEV</td>
<td>TPM</td>
<td>OXC</td>
<td>SL</td>
<td>LTG</td>
</tr>
</tbody>
</table>

PLA - Placebo
LTG - Lamotrigine
LEV - Levetiracetam
TPM - Topiramate
GBP - Gabapentin
10.11.3.1 Sulthiame monotherapy versus Placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Significantly more patients taking sulthiame monotherapy were seizure free compared to placebo. (HIGH QUALITY)

Efficacy – statistically non-significant results
No significant difference between sulthiame monotherapy and placebo for withdrawal due to adverse events. (HIGH QUALITY)

Adverse events – statistically non-significant results
No significant difference between sulthiame monotherapy and placebo for withdrawal due to lack of efficacy. (LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:
• at least 50% reduction in seizure frequency
• time to first seizure
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• cognitive outcomes
• quality of life outcomes

Cost-effectiveness
No economic evidence comparing sulthiame monotherapy to placebo was identified.

10.11.3.2 Levetiracetam monotherapy versus oxcarbazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search. Levetiracetam monotherapy and oxcarbazepine monotherapy were compared as part of the NCGC economic model evaluating different monotherapy AEDs used in the treatment of adults with newly diagnosed focal epilepsy.
For a description and results of the analysis, see section 10.2.6. No similar comparison was available for the economic model built to evaluate AEDs for children with newly diagnosed focal epilepsy.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for seizure freedom. (VERY LOW QUALITY)

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for the incidence of decreased appetite. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing levetiracetam monotherapy to oxcarbazepine monotherapy was identified in a population of patients with BECTS. In an adult population with newly diagnosed focal epilepsy oxcarbazepine monotherapy was less costly and more effective than levetiracetam monotherapy. This analysis has minor limitations and is partially applicable to this review.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes
10.11.3.3   Topiramate monotherapy versus carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search. Topiramate monotherapy and carbamazepine monotherapy were compared as part of the NCGC economic model evaluating different monotherapy AEDs used in the treatment of adults with newly diagnosed focal epilepsy. For a description and results of the analysis, see section 10.2.6. No similar comparison was available for the economic model built to evaluate AEDs for children with newly diagnosed focal epilepsy.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for seizure freedom (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants in the carbamazepine monotherapy group had an incidence of rash compared to participants in the topiramate monotherapy group. (LOW QUALITY)

Adverse events – statistically non-significant results

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for withdrawal due to adverse events (VERY LOW QUALITY).

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for the incidence of somnolence (VERY LOW QUALITY).

Cost-effectiveness

No studies comparing topiramate monotherapy to carbamazepine monotherapy were identified. In an adult population with newly diagnosed focal epilepsy carbamazepine monotherapy was less costly and more effective than topiramate monotherapy. This analysis has minor limitations and is partially applicable to this review.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- cognitive outcomes
- quality of life outcomes
10.11.4 Recommendations and link to evidence

First line treatment in children with BECTs and BEOP

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Discuss with the child and their family and/or carers whether AED treatment for BECTs or BEOP in the individual circumstance is indicated. [new 2011]</th>
</tr>
</thead>
</table>

Relative values of different outcomes

Seizure freedom and reduction in seizure frequency are important outcomes, but so too is the avoidance of adverse effects of drug treatment.

Trade off between clinical benefits and harms

We found evidence that sulthiame was more effective than placebo, however this drug is unlicensed in the UK. There were no differences in efficacy or tolerability between levetiracetam and oxcarbamazepine and carbamazepine compared to topiramate apart from carbamazepine (which had significantly higher rates of rash than topiramate). Due to the limited evidence (two studies unblinded and single blinded) the GDG decided to extrapolate the results for BECTS and BEOP from the focal seizures review because BECTS is an epilepsy characterised by focal seizures.

The balance between treating BECTs and the adverse effects of drug treatment should be evaluated in conjunction with family and/or carer to determine whether the child requires treatment. In some cases, seizures are so infrequent that the child and their family and/or carers may decide to forgo treatment in order to avoid the possible side.

Economic considerations

No economic evidence in this population was available, however, the decision as to whether treatment is indicated or not should be made very carefully as the possible cost and quality of life consequences could be substantial if a patient’s seizures are poorly controlled. If seizures were poorly controlled, the cost savings generated by opting against drug treatment could be quickly offset by hospital admissions, outpatient appointments and/or GP consultations.

Quality of evidence

The quality of evidence ranged from high to very low depending on outcome and there was no evidence comparing drug treatment to no treatment. This recommendation was based on GDG consensus opinion.

Other considerations

No other considerations.
Recommendation

Offer carbamazepine*, lamotrigine*, oxcarbazepine* or sodium valproate as first-line treatment to children with BECTS or BEOP when treatment is indicated. Offer levetiracetam* if first-line treatments are contraindicated. [new 2011]

Relative values of different outcomes

Seizure freedom and reduction in seizure frequency are important outcomes, as are the avoidance of adverse effects of drug treatment.

Trade off between clinical benefits and harms

We found evidence that sulthiame was more effective than placebo, however this drug is unlicensed in the UK. There were no differences in seizure freedom, withdrawal due to lack of efficacy, withdrawal due to adverse events or incidence of adverse events between levetiracetam and oxcarbazepine and carbamazepine compared to topiramate, apart from carbamazepine had significantly higher rates of rash than topiramate. Due to the limited evidence (two studies unblinded and single blinded) the GDG decided to extrapolate the results for BECTS and BEOP from the focal seizures review because BECTS is an epilepsy characterised by focal seizures. The extrapolated results from partial seizures found no drugs statistically significantly better than carbamazepine in the network meta-analysis for efficacy but sodium valproate was the most effective in the network meta-analysis simulations and the health economic evidence.

Lamotrigine has a better adverse events profile than carbamazepine. Lamotrigine requires slow titration to reduce risk of rash, which may make it unsuitable for individuals requiring rapid control. The network meta-analysis and the traditional meta-analysis found statistically significantly more participants on carbamazepine compared to lamotrigine withdrew due to adverse events and the traditional meta-analysis found carbamazepine to have a shorter time to withdrawal than lamotrigine. Oxcarbazepine has a similar adverse events profile to carbamazepine and lamotrigine.

Carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse events profile, with avoidance of high peak concentrations.

Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity.

In children, lamotrigine and carbamazepine have similar efficacy and adverse events profiles, with the exception of incidence of dizziness which is more prominent with carbamazepine.

The GDG suggested that children are likely to respond to the first AED they are given. Choice will be dependant on the

* Please see appendix K for licensing details.
adverse events profile for the individual AEDs.

Although both levetiracetam and carbamazepine-extended release had very similar findings in terms of efficacy, levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine-extended release which is why it was not recommended as the drug of first choice. However it may be useful for people where the first line AEDs are contraindicated.

GDG considered that levetiracetam has a lack of interaction with other drugs. However it was considered generally better to titrate levetiracetam slowly.

**Economic considerations**

Although no economic evidence on the relative cost-effectiveness of AEDs was available for this population specifically, the GDG considered the results of the economic modelling undertaken for the treatment of focal epilepsy to be applicable to this group of patients as well. As children with BECTS and BEOP are likely to respond to the first AED offered and are likely to experience spontaneous remission during adolescence, these drugs may be even more cost-effective in this group than in the general population of patients with focal epilepsy.

**Quality of evidence**

There was no evidence for BEOPS and little evidence available for BECTS. The studies that did exist for BECTs showed no significant differences except for sulthiame, which is not licensed in the UK. The quality of this evidence was mainly very low and there was a lack of blinding and allocation concealment. The sulthiame study was high quality.

As we extrapolated the results from partial seizures, the quality is relevant for these studies. The studies included in the evidence were of very low quality due to serious limitations in the study design, serious inconsistency and serious indirectness. There was a lack of either blinding or high dropout rates. In the SANAD trial, there was no allocation concealment and the randomisation was based on post clinician’s treatment decision.

**Other considerations**

The GDG considered that the condition will remit by the age of 14 years and therefore treatment is of short duration.

Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose.
10.11.5 Deleted recommendations from the 2004 Guideline (pharmacological management section)

10.11.5.1 The newer AEDs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin, within their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:

- there are contraindications to the drugs
- they could interact with other drugs the person is taking (notably oral contraceptives)
- they are already known to be poorly tolerated by the individual
- the person is a woman of childbearing potential.

10.11.5.2 The newer AEDs gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:

- there are contraindications to the drugs
- they could interact with other drugs the child is taking (notably oral contraceptives)
- they are already known to be poorly tolerated by the child
- the child is currently of childbearing potential or is likely to need treatment into her childbearing years.
10.12 Prolonged seizures and Convulsive Status Epilepticus

10.12.1 Introduction

Generalised seizures (TC, tonic, clonic)

In the past, Status Epilepticus (SE) was defined as a seizure lasting longer than 30 minutes or two or more seizures lasting longer than 30 minutes without returning to the baseline level of consciousness between seizures. More recently, the definition evolved to be a seizure longer than 5 minutes or two or more seizures without a return of consciousness between seizures. Serial seizures are defined as 3 or more convulsive seizures in an hour.

SE can be divided into a number of subtypes, either by seizure type or by response to treatment. Clinical SE can be either focal or generalised, and each of these types can be divided by duration:

- Early SE (5-30 minutes)
- Established SE (>30 minutes)
- Refractory SE (seizures persist despite treatment with adequate doses of two or three initial anticonvulsant medications).

The BNF states that: immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine should be considered if alcohol abuse is suspected; pyridoxine should be given if the status epilepticus is caused by pyridoxine deficiency.

Convulsive SE should be treated urgently with intravenous lorazepam, repeated once after 10 minutes if seizures recur. Intravenous diazepam is effective but it is associated with a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Clonazepam can also be used as an alternative.

Where facilities for resuscitation are not immediately available, diazepam can be administered as a rectal solution or midazolam (unlicensed use) can be given into the buccal cavity.

The BNF states that it is important that if seizures recur or fail to respond within 30 minutes, phenytoin sodium, fosphenytoin, or phenobarbital sodium should be used. If these measures fail to control seizure within 60 minutes, anaesthesia with thiopental, midazolam, or in adults, a non-barbiturate anaesthetic such as propofol (unlicensed indication), should be instituted with full intensive care support.

Phenytoin sodium may be given by slow intravenous injection, with ECG monitoring, followed by the maintenance dosage. Intramuscular use of phenytoin is not recommended (absorption is slow and erratic).

Alternatively, fosphenytoin, a pro-drug of phenytoin, can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin. Intravenous administration requires ECG monitoring. Although it can also be given intramuscularly, absorption is too slow by
this route for treatment of status epilepticus. Doses of fosphenytoin should be expressed in terms of phenytoin sodium.

Paraldehyde also remains a valuable drug. Given rectally it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

10.12.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people with prolonged seizures and convulsive status epilepticus.

10.12.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for people with Prolonged Seizures and Convulsive Status Epilepticus. The following interventions were included in our search: lorazepam, diazepam, midazolam, clonazepam, paraldehyde, phenytoin, fosphenytoin, phenobarbital, propofol, thiopental, isoflurane, sodium valproate, levetiracetam, phenobarbital and lidocaine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified separately for adults and children. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

10.12.3.1 Matrix of the evidence for the treatment of convulsive status epilepticus in adults (community)
### 10.12.3.2 Matrix of the evidence for the treatment of Convulsive Status Epilepticus in children (community)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Buccal/intranasal midazolam</td>
<td></td>
</tr>
<tr>
<td>Rectal/intravenous diazepam</td>
<td>1292-294</td>
</tr>
<tr>
<td>Pla</td>
<td>B IN MDM</td>
</tr>
</tbody>
</table>

### 10.12.3.3 Matrix of the evidence for the treatment of acute repetitive seizures (children and adults)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Diazepam gel</td>
<td>2*295,296</td>
</tr>
<tr>
<td>Pla</td>
<td></td>
</tr>
</tbody>
</table>

### 10.12.3.4 Matrix of the evidence for the treatment of Convulsive Status Epilepticus in adults (initial treatment in ER)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Intravenous lorazepam</td>
<td></td>
</tr>
<tr>
<td>Intravenous diazepam</td>
<td>1297</td>
</tr>
<tr>
<td>Intravenous diazepam and phenytoin</td>
<td>1298</td>
</tr>
<tr>
<td>Intravenous phenytoin</td>
<td>1298</td>
</tr>
<tr>
<td>Intravenous phenobarbitone</td>
<td>1298</td>
</tr>
<tr>
<td>Intravenous phenobarbitone and phenytoin</td>
<td>1299</td>
</tr>
<tr>
<td>Intravenous sodium valproate</td>
<td>2*300,301</td>
</tr>
<tr>
<td>Pla</td>
<td>IV LZP, IV DZP, IV DZP, PHT, IV PHT, IV PBT, PHT, IV VPA</td>
</tr>
</tbody>
</table>

* Included adults and children
### 10.12.3.5 Matrix of the evidence for the treatment of Convulsive Status Epilepticus in children (initial treatment in ER)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Buccal/intranasal midazolam</th>
<th>Rectal/intravenous diazepam</th>
<th>Intramuscular midazolam</th>
<th>Intravenous diazepam</th>
<th>Intranasal lorazepam</th>
<th>Intramuscular paraldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

### 10.12.3.6 Matrix of the evidence for the treatment of Refractory Status Epilepticus in children

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Intravenous diazepam</th>
<th>Intranasal lorazepam</th>
<th>Sodium valproate infusion</th>
<th>Midazolam infusion</th>
<th>Diazepam infusion</th>
<th>Rectal sodium valproate</th>
<th>Intravenous midazolam</th>
<th>Intravenous lidocaine</th>
<th>Intravenous propofol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Updated 2011
<table>
<thead>
<tr>
<th></th>
<th>Placebo (Pla)</th>
<th>Diazepam gel (DZP gel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Intravenous lorazepam (IV LZP)</td>
<td>Rectal Intravenous lorazepam ()</td>
</tr>
<tr>
<td>3</td>
<td>Intravenous diazepam (IV DZP)</td>
<td>Rectal Intravenous diazepam (R IV DZP)</td>
</tr>
<tr>
<td>4</td>
<td>Intravenous phenytoin (IV PHT)</td>
<td>Intravenous diazepam and phenytoin (IV DZP, PHT)</td>
</tr>
<tr>
<td>5</td>
<td>Intravenous phenobarbitone (IV PBT)</td>
<td>Intravenous phenobarbitone and phenytoin (IV PBT, PHT)</td>
</tr>
<tr>
<td>6</td>
<td>Intravenous sodium valproate (IV VPA)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Placebo (Pla)</td>
<td>Buccal Intranasal midazolam (B IN MDM) Rectal Intravenous diazepam (R IV DZP)</td>
</tr>
<tr>
<td>8</td>
<td>Intramuscular midazolam (IM MDM)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Intranasal lorazepam (IN LZP)</td>
<td>Rectal sodium valproate (R VPA) Intramuscular paraldehyde (IM PLH)</td>
</tr>
<tr>
<td>10</td>
<td>Intravenous diazepam (IV DZP) Intravenous propofol (IV PRF) Intravenous midazolam (IV MDM) Sodium</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Valproate infusion (VPA IF) Diazepam infusion (DZP IF) Midazolam infusion (MDM IF)</td>
<td></td>
</tr>
</tbody>
</table>
10.12.4 AEDs for the treatment of Prolonged Seizures and Convulsive Status Epilepticus in the community

10.12.4.1 AEDs for the treatment of Prolonged Seizures and Convulsive Status Epilepticus in adults in the community

10.12.4.1.1 Intravenous Diazepam versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically significant results
Significantly more patients receiving intravenous diazepam were seizure free compared to placebo. (HIGH QUALITY)
Efficacy – statistically non-significant results
No statistically significant difference between intravenous diazepam and placebo for the incidence of:
- hypotension, cardiac dysrhythmia or respiratory intervention (MODERATE QUALITY)
- the proportion of participants moved to the ICU (MODERATE QUALITY)

Adverse events – statistically significant results
Intravenous diazepam had a significantly lower incidence of death than placebo, however there is uncertainty of the magnitude of the effect. (MODERATE QUALITY)

Cost-effectiveness
No economic evidence comparing IV diazepam to placebo in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
- time to cessation of seizure.
10.12.4.1.2 Intravenous Lorazepam versus placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Significantly more patients receiving intravenous lorazepam were seizure free compared to placebo. (HIGH QUALITY)

Adverse events – statistically non-significant results
No statistically significant difference between intravenous lorazepam and placebo for:
- incidence of hypotension, cardiac dysrhythmia or respiratory intervention (LOW QUALITY)
- proportion of participants moved to the ICU (LOW QUALITY)
- death (LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV lorazepam to placebo in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
- time to cessation of seizure.

10.12.4.1.3 Rectal/intravenous Lorazepam versus rectal/intravenous Diazepam

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between intravenous lorazepam and intravenous diazepam in achieving seizure freedom. (MODERATE QUALITY)
**Adverse events – statistically non-significant results**

No statistically significant difference between intravenous lorazepam and intravenous diazepam for the incidence of the following events:

- proportion of participants moved to the ICU (LOW QUALITY)
- hypotension, cardiac dysrhythmia or respiratory intervention (LOW QUALITY)
- death (LOW QUALITY).

**Cost-effectiveness**

No economic evidence comparing lorazepam to diazepam in patients with convulsive status epilepticus was identified.

**Outcomes with no evidence**

There were no studies that reported:

- time to cessation of seizure.

### 10.12.4.2 Treatment of Prolonged Seizures and Convulsive Status Epilepticus in children (community)

Care must be taken to secure the individual’s airway and assess his or her respiratory and cardiac function. [2004]

Treatment should be administered by trained clinical personnel or, if specified by an individually agreed protocol drawn up with the specialist, by family members or carers with appropriate training. [2004]

### 10.12.4.2.1 Buccal & intranasal midazolam versus rectal/IV diazepam

**Clinical evidence**

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Health economic evidence**

No studies were identified in the economic literature search.

**Evidence statements**

**Efficacy – statistically significant results**

Significantly fewer children taking intranasal/buccal midazolam had experienced recurrence of seizures (within one hour) compared to intravenous/rectal diazepam. (MODERATE QUALITY)
Efficacy – statistically non-significant results

No significant difference between intranasal/buccal midazolam and intravenous/rectal diazepam for:

- the proportion of seizure-free participants within 10 minutes (VERY LOW QUALITY)
- the proportion of seizure-free participants within 5 minutes (MODERATE QUALITY)
- proportion of participants who experienced a seizure recurrence within 24 hours (LOW QUALITY)
- the time to cessation of seizures.

Cost-effectiveness

No economic evidence comparing buccal or intranasal midazolam to rectal or IV diazepam in children with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- incidence of adverse events.

10.12.5 Treatment of acute repetitive seizures (children and adults)

10.12.5.1 Diazepam gel versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non significant results

No significant difference was found between diazepam gel and placebo for the proportion of seizure free participants. (LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants receiving diazepam gel experienced somnolence than placebo. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing diazepam gel to placebo in patients with acute repetitive seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizures.
10.12.6 Treatment of convulsive status epilepticus in hospitals

10.12.6.1 Treatment of convulsive status epilepticus in adults in hospitals

10.12.6.1.1 Diazepam and phenytoin versus phenobarbitone

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No statistically significant difference between intravenous diazepam with phenytoin and phenobarbitone in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events - statistically non-significant results
No significant difference between intravenous diazepam with phenytoin and phenobarbitone for the incidence of:

• Hypoventilation (VERY LOW QUALITY)
• Hypotension (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV diazepam and phenytoin to IV phenobarbitone in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:

• time to cessation of seizures.

10.12.6.1.2 IV Diazepam and phenytoin versus IV phenobarbitone and optional phenytoin

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.
Evidence statements

Efficacy – statistically significant results
Significantly more participants in intravenous phenobarbitone and optional phenytoin were seizure free compared to intravenous diazepam and phenytoin, however there is uncertainty in the magnitude of the clinical effect. (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between intravenous diazepam with phenytoin and phenobarbitone and optional phenytoin for time to cessation of seizures.

Adverse events – statistically non-significant results
No significant difference between intravenous diazepam with phenytoin and intravenous phenobarbitone with optional phenytoin for the incidence of:

- hypotension (VERY LOW QUALITY)
- intubation (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV diazepam and phenytoin to IV phenobarbitone and optional phenytoin in patients with convulsive status epilepticus was identified.

10.12.6.1.3 IV Diazepam and phenytoin versus IV phenytoin

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No statistically significant difference between intravenous diazepam with phenytoin and phenytoin in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No statistically significant difference between intravenous diazepam with phenytoin and phenytoin for the incidence of:

- Hypoventilation (VERY LOW QUALITY)
- hypotension. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV diazepam and phenytoin to IV phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
1. time to cessation of seizures.

10.12.6.1.4 IV Lorazepam versus IV diazepam

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between intravenous lorazepam and intravenous diazepam for proportion of seizure free participants (after one dose and second dose). (LOW and VERY LOW QUALITY)
No significant difference between intravenous lorazepam and intravenous diazepam for time to cessation of seizures. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV lorazepam to IV diazepam in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:

• Incidence of adverse events.

10.12.6.1.5 IV Lorazepam versus IV diazepam plus phenytoin

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No statistically significant difference between intravenous lorazepam and intravenous diazepam and phenytoin in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No statistically significant difference between intravenous lorazepam and intravenous diazepam and phenytoin for the incidence of:

• Hypoventilation (VERY LOW QUALITY)
• Hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to IV diazepam and phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizures.

10.12.6.1.6 IV lorazepam versus IV phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy — statistically significant results

Significantly more participants in intravenous lorazepam experienced seizure freedom compared to intravenous phenytoin, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Adverse events — statistically non-significant results

No significant difference between intravenous lorazepam and intravenous phenytoin for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to IV phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizures.
10.12.6.1.7 IV phenytoin versus IV phenobarbitone

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between intravenous phenytoin and intravenous phenobarbitone for the proportion of participants achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between intravenous phenytoin and intravenous phenobarbitone for the incidence of:
- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV phenytoin to IV phenobarbitone in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
- time to cessation of seizures.

10.12.6.1.8 IV phenytoin versus IV sodium valproate

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between intravenous phenytoin and intravenous sodium valproate for the proportion of seizure free participants. (LOW QUALITY)

No significant difference between intravenous phenytoin and intravenous sodium valproate for the seizure recurrence (within 12 hours). (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between intravenous phenytoin and intravenous sodium valproate for the incidence of:

- cardiac side effects (VERY LOW QUALITY)
- respiratory side effects (VERY LOW QUALITY)
- liver dysfunction (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)
- death (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing IV phenytoin to IV sodium valproate in patients with convulsive status epilepticus was identified.

10.12.6.1.9 IV Phenytoin versus IV fosphenytoin

Clinical evidence

No studies were identified

Health economic evidence

Four cost-minimisation studies\(^309-312\) comparing intravenous phenytoin to intravenous fosphenytoin were identified in the economic literature search. All four were excluded from the health economic evidence review due to the fact that they had poor applicability and potentially serious methodological limitations. See economic evidence table in appendix M for details.

Despite the poor applicability and potentially serious limitations of these studies, they highlight important economic considerations. The studies assume that phenytoin and fosphenytoin are bioequivalent and have equivalent efficacy, therefore there should be no between-drug differences in terms of the proportion of patients achieving seizure control. Thus, differences in treatment related costs between the drugs are likely to be driven by the time spent in the emergency department and the management of drug-related adverse events. The studies assert that fosphenytoin can be administered more rapidly and that it has a lower incidence of adverse events than phenytoin. Consequently, cost differences based on these outcomes may favour fosphenytoin. However, without published evidence specifically comparing fosphenytoin with phenytoin in patients with convulsive status epilepticus, any extrapolation of the results conducted in other patient groups must be treated with caution.
1.10.12.6.2 Treatment of convulsive status epilepticus in children in hospitals

1.10.12.6.2.1 Intramuscular midazolam versus IV diazepam

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No significant difference between intramuscular midazolam and intravenous diazepam for the proportion of seizure free participants. (VERY LOW QUALITY)
No significant difference between intramuscular midazolam and intravenous diazepam for the recurrence of seizures. (VERY LOW QUALITY)
No significant difference between intramuscular midazolam and intravenous diazepam for the time to cessation of seizures. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing intramuscular midazolam to IV diazepam in patients with convulsive status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
• Incidence of adverse events.

1.10.12.6.2.2 Intranasal lorazepam versus intramuscular paraldehyde

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Significantly fewer participants in Intranasal lorazepam required two or more AEDs compared to participants in intramuscular paraldehyde group. (MODERATE QUALITY)

Efficacy – statistically non-significant results
No significant difference between intranasal lorazepam and intramuscular paraldehyde for the proportion of seizure free participants. (LOW QUALITY)
No significant difference between intranasal lorazepam and intramuscular paraldehyde for the seizure recurrence within 24 hours. (VERY LOW QUALITY)

No significant difference between intranasal lorazepam and intramuscular paraldehyde for the time to cessation of seizures.

**Adverse events – statistically significant results**

A higher proportion of participants taking intranasal lorazepam had a drop in diastolic blood pressure by at least 5mmHg, however there is uncertainty in the magnitude of this clinical effect. (LOW QUALITY)

**Adverse events – non-statistically significant results**

No statistically significant difference between intranasal lorazepam and intramuscular paraldehyde for the:

- incidence of death (VERY LOW QUALITY)
- drop in systolic blood pressure by at least 5mmHg (VERY LOW QUALITY).

**Cost-effectiveness**

No economic evidence comparing intranasal lorazepam to intramuscular paraldehyde in children with convulsive status epilepticus was identified.

**10.12.6.2.3 IV/rectal lorazepam versus IV/rectal diazepam and phenytoin**

**Clinical evidence**

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

**Health economic evidence**

No studies were identified in the economic literature search.

**Evidence statements**

**Efficacy – statistically non-significant results**

No significant difference between IV/rectal lorazepam and IV/rectal diazepam and phenytoin for the proportion of seizure free participants. (MODERATE QUALITY)

No difference between intranasal IV/rectal lorazepam and IV/rectal diazepam and phenytoin for the seizure recurrence within 18 hours. (VERY LOW QUALITY)

**Adverse events – non-statistically significant results**

No statistically significant difference between IV/rectal lorazepam and IV/rectal diazepam and phenytoin for the:

- incidence of respiratory depression (VERY LOW QUALITY)

**Cost-effectiveness**

No economic evidence comparing IV/rectal lorazepam and IV/rectal diazepam and phenytoin in children with convulsive status epilepticus was identified.
10.12.6.2.4 Buccal midazolam versus IV diazepam

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Time to cessation of seizures was significantly less in children receiving IV diazepam compared to children receiving buccal midazolam. (LOW QUALITY)

Efficacy – statistically non-significant results
No significant difference between buccal midazolam and IV diazepam for the proportion of seizure free participants. (MODERATE QUALITY)

Adverse events – non-statistically significant results
No difference between intranasal buccal midazolam and IV diazepam for the incidence of the following adverse events:

- Unusual CNS depression
- Respiratory depression
- Apnea
- Cardiac dyshrythmia.

Cost-effectiveness
No economic evidence comparing buccal midazolam and IV diazepam in children with convulsive status epilepticus was identified.

10.12.7 Treatment of refractory status epilepticus in children

Regular medication should be continued at optimal doses and the reasons for status epilepticus should be investigated. [2004]

As the treatment pathway progresses, the expertise of an anaesthetist/intensivist should be sought. [2004]

If either the whole protocol or intensive care is required the tertiary centre should be consulted. [2004]

An individual treatment pathway should be formulated for people who have recurrent convulsive status epilepticus. [2004]
10.12.7.1  IV Diazepam versus sodium valproate infusion

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results
Sodium valproate infusion had a significantly lower time to cessation of seizures than intravenous diazepam, however there is uncertainty over the magnitude of this clinical effect. (MODERATE QUALITY)

Efficacy – statistically non-significant results
No statistically significant difference between intravenous diazepam and sodium valproate infusion for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically significant results
Significantly more participants in the intravenous diazepam group experienced respiratory depression compared to the sodium valproate group, however there is uncertainty over the magnitude of this clinical effect. (VERY LOW QUALITY)

Significantly more participants in the intravenous diazepam group experienced hypotension compared to the sodium valproate group, however there is uncertainty over the magnitude of this clinical effect. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV diazepam to sodium valproate infusion in children with refractory status epilepticus was identified.

10.12.7.2  Midazolam infusion versus diazepam infusion

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
No statistically significant difference between midazolam infusion and diazepam infusion for:

• the proportion of seizure freedom (VERY LOW QUALITY)
• time to cessation of seizures (VERY LOW QUALITY)
Adverse events – statistically non-significant results

No significant difference between midazolam infusion and diazepam infusion for the incidence of:

- hypotension (VERY LOW QUALITY)
- the number of patients requiring intubation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing midazolam infusion to diazepam infusion in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizures.

10.12.7.3 Midazolam infusion versus IV lidocaine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between midazolam infusion and intravenous lidocaine for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between midazolam infusion and intravenous lidocaine for the incidence of:

- Hypothermia (VERY LOW QUALITY)
- Acidosis (VERY LOW QUALITY)
- Ventilation requirement (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing midazolam infusion to IV lidocaine in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizures.
10.12.7.4 IV Midazolam versus rectal sodium valproate

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between midazolam infusion and rectal sodium valproate for the proportion of seizure free participants. (VERY LOW QUALITY)
No significant difference between midazolam infusion and rectal sodium valproate for the time to cessation of seizures. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing IV midazolam to rectal sodium valproate in children with refractory status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
- Incidence of adverse events.

10.12.7.5 IV Midazolam versus IV propofol

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference between intravenous midazolam infusion and intravenous propofol for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results
No significant difference between intravenous midazolam infusion and intravenous propofol for the incidence of:
- Elevated serum creatine phosphokinase (VERY LOW QUALITY)
- Serum triglyceride cholesterol (VERY LOW QUALITY)
- Apnea (VERY LOW QUALITY)
Cost-effectiveness
No economic evidence comparing IV midazolam to IV propofol in children with refractory status epilepticus was identified.

Outcomes with no evidence
There were no studies that reported:
- time to cessation of seizures.

10.12.8 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Follow local or national protocols for treating status epilepticus in children [new 2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>Cessation of the seizure(s) is considered the most important outcome</td>
</tr>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>Following a locally adopted protocol will lead to prompt treatment and likely cessation of seizures.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic data were available to inform on cost effectiveness of relative treatments. However prompt treatment of a prolonged or cluster of seizures is more likely to lead to cessation and reduced need/shorter duration of hospitalisation.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The GDGs view was that it was important to state that health care professionals should have protocols in place, that they should be aware of these and that local or national protocols for treating status epilepticus should be followed, however no particular guidance produced by other organisations has been recommended, in line with NICE process.</td>
</tr>
</tbody>
</table>
Other considerations

None.

**First-line treatment for people with prolonged or repeated generalised, convulsive (tonic-clonic, tonic or clonic) seizures in the community**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Give immediate emergency care and treatment to adults and children who have prolonged (lasting 5 minutes or more) or repeated (three or more in an hour) convulsive seizures in the community. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**

Seizure freedom is the most important outcome. All evidence has used the criterion that a prolonged seizure is that continuing beyond 5 minutes.

**Trade off between clinical benefits and harms**

There is a risk of serious immediate and long term morbidity and mortality if convulsive seizure not terminated by 30 minutes and therefore treatment is required urgently.

**Economic considerations**

Urgent and appropriate care with consequent successful treatment delivered in the community is likely to reduce visits to A+E and subsequent hospitalisation. Early control of seizures may also reduce the mortality and morbidity risks associated with prolonged tonic-clonic seizures.

**Quality of evidence**

This recommendation was based on the consensus opinion of the GDG.

**Other considerations**

No further evidence has been published to overturn the recommendation from the previous edition of this guideline (2004). The GDG recognise that in some situations a personalised care plan may differ from the above.
Recommendation

Use buccal midazolam* as first-line treatment to adults and children with prolonged or repeated seizures. Use rectal diazepam if buccal midazolam* is not available. If intravenous access is already established and resuscitation facilities are available, offer intravenous lorazepam. [new 2011]

Relative values of different outcomes
Cessation of episodes (seizure freedom) was considered the most important outcome. Ease and acceptability of administration of buccal midazolam is also important.

Trade off between clinical benefits and harms
Buccal midazolam is more effective and more socially acceptable than rectal diazepam. The advantage of lorazepam over diazepam lies on the pharmacokinetics and its longer half life, however IV lorazepam is only appropriate in situations where IV access is established and resuscitation facilities are available.

   The risks of potential side effects of these drugs are outweighed by the need to stop seizures rapidly

Economic considerations
No economic evidence was available to inform the GDG on the relative cost-effectiveness of buccal midazolam, rectal diazepam and IV lorazepam. Acquisition costs of buccal midazolam are greater than rectal diazepam, but the clinical evidence shows it to be more effective in terms of controlling seizures and preventing recurrence of seizures. In addition to being more effective, buccal midazolam also has some process advantages in terms of its buccal over rectal administration. Buccal administration is a more preferable route of administration for both patients and carers and requires fewer additional rescue or emergency drugs to treat the initial episode. Delays to effective administration of treatment at this acute stage can have a very important impact on subsequent costs and outcomes for this group of patients.

Quality of evidence
In adults, the quality of evidence use was moderate as it was a double blinded study with good randomization and allocation concealment. This study included intravenous route of administration but was delivered by paramedics out of hospital. In children, three RCTs were included; two double blinded and one unblinded. There were different routes of drug administration between studies.

Other considerations
Buccal midazolam is at present unlicensed and use is off-label.

* Please see appendix K for licensing details.
**Recommendation**

Only prescribe rectal diazepam or buccal midazolam for adults and children who have had a previous episode of prolonged or repeated convulsive seizures. [new 2011]

**Relative values of different outcomes**

Seizure freedom, adverse effects and drug tolerance are the most important outcomes. It is important that patients requiring emergency medications have access to them, but it is also important that they not be overprescribed, particularly in groups unlikely to require them.

**Trade off between clinical benefits and harms**

Overuse of buccal midazolam-emergency benzodiazepines can lead to drug tolerance and incidence of adverse events, such as sedation and respiratory suppression. The GDG considered that over prescription of emergency benzodiazepines should not serve as a substitute for alleviation of parental anxiety.

**Economic considerations**

No economic evidence was available to inform the GDG on the relative cost-effectiveness of selective or general prescribing of emergency benzodiazepines. However, the GDG considered it important to direct clinicians to more appropriate and more selective prescribing of these emergency medications as they can be very costly and carry serious risks if administered incorrectly. Targeting their usage in the community to those patients with a known risk of prolonged or repeated convulsive seizures has the potential to save NHS resources both in terms of the medications themselves and in terms of avoiding hospitalisation due to inappropriate administration.

**Quality of evidence**

There was no clinical evidence. This recommendation was based on consensus opinion of the GDG.

**Other considerations**

There may be access and equality issues arising from the exclusion of children in need of emergency benzodiazepines from normal activities due to a lack of trained personnel.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Inform individuals and their families and/or carers that buccal midazolam* is currently unlicensed. [2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative values of different outcomes</strong></td>
<td>Cessation of episodes (seizure freedom) was considered the most important outcome. Ease and acceptability of administration of buccal midazolam is also important.</td>
</tr>
<tr>
<td><strong>Trade off between clinical benefits and harms</strong></td>
<td>Buccal midazolam is more effective and more socially acceptable than other AEDs (e.g. rectal diazepam).</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>No economic evidence was relevant to inform GDG on this recommendation.</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>There was no clinical evidence. This recommendation was based on consensus opinion of the GDG.</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>Buccal midazolam is at present unlicensed and use is off-label.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Depending on response to treatment, the person’s situation and any personalised care plan, call an ambulance, particularly if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- the seizures continue for 5 minutes without response to emergency medication</td>
<td></td>
</tr>
<tr>
<td>- there is a high risk of recurrence</td>
<td></td>
</tr>
<tr>
<td>- this is the first episode requiring emergency treatment</td>
<td></td>
</tr>
<tr>
<td>- there are concerns or difficulties monitoring the person’s condition [new 2011]</td>
<td></td>
</tr>
</tbody>
</table>

| **Relative values of different outcomes** | Rapid seizure freedom is the most important outcome. All evidence has used the criterion that a prolonged seizure is that continuing beyond 5 minutes. |
| **Trade off between clinical benefits and harms** | There is a risk of serious immediate and long term morbidity and mortality if convulsive seizure not terminated by 30 minutes. Therefore the aim should be for individual to reach hospital situation before this duration has passed. There can be an unknown risk of side effects on first time administration of emergency medication and a possibility that further seizures will require treatment with intravenous medication |
| **Economic considerations** | Prompt and effective treatment of prolonged and repeated seizures is likely to lead to less and shorter duration of hospitalisation. |
| **Quality of evidence** | There is no clinical evidence. This recommendation was based on the consensus opinion of the GDG. |

* Please see appendix K for licensing details.
Other considerations

This recommendation is a modification of one in the first edition of this guideline (2004), as the view of the GDG was that further clarification was required as part of the management of convulsive status epilepticus.

Recommendation

For adults and children with ongoing generalised tonic-clonic seizures (status epilepticus) who are in hospital, immediately:

- secure airway
- give high-concentration oxygen
- assess cardiac and respiratory function
- check blood glucose levels using a finger prick test
- secure intravenous access in a large vein. [new 2011]

Relative values of different outcomes

Status epilepticus should be regarded as a medical emergency and consequently basic resuscitation guidelines for initial treatment should be followed. Further, hypoglycaemia should be excluded as a cause of a generalised tonic clonic seizure.

Trade off between clinical benefits and harms

Basic resuscitative procedures should not delay the treatment targeted at cessation of the seizures.

Economic considerations

No economic data was available to inform on the relative cost effectiveness of emergency measures. However, basic resuscitative procedures recommended to reduce intensive care admission and longer term morbidity.

Quality of evidence

This recommendation was based on the consensus opinion of the GDG.

Other considerations

Modified recommendation from original guideline (GPP), as the view of the GDG was that further clarification was required as part of the management of convulsive status epilepticus. Local protocols should be followed where available.
**Recommendation**

Use intravenous lorazepam as a first-line treatment in hospital for adults and children with ongoing generalised tonic-clonic seizures (status epilepticus). Use buccal midazolam* if unable to secure immediate intravenous access. Use only a maximum of two doses of the first-line treatment (including pre-hospital treatment). [new 2011]

**Relative values of different outcomes**

Seizure freedom was considered the most important outcome.

**Trade off between clinical benefits and harms**

The benefits outweigh harms for the use of IV lorazepam. The advantage of lorazepam over other AEDs lies in its pharmacokinetics as it tends to work quickly and for a longer time (longer half life) and consequently patients need fewer additional rescue drugs.

**Economic considerations**

No economic evidence was available to inform the GDG on the relative cost-effectiveness of different emergency AEDs used to treat patients with status epilepticus once they have reached hospital. Lorazepam is an inexpensive drug (£0.35 per 4 mg dose) and the evidence showed it to be effective compared to a range of other drugs (diazepam, paraldehyde, phenytoin). Midazolam was shown to be effective in the community setting, and its greater effectiveness over diazepam almost reached statistical significance in the hospital setting. Its greater cost compared to lorazepam may be justified if more immediate access is required.

**Quality of evidence**

The evidence for this recommendation was retrieved from two double blinded RCTs of poor quality, without information on randomization and allocation concealment.

**Other considerations**

Due to the potential risk of respiratory compromise associated with the use of benzodiazepines, facilities for supporting respiratory depression or failure should be immediately available.

No further published evidence overturns the original recommendation.

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* Please see appendix K for licensing details.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>If seizures continue, use intravenous phenobarbital, phenytoin or sodium valproate as second-line treatment in hospital to adults and children with ongoing generalised tonic-clonic seizures (status epilepticus) [new 2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>Seizure freedom was considered to be the most important outcome.</td>
</tr>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>Phenytoin with benzodiazepines was equally effective as phenobarbital. Both emergency AEDs are equal in terms of adverse events. No difference was found in efficacy and the incidence of adverse events between sodium valproate and phenytoin.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic evidence was available to inform the GDG on the relative cost-effectiveness of different emergency AEDs used to treat patients with convulsive status epilepticus once they have reached hospital. The GDG considered that the unit cost of iv phenobarbital, phenytoin or sodium valproate was broadly similar and that each have similar efficacy profiles. Electrocardiographic (ECG) and blood pressure monitoring must accompany the intravenous administration of phenytoin.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The quality of evidence for this recommendation was moderate to poor; one study was double blinded study with no allocation concealment and three studies were unblinded with partial or no allocation concealment.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>None</td>
</tr>
</tbody>
</table>
## Refractory convulsive status epilepticus

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Follow local or national protocols for treating refractory status epilepticus in secondary care. [2011]</th>
</tr>
</thead>
</table>

### Relative values of different outcomes
- Cessation of the seizure(s) is considered the most important outcome.

### Trade off between clinical benefits and harms
- Following a locally adopted protocol will lead to prompt treatment and likely cessation of seizures.

### Economic considerations
- No economic data were available to inform on cost effectiveness of relative treatments. However, prompt treatment of a prolonged or cluster of seizures is more likely to lead to cessation and reduced need/shorter duration of hospitalisation.

### Other considerations
- The GDGs view was that it was important to state that health care professionals should have protocols in place, that they should be aware of these and that local or national protocols for treating status epilepticus should be followed, however no particular guidance produced by other organisations has been recommended, in line with NICE process.
**Recommendation**

**Use propofol* or thiopental* in adults with refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required. [2011]**

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>The GDG considered cessation of seizures and time to cessation of seizures as the most important outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>Use of thiopental requires adequate critical care support with continuous EEG monitoring to ensure seizure cessation. Continual review required of duration of treatment vs seizure cessation with propofol or thiopental.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic data was available to inform cost effectiveness of treatment. Shorter duration of status epilepticus likely to reduce long term intensive care admission and long term sequelae.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>No RCT evidence was found for adult refractory population. This recommendation was based on GDG expertise.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The GDG stated that no further published evidence overturns the original recommendation.</td>
</tr>
</tbody>
</table>

**Recommendation**

**Use midazolam or thiopental* in children with refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required. [2011]**

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>The GDG considered cessation of seizures and time to cessation of seizures as the most important outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>Use of thiopental requires adequate critical care support with continuous EEG monitoring to ensure seizure cessation. Continual review required of duration of treatment vs seizure cessation. Propofol not recommended for treatment of status epilepticus in children.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic data was available to inform cost effectiveness of treatment. Shorter duration of status epilepticus likely to reduce long term intensive care admission and long term sequelae.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The recommendation of midazolam was retrieved from 5 unblinded RCTs of poor quality. The recommendation of thiopental was based on GDG expertise and consensus, including British Paediatric Neurology Association prepared guidelines (appendix C).</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The GDG stated that no further published evidence overturns the original recommendation.</td>
</tr>
</tbody>
</table>

* Please see appendix K for licensing details.
10.12.9  Research recommendations (for full list see section 2.11)

10.12.9.1  Treatment of refractory status epilepticus

What is the most effective and safest anticonvulsant to treat refractory status epilepticus (RCSE)?

Why is this important

CSE that is refractory or resistant to first-line drug treatment is rare and often complicated by irreversible neurological and intellectual sequelae, including death. Reasons for these complications include the underlying cause of RCSE and its duration but also its management. The majority, if not all patients with refractory CSE (RCSE) will be managed on an intensive care unit (ICU). There are no agreed drugs or treatment protocols for treating refractory CSE. The three most commonly-used anticonvulsants are thiopentone, midazolam and propofol (although this latter drug is rarely used in children). There are very limited and all anecdotal data on the treatment and outcome of RCSE in adults and children. A two-year audit of all children with RCSE treated on a paediatric intensive care unit in England, Wales and Scotland has recently been completed. This will provide unique epidemiological data on paediatric RCSE and its current management. These data will facilitate the design of an RCT of specific drug treatments and protocols.

Research should include:

- A multi-centre, randomised comparative trial on intensive care units – this could involve adult and paediatric care units (it will not be able to be a blinded study, and randomisation may have to exclude propofol for children).
- Primary outcome should be cessation of the RCSE.
- Secondary outcomes will include a recurrence with a designated period (12 hours), mortality and morbidity.
- Cost data will include treatment costs and days on intensive care.
10.13  Deleted recommendations from the 2004 guideline

10.13.1  An individual who has prolonged convulsive seizures (lasting 5 minutes or more) or serial seizures (three or more seizures in an hour) in the community should receive urgent care and treatment.

10.13.2  Rectal diazepam is safe and effective in first-line treatment of prolonged seizures and is recommended in the majority of cases.

10.13.3  For many individuals and in many circumstances, buccal midazolam* is more acceptable than rectal diazepam and is easier to administer. It should be used according to an agreed protocol drawn up by the specialist and only used following training.

10.13.4  Depending on response and the individual’s situation, emergency services should be contacted, particularly if:

- seizures develop into status epilepticus
- there is a high risk of recurrence
- this is the first episode
- there may be difficulties monitoring the individual’s condition.

10.13.5  In hospital, individuals with generalised tonic–clonic status epilepticus should be managed immediately, as follows (with local protocols being in place – see suggested guideline in Appendix Ca of the full guideline):

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure intravenous (IV) access in a large vein.

10.13.6  Lorazepam should be used as a first-line treatment in status epilepticus (see Appendix C of the full guideline).
10.14 Non-convulsive status epilepticus

Non-convulsive status epilepticus is uncommon and management is less urgent. [2004]

10.14.1 Introduction

Nonconvulsive status epilepticus is an underdiagnosed syndrome whereby clinically subtle or unapparent seizures result in a depressed level of consciousness. Nonconvulsive status epilepticus is divided into two main subgroups: generalised nonconvulsive status and complex partial status.

Subtle generalised convulsive status was defined in the study conducted by Treiman et al as the stage of generalised convulsive status when the patient is in continuous coma but only subtle motor convulsions are seen. Tomson et al defined nonconvulsive status epilepticus as a state of impaired consciousness or responsiveness without convulsions lasting at least 60 minutes.

For this clinical question, we additionally searched for any observational studies as it was initially thought that no randomised evidence on nonconvulsive status epilepticus was available.

The BNF states that: the urgency to treat non-convulsive status epilepticus depends upon the severity of the patient’s condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

10.14.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

No RCTs (blinded or unblinded) were found for this evidence review so observational studies were included as a study design providing lower quality of evidence.

For this review we included adults and children with non-convulsive status epilepticus. The only outcome measures included in this review were: the proportion of participants whose seizure was stopped (seizure free), duration of time to cessation of seizure, and incidence of adverse events.

10.14.3 AEDs for the treatment of nonconvulsive Status Epilepticus

(observational study)

10.14.3.1 IV Diazepam versus IV Clonazepam

Clinical evidence

Thirty two patients with nonconvulsive status epilepticus were diagnosed at the department of Neurology at the Soder Hospital in Sweden, as part of a prospective study carried out by
Tomson et al1. Nonconvulsive status epilepticus was defined as a state of impaired consciousness or responsiveness without convulsions lasting at least 60 minutes. An ictal EEG showing continuous or almost continuous seizure activity was required for inclusion. The median age at onset was 51 years. Ten patients had status as their first epileptic manifestation, but most patients had a previous history of epilepsy. The median duration of epilepsy at onset of status was 4 years.

Three patients recovered spontaneously from status during EEG recording. Twenty-five patients were treated with IV diazepam (5-10mg), 3 patients were treated with Clonazepam (1mg), and 1 with both. The effect on EEG and clinical state was immediate and lasting in 10 patients and immediate but followed by recurrence of the status within hours in 18 patients. In 1, no immediate effect was evidence. In 8 patients, as lasting effect was not achieved until IV phenytoin (250-500mg) was added.

**Health economic evidence**

No studies were identified in the economic literature search.

**10.14.4 Recommendations and link to evidence**

No new recommendations were developed

**10.14.5 Generic prescribing**

This was not a key clinical question, and therefore no evidence review was undertaken. This is an important issue in the prescribing of AEDs, and prescriber is advised to consult the BNF for specific advice for different AEDS. For example, for carbamazepine, the BNF states that ‘different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation’; for phenytoin, that ‘on the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients’.
10.15 How many times should monotherapy be tried before combination therapy is considered?

It is recommended that individuals should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period. [2004]

It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the individual, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. [2004]

If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slow. [2004]

If the second drug is unhelpful, either the first or second drug may be tapered, depending on relative efficacy, side effects and how well the drugs are tolerated before starting another drug. [2004]

Evidence statements

There is no evidence to show whether alternative substitution or add-on therapy is more effective as a treatment strategy. (III)

Evidence for combination therapy with the newer antiepileptic drugs showed that a significant proportion of adults and children who do not achieve seizure freedom on monotherapy could derive worthwhile benefit from combination therapy. Expert opinion suggested that before combination therapy is considered, adults and children should be given a trial of all appropriate monotherapy regimens, and that caution is needed during changeover periods between drugs. (Ia NICE)

Details

No systematic reviews of RCTs were identified. One RCT was identified that compared alternative monotherapy with combination therapy in individuals with recently diagnosed epilepsy.315 However, participants may have tried several monotherapy regimes before inclusion, so this RCT was excluded. No other RCTs were identified.

Other evidence

Kwan 2000316

A prospective study evaluated the effectiveness of substitution therapy and add-on therapy after treatment with a first AED failed in individual with newly diagnosed epilepsy. Individuals were assessed as seizure free if they had no seizures for one year.
248 individuals, both adults and children, were included in the study cohort. Of all individuals with inadequate seizure control on the first tolerated AED, 42 received add-on therapy and 35 received substitution. There were no significant differences in seizure freedom (add-on 26%, substitution 17%) and incidence of adverse events leading to withdrawal (add-on 12%, substitution 26%) between the two groups (p=0.25).

Deickers 2003

At the 5th European Congress on Epileptology, the topic of substitution of alternative monotherapy of add-on therapy in adults was discussed. A literature review prepared for the discussion group was prepared. Nine papers were reviewed; four evaluating alternative monotherapy and five add-on therapy. However, it was not always clear whether the substitution drug or the add-on drug was the second AED tried in individuals.

The author concluded that ‘based on published data, there is no conclusive evidence in favour of either alternative monotherapy or second-line polytherapy’. The suggested practice was to try add-on therapy before an alternative monotherapy, and withdraw the first drug if the combination is successful.
10.15.1 When should AED treatment in adults and children be started?

Treatment with AED therapy is generally recommended after a second epileptic seizure. [2004]

The decision to initiate AED therapy should be taken between the individual, their family and/or carers (if appropriate) and the specialist after a full discussion of the risks and benefits of treatment. This discussion should take into account details of the individual’s epilepsy syndrome, prognosis and lifestyle. [2004]

AED therapy should be considered and discussed with individuals and their family and/or carers as appropriate after a first unprovoked seizure if:

- the individual has a neurological deficit
- the EEG shows unequivocal epileptic activity
- the individual and/or their family and/or carers consider the risk of having a further seizure unacceptable
- brain imaging shows a structural abnormality. [2004]

It should be recognised that some individuals (through their families and/or carers, in some instances) may choose not to take AED therapy following a full discussion of the risks and benefits. [2004]

Evidence statements

In adults and children who present with a first unprovoked seizure the risk of recurrence varies widely. (IIb)

Factors which are associated with an increased risk of recurrence include:

- presence of neurological abnormalities
- epileptiform abnormalities on EEG
- seizure type and/or epilepsy syndrome. (IIb)

Treatment of a first unprovoked seizure reduces the risk of recurrence in the short-term. (Ia children, Ib adults)

In children, treatment of a first unprovoked seizure does not alter the long-term prognosis for seizure remission. (Ia)
In adults and children who present with a single seizure what are the features (from history and investigations) which predict risk of further seizures?

Secondary evidence

Berg 1991

A systematic review of the risk of seizure recurrence following a first unprovoked seizure was undertaken by Berg & Shinnar in 1991. Their literature review reviewed all relevant studies up to 1990. The authors conducted a meta-analysis of 16 studies and found that three methodological factors explained much of the reported variation:

- study inclusion criteria (whether participants were enrolled at the time of their first seizure or if those with prior seizures were included);
- retrospective versus prospective ascertainment of participants;
- the interval between the first seizure and time at which risk was assessed.

Overall risk of recurrence

From the 16 studies reviewed the overall pooled estimate of risk of recurrence was 51% (95% CI 49% to 53%). To allow for comparable results the risk of recurrence at two years was calculated. The risk was 36% (95% CI 32% to 39%) in the prospective first seizure studies reviewed and 43% (95% CI 40% to 47%) in the retrospective first seizure studies reviewed.

Factors predictive of risk of recurrence

Aetiology (Neurological abnormality) - All reviewed studies found increases in risk of recurrence associated with abnormal neurological status (congenital and acquired neurological deficits) with a pooled relative risk of 1.8 (95% CI 1.5 to 2.1).

EEG - Children (3 studies reviewed) with epileptiform abnormalities on EEG are more likely to have a recurrence than children with normal EEGs (pooled RR 2.0, 95% CI 1.6 to 2.6).

Aetiology and EEG - Three studies provided information about risk of recurrence as a function of aetiology and EEG together. The risk was lowest in the cryptogenic group who had normal EEGs (24%, 95% CI 19% to 29%) and highest in the group with abnormal neurological status and an abnormal EEG (65%, 95% CI 55% to 76%).

Hirtz 2003

This practice parameter of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society systematically reviewed the published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations (see below). The authors reviewed the evidence base up to 2001.

How likely is a second seizure?

The probability of having a second seizure had been explored in several large, cohort studies with long-term follow-up. The cumulative risk of recurrence increased over time; however, in studies where the information was available, the majority of the recurrences occurred early (within
the first 1 to 2 years). At any given time, the reported risk of recurrence was highly variable. For example, at 1 year, it ranged from a low of 14% to a high of 65%. In all these cohort studies there was variability in the mix of participants and the distributions of important prognostic factors. Treatment was also not randomised. Some methodological differences in seizure identification, age ranges included, recruitment, and follow-up of study participants may have contributed to this variability.\cite{318}

Are there factors that increase the risk of recurrence?

The authors cited the findings of the Berg & Shinnar review\cite{98} that the underlying aetiology and whether the EEG is normal or abnormal were consistently related to the risk of recurrence.\cite{318}

Primary evidence

Hart 1990\cite{319}

This large-scale prospective community-based study (National General Practice Study of Epilepsy) aimed to determine the risk of recurrence after a first seizure. 564 individuals classified as having definite seizures were followed up for 2 to 4 years. 67% (95% CI 63% to 71%) had a recurrence within 12 months of the first seizure, and 78% (95% CI 74% to 81%) had a recurrence within 36 months. Seizures associated with a neurological deficit presumed present at birth had a high rate of recurrence (100% by 12 months), whereas seizures that occurred within 3 months of an acute insult to the brain, such as head injury or stroke, or in the context of an acute precipitant such as alcohol, carried a much lower risk of recurrence (40%, 95% CI 29% to 51%, by 12 months). Other factors affecting the risk of recurrence were:

- age;
  the highest risk being for those under the age of 16 (83%, 95% CI 77% to 89%, by 36 months) or over the age of 59 (83%, 95% CI 76% to 90%, by 36 months).

- type of first seizure;
  the risk of recurrence being much higher for those with simple partial or complex partial seizures (94%, 95% CI 90% to 99%, by 36 months) than for those with generalised tonic clonic seizures (72%, 95% CI 67% to 77%, by 36 months).

Macdonald 2000\cite{11}

This large-scale prospective community-based study (National General Practice Study of Epilepsy) aimed to identify the factors, at the time of diagnosis, that determine the prognosis for remission of epilepsy. A prospective community-based cohort study of 792 individuals recruited at the time of first diagnosis of epileptic seizures was undertaken; in those classified 6 months after presentation, the median follow-up period was 7.2 years (quartiles at 6.2 and 8.2 years) after presentation. Data were analysed from 6 months after the first identified seizure, which prompted the diagnosis of epilepsy, to allow aspects contingent on a diagnostic assessment to be factored in. Baseline clinical and demographic data were analysed using the Cox proportional hazards regression model with remission of epilepsy for 1, 2, 3, and 5 years as outcome measures. The dominant clinical feature predicting remission was the number of seizures in the 6-month diagnostic assessment period. Thus, the chance of entering one year of remission by 6 years for an individual who had 2 seizures during this initial 6 months was 95%; for 5 years of remission, it was 47% as opposed to 75% for 1 year of remission and 24% for 5 years of remission.
remission if there had been 10 or more seizures during this period. The authors concluded that
the number of seizures in the early phase of epilepsy (here, taken as the first 6 months after
presentation) is the single most important predictive factor for both early and long-term remission
of seizures.\textsuperscript{11}

\section{In adults and children who present with a single seizure, does treatment with
antiepileptic medication reduce the risk of further seizures?}

\textbf{Secondary evidence}

\textit{Berg 1991\textsuperscript{98}}

A systematic review of the risk of seizure recurrence following a first unprovoked seizure was
undertaken by Berg & Shinnar in 1991. Their literature review reviewed all relevant studies up
to 1990. The authors identified one RCT\textsuperscript{320} in which treatment of a first seizure was associated
with a significant reduction in risk of recurrence.

\textit{Hirtz 2003\textsuperscript{318}}

This practice parameter of the Quality Standards Subcommittee of the American Academy of
Neurology and the Practice Committee of the Child Neurology Society systematically reviewed the
published literature relevant to the decision to begin treatment after a child or adolescent
experiences a first unprovoked seizure and presents evidence-based practice recommendations
(see below). The authors reviewed the evidence base up to 2001.

\textit{How effective is treatment after a first seizure in prevention of recurrences?}

There were four randomised clinical trials including children and adolescents that examined the
efficacy of treatment after a first seizure. Only one of these studies consisted solely of children
randomised to treatment versus no treatment after a first nonfebrile seizure.\textsuperscript{320} In this study with
a total of 31 children, 2 of 14 children (14\%) treated with carbamazepine (CBZ) experienced a
recurrence compared with 9 of 17 (53\%) who were not treated. Follow-up was for 1 year, and
compliance was monitored. Although the recurrence rate up to 1 year was significantly lower in
the treated group, only 6 of 14 (43\%) children randomised to CBZ completed the year with no
significant side effects or seizure recurrence and 7 of 17 (41\%) assigned to no medication had no
seizure recurrence.\textsuperscript{320}

In studies involving both children and adults, outcome was not provided based on age. One
study\textsuperscript{321} in which 228 subjects were randomised to valproic acid (VPA) or placebo included 33
adolescents between the ages of 16 and 19. The follow-up period for this trial was between 9
months and 5 years. Five (4\%) of the treated group experienced a recurrence compared with 63
(56\%) of those treated with placebo.\textsuperscript{321}

However, these results were not found in another randomised study\textsuperscript{322} (n=419), in which 114
subjects were between 2 and 16 years old. Twenty-four percent of those treated after a first
seizure and 42\% untreated individuals had a recurrence by 1 year, but no difference by initial
treatment assignment was seen after 2 years; 32\% of those treated and 40\% of those untreated
had a recurrence by 2 years.
The findings of other published studies in children were not reported as although the cohorts were prospectively followed, treatment was not randomly assigned and therefore baseline factors affecting risk of recurrence were not comparable.

Does treatment with AED after a first seizure change the long-term prognosis for seizure remission?

Although treatment after a first unprovoked seizure may reduce the risk of a second seizure, does treatment at this time make any difference in the long-term prognosis for seizure control? This question was addressed in two randomised, prospective, but not placebo-controlled first seizure studies.

One study had 419 subjects, of whom 114 were between 2 and 16 years of age. This study compared the probability of experiencing a remission, that is, 1 or 2 seizure-free years, in those treated after a first seizure versus in people treated after a second seizure. Follow-up was for at least 3 years or a minimum of 2 years seizure-free. Individuals treated after the first seizure and those treated after a second seizure had the same probability of achieving a 1- or 2-year seizure remission (68%, n=215 versus 60%, n=204) (relative risk 1.04, 95% CI 0.82 to 1.30).

Another smaller study of 31 children randomised to CBZ (n=14) or no treatment (n=17) found similar results. After a 15-year follow-up, the rate of 2-year terminal remission was the same in both the treated and the untreated groups (relative risk 0.79, 95% CI 0.3 to 2.1).

Primary evidence (adults & children)

No studies were identified since the Hirtz review.

10.15.2 Who should start AED treatment in adults and children?

AED therapy should be initiated in adults on the recommendation of a specialist.

AED therapy in children should be initiated by a specialist.

AED therapy should only be started once the diagnosis of epilepsy is confirmed, except in exceptional circumstances that require discussion and agreement between the prescriber, the specialist and the individual and their family and/or carers as appropriate.

Evidence statement

No evidence was identified.
Details

No evidence that specifically addressed the question as to ‘Who should initiate treatment?’ was found. The evidence on rates and consequences of misdiagnosis reviewed in section 7 was considered by the GDG and formed the basis for the GPPs above.

10.15.3 In adults and children with epilepsy on AEDs does management of continuing drug therapy by a generalist as opposed to a specialist lead to different clinical outcomes?

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing AED therapy should be planned by the specialist. It should be part of the individual’s agreed treatment plan, which should include details of how specific drug choices were made, drug dosage, possible side effects, and action to take if seizures persist. [2004]</td>
</tr>
<tr>
<td>If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. [2004]</td>
</tr>
<tr>
<td>The needs of the individual and their family and/or carers as appropriate should be taken into account when healthcare professionals take on the responsibility of continuing prescribing. [2004]</td>
</tr>
<tr>
<td>The prescriber must ensure that the individual and their family and/or carers as appropriate are fully informed about treatment including action to be taken after a missed dose or after a gastrointestinal upset. [2004]</td>
</tr>
</tbody>
</table>

A key issue here is the general issue of who should prescribe medication when the AED may be unlicensed for a particular clinical indication.

Evidence statement

No evidence was identified on who should continue to prescribe AED treatment.

Details

No systematic reviews or RCTs were identified.

Consensus statements

No consensus statements from professional bodies were identified that described which healthcare professional should prescribe continuing AED treatment.
10.15.4 What is the role of monitoring in adults and children with epilepsy?

Regular blood test monitoring in adults is not recommended as routine, and should be done only if clinically indicated. [2004]

Regular blood test monitoring in children is not recommended as routine, and should be done only if clinically indicated and recommended by the specialist. [2004]

Indications for monitoring of AED blood levels are:

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- management of pharmacokinetic interactions
- specific clinical conditions; for example, status epilepticus, organ failure, and pregnancy. [2004]

Examples of blood tests include:

- before surgery – clotting studies in those on valproate
- full blood count, electrolytes, liver enzymes, vitamin D levels, and other tests of bone metabolism (for example, serum calcium and alkaline phosphatase) every 2–5 years for adults taking enzyme-inducing drugs. (adults only) [2004]

Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication. [2004]

Annual review should include an enquiry about side effects and a discussion of the treatment plan to ensure concordance and adherence to medication. [2004]

Treatment should be reviewed at regular intervals to ensure that individuals with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained. [2004]

Evidence statements

Routine monitoring of AED blood levels does not lead to improved seizure control for people with epilepsy. (Ib)

There is no good quality evidence that shows routine monitoring of side effects leads to better health outcomes for individuals. (IV)

There is no evidence that shows routine monitoring of drug usage leads to better health outcomes for individuals. (IV)
In adults/children with epilepsy, does ‘routine’ monitoring of AED blood levels lead to better outcomes (e.g. seizure recurrence, side effects) when compared with those who receive no monitoring or monitoring only when clinically indicated?

**Details**

- AED blood levels
- side effects
- drug usage

Secondary evidence

**AHRQ 2001**

This systematic review on the management of people with newly diagnosed epilepsy reviewed 24 prospective interventional studies that had a monitoring component. None of these studies had as a primary objective the testing of monitoring interventions necessary for optimal care but in nearly all, this was a monitoring intervention dictated by a research study protocol and not optimal care. Therefore, the review was excluded.

**Swedish Council on Technology Assessment in Healthcare 1998**

This assessment of therapeutic drug monitoring in the treatment of epilepsy identified one prospective randomised study. 127 people with epilepsy were randomised either to treatment with or without the support of therapeutic drug monitoring. Samples were taken from both groups, but results for those in the treatment group only were presented to the attending physician. 105 individuals were followed up after 12 months. No differences were found in seizure control. However, a large percentage of all participants (equally large in both groups) showed drug levels outside of the target area.

On the basis of the study above and one other retrospective study, the technology assessment report concluded that there was poor evidence to demonstrate the benefits of therapeutic drug monitoring.

Primary evidence

**Jannuzzi 2000**

This RCT assessed the clinical impact of monitoring serum concentrations of antiepileptic drugs (AEDs) in individuals with newly diagnosed epilepsy. 180 people with partial or idiopathic generalized non-absence epilepsy, aged 6 to 65 years, requiring initiation of treatment with carbamazepine (CBZ), valproate (VPA), phenytoin (PHY), phenobarbital (PB), or primidone (PRM)
were randomly allocated to two groups according to an open, prospective parallel-group design. In one group, dosage was adjusted to achieve serum AED concentration within a target range, whereas in the other group, dosage was adjusted on clinical grounds. Individuals were followed up for 24 months or until a change in therapeutic strategy was clinically indicated.

Baseline characteristics did not differ between the two groups. A total of 116 people completed 2-year follow-up, and there were no differences in exit rate from any cause between the monitored group and the control group. The proportion of assessable participants with mean serum drug levels outside the target range (mostly below range) during the first 6 months of the study was 8% in the monitored group compared with 25% in the control group (p<0.01). There were no significant differences between the monitored group and the control group with respect to individuals achieving 12-month remission (60% vs. 61%), individuals remaining seizure free since initiation of treatment (38% vs. 41%), and time to first seizure or 12-month remission. Frequency of adverse effects was almost identical in the two groups. With the AEDs most commonly used in this study, early implementation of serum AED level monitoring did not improve overall therapeutic outcome, and the majority of people could be satisfactorily treated by adjusting dose on clinical grounds.

To evaluate whether knowledge of plasma levels of antiepileptic drugs has an effect on therapeutic outcome, 127 people with epilepsy were randomly assigned to two groups (A and B). Plasma levels of group A were reported to the treating physician who attempted to keep the plasma levels within the ‘therapeutic range’. The treating physician was not informed of the results of plasma level determinations of group B. Data from 105 participants were available for assessment at the end of the study year.

Seizure control improved to a similar degree in both groups. Therapeutic results of groups A and B were not significantly different. The reduction in seizure frequency was associated with an increase in plasma concentrations of the antiepileptic drugs. The proportion of individuals with serum AED levels outside the optimal range did not change substantially. The authors suggested that the physicians did not use the information correctly. They therefore concluded that, under the conditions of the study, knowledge of plasma levels of antiepileptic drugs did not improve therapeutic results.

10.15.4.2 In adults and children with epilepsy, does ‘routine’ monitoring of side effects lead to better clinical outcomes when compared with those who receive no monitoring or monitoring only when clinically indicated?

Secondary evidence

A search for published papers on carbamazepine and valproate monotherapy (1991–1995) identified 7 relevant papers. Details of the frequency of adverse events associated with carbamazepine or valproate monotherapy were also extracted from a clinic database. The methods of detection for different adverse events were compared across the included trials and the database information. Methods included self-reporting, physical examination, laboratory investigations, adverse event checklists, specific toxicity scales, and neuropsychological testing.
For certain adverse events (diplopia, dysarthria, affect and mood disturbances, headache, dizziness, GI disturbances, dermatological disturbances, and idiosyncratic reactions) there was no difference in how the adverse events were detected. But sedation, cognitive impairments, sexual dysfunction, hair changes, nystagmus, gait disturbances, tremor, and weight change were reported more frequently when routinely checked.

This review did not link the detection of side effects with clinical outcomes. However, it is obvious that if an individual is experiencing adverse events their quality of life may be affected, and that particularly for serious adverse events such as toxicity, monitoring may be useful.

Primary evidence

No RCTs were identified.

Position statements

In 1993, the ILAE Commission on Antiepileptic Drugs published guidelines for therapeutic monitoring of AEDs. They highlighted three areas of concern:

a) The lack of strict correlation between efficacy and/or toxicity of AEDs and their blood levels for individuals.

b) Blood levels judged on an individual sampling may be misleading where there exists wide diurnal variation.

c) Accuracy of measurements must be considered.

In conclusion, the Commission recommended that

- Indiscriminate use of blood level determinations is not recommended.
- The use of blood levels to adjust dosage so that levels fall within the defined ‘therapeutic range’ is a waste of time and money, and may even be dangerous.
- A target range is better developed for each individual based on the severity of the epilepsy and tolerance of side effects.

A list of situations where blood levels may be useful was presented. This included routine determinations for all individuals based on theoretical grounds only, tailored determinations with specific purposes (for example, when an individual complains of toxic signs that may be dose related, or in specific physiologic states such as pregnancy), and those where blood levels should never be used.
10.15.4.3 In adults and children with epilepsy, does ‘routine’ monitoring of drug usage lead to better clinical outcomes when compared with those who receive no monitoring or monitoring only when clinically indicated?

No systematic reviews or RCTs were identified. The ILAE Statement (see above) on monitoring was considered when making recommendations in this area.

10.15.5 What influences AED treatment concordance in adults and children?

Adherence to treatment can be optimised with the following:

- educating individuals and their families and/or carers in understanding of their condition and the rationale of treatment
- reducing the stigma associated with the condition (see also Section on coping with epilepsy)
- using simple medication regimens
- positive relationships between healthcare professionals, the individual with epilepsy, and their family and/or carers. [2004]

Healthcare professionals have a responsibility to educate others about epilepsy so as to reduce the stigma associated with it. They should provide information about epilepsy to all people who come into contact with people with epilepsy, including school staff, social care professionals and others. [2004]

Evidence statements

Adherence to treatment is associated with many factors. (III)

No evidence on factors associated with other aspects of concordance was identified. (III)

Details

Methodological issues

Concordance refers to a consultation process between a healthcare professional and an individual. Compliance or adherence refers to a specific behaviour: was the medicine taken in accordance with the wishes of the healthcare professional? Compliance is a problematic term. Medical studies of ‘compliance’ with doctors’ instructions have often used an image of the ‘patient’ as a passive, obedient and unquestioning recipient of medical instructions. Divergence from this image, ‘defaulting’, has, in the past, often been seen as irrational from the purely medical perspective and the blame for ‘default’ is put upon the individual.

It is important to note that much of the published literature on AED treatment adherence uses the term ‘compliance’ and attempts to determine individual variables that may be associated with ‘high’ or ‘low’ levels of compliance. In this guideline, the term compliance is not endorsed and the term adherence is preferred.
The systematic review considered includes lower level evidence than RCT or cohort studies; hence the grading of the evidence statements and recommendations.

Secondary evidence

One systematic review of concordance in people with epilepsy was identified.\textsuperscript{331}

The authors reviewed the research evidence and identified the following factors associated with adherence to medication:

Table 10-28: Factors affecting adherence to medication regimens in people with epilepsy\textsuperscript{331}

<table>
<thead>
<tr>
<th>Factors related to good adherence</th>
<th>Factors related to poor adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged over 60 years</td>
<td>Aged under 60 years</td>
</tr>
<tr>
<td>Aged over 19 years</td>
<td>Teenager (aged under 19 years)</td>
</tr>
<tr>
<td>Once-daily dose</td>
<td>Four-times daily dose</td>
</tr>
<tr>
<td>Feeling that it is important to take medication as prescribed</td>
<td>Feeling stigmatised</td>
</tr>
<tr>
<td>Finding the GP easy to talk to</td>
<td>Experience of side effects</td>
</tr>
<tr>
<td>Concerned about health or health risks</td>
<td></td>
</tr>
<tr>
<td>Absence of barriers, such as costs, inability to obtain medication</td>
<td></td>
</tr>
</tbody>
</table>

Interventions to improve adherence were also reviewed. Although the literature was limited, the authors concluded that multi-faceted communication and support programmes designed to promote empowerment were most likely to be effective.
10.15.6 When and how should AED treatment be discontinued in adults and children?

The risks and benefits of continuing or withdrawing AED therapy should be discussed with individuals, and their families and/or carers as appropriate, who have been seizure free for at least 2 years (see Appendix H). [2004]

The decision to continue or withdraw medication should be taken by the individual, their family and/or carers as appropriate, and the specialist after a full discussion of the risks and benefits of withdrawal. At the end of the discussion individuals, and their family and/or carers as appropriate, should understand the individual's risk of seizure recurrence on and off treatment. This discussion should take into account details of the individual's epilepsy syndrome, prognosis and lifestyle. [2004]

When AED treatment is being discontinued in a individual who has been seizure free it should be carried out slowly (at least 2-3 months) and one drug should be withdrawn at a time. [2004]

Particular care should be taken when withdrawing benzodiazepines and barbiturates (may take up to 6 months or longer) because of the possibility of drug-related withdrawal symptoms and/or seizure recurrence. [2004]

There should be a failsafe plan agreed with individuals and their families and/or carers as appropriate, whereby if seizures recur, the last dose reduction is reversed and medical advice is sought. [2004]

Evidence statements

Characteristics that predict a decreased risk of recurrence of seizures after AED withdrawal in adults with epilepsy are the:

- duration of seizure freedom before withdrawal (Ib)

Characteristics that predict an increased risk of recurrence of seizures after AED withdrawal in adults with epilepsy are:

- history of focal seizures
- history of myoclonic seizures
- history of tonic-clonic seizures
- seizures after commencement of AED treatment
- on more than one AED (Ib)

Characteristics that predict a decreased risk of recurrence of seizures after AED withdrawal in children with epilepsy are:

- period seizure free (2 years or more) (Ia)
Characteristics that predict an increased risk of recurrence of seizures after AED withdrawal in children with epilepsy are:

- history of focal seizures
- epileptiform abnormalities on EEG (Ia)
- presence of learning disabilities (Ib)

There is no good quality evidence (see Evidence Tables in Appendix F for methodological issues) that tapering AED medication at different rates has a difference on outcomes for people with epilepsy. (Ib children, no evidence for adults)

10.15.6.1 In adults and children with epilepsy on AEDs what are the features (from history and investigations) which predict risk of further seizures if medication is discontinued?

Secondary evidence

Berg 1994

A systematic review was undertaken to determine the risk of relapse at 1 and 2 years after discontinuation of antiepileptic medication and to examine the strength of association between the risk of relapse and three commonly assessed clinical factors:

- age of onset of epilepsy
- presence of an underlying neurologic condition
- and an abnormal EEG.

The authors used explicit strategies to identify papers, select studies and extract data.

Forty two studies were identified, of which 25 met their inclusion criteria. Data on 5354 individuals were included. The proportion of those who relapsed ranged from 12% to 67%. Overall, the risk of relapse at 1 year was 0.25 (95% CI, 0.21 to 0.30) and at 2 years it was 0.29 (95% CI, 0.24 to 0.34). Relative to epilepsy of childhood onset, epilepsy of adolescent onset was associated with a relative risk of relapse of 1.79 (95% CI, 1.46 to 2.19). Compared with childhood-onset epilepsy, adult-onset epilepsy was associated with a relative risk of 1.34 (95% CI, 1.00 to 1.81). Individuals with remote symptomatic seizures were more likely to relapse than those with idiopathic seizures; the relative risk was 1.55 (95% CI, 1.21 to 1.98). An abnormal EEG was associated with a relative risk of 1.45 (95% CI, 1.18 to 1.79).

Quality Standards Subcommittee of the American Academy of Neurology 1996

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) developed a practice parameter intended to help physicians in their decisions to withdraw AEDs.

---

bb Seizures are defined as ‘remote symptomatic’ if the individual had a static encephalopathy before the seizure (from birth or acquired) or sustained a prior neurologic insult such as a stroke or significant head trauma.
This practice parameter systematically reviewed the evidence on discontinuation of AEDs. The authors reviewed the evidence base up until 1994.

53 studies were identified that investigated the risk of recurrence of seizures following discontinuation of medication. The authors identified one RCT (MRC discontinuation study – see below). The nine factors or clinical characteristics identified were: sex, age of onset, seizure type, aetiology, neurological examination/I.Q., duration of seizure freedom on AEDs, treatment regimen, age at relapse, and normalization of the EEG. Only 17 studies discussed all nine factors. The negative health outcome was relapse, and the positive was becoming seizure-free without medication. Individuals maintained on reduced dose of medication were not included.

The relapse rates reported in the 17 studies were summarized and weighted according to the number of cases in that study. An analysis of the studies yielded a weighted mean (by number of cases) relapse rate of 31.2% for children and 39.4% for adults. From the studies, certain clinical characteristics emerged that may predict successful remission. The longer the duration of seizure control with AEDs, the better the prognosis. The evidence presented in the 17 studies suggested that although their recurrence risk rates differ, both children and adults meeting the following profile have the greatest chance for successful drug withdrawal:

- seizure-free 2 to 5 years on AEDs (mean 3.5 years);
- single type of partial or generalized seizure;
- normal neurological examination and normal I.Q.;
- EEG normalized with treatment.333

Sirven 2003334

This Cochrane Review sought to:

a) quantify seizure relapse risk after early (less than two seizure free years) versus late (more than two seizure free years) AED withdrawal in adults and children;

b) assess which variables modify the risk of seizure recurrence.

The authors searched the Cochrane Epilepsy Group trials register, the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 1, 2003), MEDLINE (January 1996 to March 2003), EMBASE, Index Medicus, CINAHL and hand-searched relevant journals.

Randomised controlled trials that evaluated withdrawal of AEDs after varying periods of seizure remission in adult and children with epilepsy were included. These studies compared an early versus late AED discontinuation.

**The MRC discontinuation study was not included in this review as entry into this study required that all individuals had been seizure free for at least two years.

Two reviewers independently extracted data and assessed trial quality. Relative risks (RR) with 95% confidence intervals (CIs) were calculated for each trial. Summary RRs and 95% CIs for dichotomous data were calculated using a random effects model. A test of statistical heterogeneity was conducted for each pooled relative risk calculation.
Seven eligible controlled trials were included in the analysis representing 924 randomised children. There were no eligible trials evaluating seizure free adults. The pooled relative risk for seizure relapse in early versus late AED withdrawal was 1.32 (95% CI 1.02 to 1.70). On the basis of this estimate, the number needed to harm, that is expose an individual to a higher risk of seizure relapse because of early withdrawal of AED, is 10. Early discontinuation was associated with greater relapse rates in people with partial seizures (pooled RR is 1.52; 95% CI 0.95 to 2.41) or an abnormal EEG (pooled RR 1.67; 95% CI 0.93 to 3.00) although this difference did not reach statistical significance.

The authors concluded that there was evidence to support waiting for at least two or more seizure free years before discontinuing AEDs in children, particularly if individuals have an abnormal EEG and partial seizures. There was insufficient evidence to establish when to withdraw AEDs in children with generalized seizures. There was no evidence to guide the timing of withdrawal of AEDs in seizure free adults (before two years).

The authors called for further blinded randomised controlled trials to identify the optimal timing of AED withdrawal and risk factors predictive of relapse.

Primary evidence (adults)

MRC AED withdrawal study group 1991

This was a pragmatic multi-centre RCT (UK/Europe) to compare seizure control under policies of slow withdrawal versus routine maintenance of drug therapy. The aim was to identify important prognostic factors in seizure recurrence.

Individuals were eligible to take part in the study if they had a history of two or more seizures, had been free of seizures for at least two years and were taking AEDs. Individuals randomised to the intervention arm (slow withdrawal) had therapy withdrawn according to guidelines suggested by the trial steering committee. The aim was to extend withdrawal to a minimum of six months, with treatment being reduced at 4 week intervals (reduction regimen per AED stated in paper). Participants in the control arm were maintained on existing doses unless there were clinical indications that necessitated a change. Individuals were on the following AEDs: carbamazepine, valproate, phenytoin, phenobarbitone, primidone and ethosuximide.

Follow up was at 3, 6 and 12 months, and then yearly.

A total of 1797 individuals were eligible for inclusion in the trial, of which 1021 (57%) agreed to randomisation. Eight randomised individuals were withdrawn, leaving a study population of 1013. The study population were adults (for control group: median age 26, 25th centile 16 years, 75th centile 39 years; intervention arm characteristics similar). The group who agreed to be randomised were younger and had a slightly longer duration of epilepsy and AED treatment. Individuals with a history of attempted AED withdrawal (Odds Ratio OR 0.6, 95% CI 0.1 to 0.8) and those with a driving licence (OR 0.13, 95% CI 0.1 to 0.18) were less likely to agree to be randomised.

By 2 years after randomisation, 78% of those in whom treatment was continued and 59% in whom it was withdrawn remained seizure free, but thereafter the differences between the two groups diminished. Non-compliance with continued treatment accounted for only a small proportion of the risk to the group continuing with treatment.
The most important factors determining outcome were longer seizure-free periods (reducing the risk) and more than one antiepileptic drug and a history of tonic-clonic seizures (increasing the risk). The factors achieving significance at 95% CI for multivariate model are presented in Table 3.

Table 10-29: Influence of individual characteristics on seizure recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk (95% CI) (multivariate model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of partial seizures, none generalized</td>
<td>2.51 (1.00, 6.30)</td>
</tr>
<tr>
<td>History of myoclonic seizures</td>
<td>1.85 (1.09, 3.12)</td>
</tr>
<tr>
<td>History of tonic-clonic seizures (primary or secondary)</td>
<td>3.40 (1.48, 7.84)</td>
</tr>
<tr>
<td>Seizures after start of treatment</td>
<td>1.57 (1.10, 2.24)</td>
</tr>
<tr>
<td>On more than one AED at randomisation</td>
<td>1.79 (1.34, 2.39)</td>
</tr>
<tr>
<td>Period seizure free at randomisation (years)</td>
<td></td>
</tr>
<tr>
<td>3 - &lt;5</td>
<td>0.67 (0.48, 0.93)</td>
</tr>
<tr>
<td>5 - &lt;10</td>
<td>0.47 (0.32, 0.69)</td>
</tr>
<tr>
<td>10 -</td>
<td>0.27 (0.15, 0.48)</td>
</tr>
</tbody>
</table>

As far as EEG status was concerned, the sample was insufficient to reach specific conclusions about the importance of any abnormality in the entry EEG.

The aim of this study was to develop and test a prognostic index for the recurrence of seizures after a minimum remission of seizures of two years in people with a history of epilepsy. This study used data from the RCT reported above to identify clinical and treatment factors of prognostic importance in determining the recurrence of seizures. A split sample approach was used to test the internal validity of predictions made on the basis of identified prognostic factors.

The Cox proportional hazards model identified several factors that increased the risk of seizures recurring. These included being 16 years or older; taking more than one antiepileptic drug; experiencing seizures after starting antiepileptic drug treatment; a history of primary or secondary generalised tonic-clonic seizures; a history of myoclonic seizures; and having an abnormal electroencephalogram. The risks of seizures recurring decreased with increasing time without seizures. The model allowed estimation of the risk of seizures recurring in the next one and two years under the policies of continued AED treatment and slow withdrawal of drugs. Split sample validation suggested that the model was well calibrated.

Validation was performed on a sample of the trial participants. An important issue here is that studies need to be conducted to validate these findings in a broader population.
Table presents the authors’ prognostic index model. This was used in the SIGN adult guideline to produce a table of risk of seizure recurrence that could easily be used by clinicians.\

### Table 10-30: Prognostic index for recurrence of seizures within one and two years after continuing AED treatment or starting slow withdrawal

Adapted from MRC AED Drug Withdrawal Group 1993 and reprinted with permission from the BMJ Publishing Group (BMJ, 1993, 306, 1374-8)

<table>
<thead>
<tr>
<th>Starting score (all individuals)</th>
<th>-175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 16 or older</td>
<td>Add 45</td>
</tr>
<tr>
<td>Taking more than one AED</td>
<td>Add 50</td>
</tr>
<tr>
<td>Seizures after start of AED treatment</td>
<td>Add 35</td>
</tr>
<tr>
<td>History of primary or secondarily generalized tonic-clonic seizures</td>
<td>Add 35</td>
</tr>
<tr>
<td>History of myoclonic seizures</td>
<td>Add 50</td>
</tr>
<tr>
<td>EEG in last year</td>
<td></td>
</tr>
<tr>
<td>not available</td>
<td>Add 15</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Add 20</td>
</tr>
<tr>
<td>Period free from seizures (t; no. of years)</td>
<td>Add 200/t</td>
</tr>
<tr>
<td><strong>TOTAL SCORE</strong></td>
<td></td>
</tr>
<tr>
<td>Divide total score by 100 and exponentiate</td>
<td>z=e^{T/100}</td>
</tr>
</tbody>
</table>

**Probability of recurrence of seizures:**

**Continued treatment**

- by one year: 1 - 0.89^z
- by two years: 1 - 0.79^z

**Slow withdrawal**

- by one year: 1 - 0.69^z
- by two years: 1 - 0.60^z

10.15.6.2 In adults and children with epilepsy on AEDs, do different rates of withdrawal lead to differing risks of seizure recurrence and/or other side effects of stopping treatment?

Secondary evidence

No systematic reviews were identified.

Primary evidence

Tennison et al 1994

The aim of this unblinded RCT was to compare a six-week (relatively short) period and a nine-month (relatively long) period of drug tapering in a group of children with epilepsy who had had no seizures for either two or four years.

All children receiving care at the paediatric epilepsy clinics at the two study institutions who had had no seizures for approximately 18 months were eligible for the study. Children who had had a single seizure or only febrile seizures were excluded, as were those with neonatal seizures or infantile spasms.

The authors randomly assigned 149 children to either a six-week or a nine-month period of drug tapering, after which therapy was discontinued. Each group was composed of children who had been seizure-free for either two or four years before drug tapering was begun. Most children...
were receiving one antiepileptic drug; none were taking more than two. The children were
evaluated periodically during and after the taper period. Sixteen individuals were lost to follow-
up before the beginning of the taper period. Proportional-hazards regression analysis was used
to assess the risk of seizure recurrence among the remaining 133.

Seizures recurred in 53 children (40%). The mean duration of follow-up was 39 months (range,
11 to 105) for those who did not have a recurrence of seizures. Neither the length of the taper
period (six weeks vs. nine months, p=0.38) nor the length of time children were free of seizures
before the taper period was begun (two years vs. four years, p=0.20) significantly influenced
the risk of seizure recurrence.

The presence of mental retardation (relative risk, 3.1; 95% CI 1.5 to 6.2) or spikes in the
electroencephalogram at the time of tapering (relative risk, 1.9; 95% CI 1.0 to 3.4) increased the
risk of seizure recurrence.338

10.15.7 In adults/children with epilepsy on AEDs does management of drug
withdrawal by a generalist as opposed to a specialist lead to different
outcomes?

Withdrawal of AEDs must be managed by, or under the guidance of, the specialist. [2004]

Evidence statement

No evidence was identified.

Secondary evidence

No systematic reviews were identified.

Primary evidence

No RCTs were identified.

Other evidence

There was no specific evidence reviewed on the discontinuation of therapy by either specialist or
generalist.
10.16 When should an individual with epilepsy be referred for assessment in a tertiary centre?

10.16.1 Introduction

Individuals with poorly controlled epilepsy may benefit from referral to a tertiary centre and further assessment, which may include assessment for epilepsy surgery. The exact number of individuals who may benefit from such a referral is unclear. There is, however, evidence that epilepsy surgery may be underused as a treatment modality for poorly controlled epilepsy in the UK owing to suitable individuals not being referred to a tertiary centre.\textsuperscript{339}

All individuals with epilepsy should have access via their specialist to a tertiary service when circumstances require. [2004]

The tertiary service should include a multidisciplinary team, experienced in the assessment of individuals with complex epilepsy, and have adequate access to investigations and treatment by both medical and surgical means. [2004]

The expertise of multidisciplinary teams involved in managing complex epilepsy should include psychology, psychiatry, social work, occupational therapy, counselling, neuroradiology, clinical nurse specialists, neurophysiology, neurology, neurosurgery and neuroanaesthesia. Teams should have MRI and video telemetry facilities available to them. [2004]

The neurosurgeon in the multidisciplinary team should have specialist experience of and/or training in epilepsy surgery and have access to invasive EEG recording facilities. [2004]

If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, individuals should be referred to tertiary services soon\textsuperscript{cc} for further assessment. Referral should be considered when one or more of the following criteria are present:

- the epilepsy is not controlled with medication within 2 years
- management is unsuccessful after two drugs
- the individual is aged under 2 years
- an individual experiences, or is at risk of, unacceptable side effects from medication
- there is a unilateral structural lesion
- there is psychological and/or psychiatric co-morbidity
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. [2004]

In children, the diagnosis and management of epilepsy within the first few years of life may be extremely challenging. For this reason children with suspected epilepsy should be referred to tertiary services early, because of the profound developmental, behavioural and psychological effects that may be associated with continuing seizures. [2004]

Behavioural or developmental regression or inability to identify the epilepsy syndrome in an individual, should result in immediate referral to tertiary services. [2004]

\textsuperscript{cc} The Guideline Development Group considered that ‘soon’ meant being seen within 4 weeks.
Individuals with specific syndromes such as Sturge–Weber syndrome, the hemispheric syndromes, Rasmussen's encephalitis and hypothalamic hamartoma should be referred to a tertiary epilepsy service. [2004]

Psychiatric co-morbidity and/or negative baseline investigations should not be a contraindication for referral to a tertiary centre. [2004]

Evidence statement

In temporal lobe epilepsy, surgery is superior to prolonged medical therapy. (Ib)

Details

This section was not subject to a full evidence review for reasons given in Chapter Two.

Chilcott 1999340

One systematic review was identified.

One RCT (comparing different forms of surgery) and 6 case series were included in this review. No quantitative analysis was possible, but a narrative summary was presented.

The authors concluded that there are strong arguments for ensuring that all young people with medically refractory seizures are evaluated by a neurologist/paediatrician or other specialist with an interest in epilepsy, so that all suitable patients are identified and may be offered surgery. Surgery has a high chance of controlling epilepsy for these people, allowing them to complete their education, integrate socially, achieve employment and avoid a lifetime of antiepileptic drugs and hospital attendance.340

Wiebe 2001341

This RCT assessed the efficacy and safety of surgery in adults with poorly controlled temporal lobe epilepsy.

Eighty participants were randomly assigned to either surgery (n=40) or treatment with AEDs for 12 months (n=40). The primary outcome was freedom from seizures that impaired awareness of self and surroundings. The analysis was done on an intention-to-treat basis.

Of the 36 who underwent surgery, 58% were free from seizures that impaired awareness at 12 months, compared with 8% in the medical group (p<0.001). 38% of those in the surgical group compared with 3% in the medical group were seizure free, including auras, at 12 months (p<0.001).

One individual died of SUDEP in the medical group. No deaths occurred in the surgical group.
The authors suggested that this trial supported the belief that prolonged trials of medication were futile and that people with temporal lobe epilepsy should be evaluated for surgery. However, they stress that the question of whether early surgery was superior to medical therapy was not addressed.

**Health economics**

Clinical research has shown that surgery is a desirable option for treatment of certain forms of refractory epilepsy. There is a lack of health economics evidence in the assessment of surgery in the management of epilepsy. One review with economic analysis and one economic evaluation on epilepsy surgery were found. However, no randomised controlled trial alongside an economic evaluation was found.

Chilcott and colleagues 1999

The objective of this systematic review is to assess the effectiveness of surgery for epilepsy in children and adults with refractory epilepsy.

The authors identified four studies investigating the economics of surgery for refractory epilepsy, but they did not identify any published study concerning the cost and effectiveness of surgery for epilepsy in the UK.

The study reported:

- the costs of evaluation and assessment of candidates for surgery, and the costs of surgery
- the costs of long term medical management with and without surgery
- the cost-effectiveness in terms of cost per seizure free year of surgery for epilepsy compared to usual care.
- comparisons of results with other, international studies.

Three stages to the evaluation were distinguished:

- **Stage 1**
  - to identify individuals suitable for further investigation. This covered outpatient visits, MRI scan, EEG, neuropsychology tests.

- **Stage 2**
  - to identify individuals with a single temporal or extra-temporal lobe focus suitable for further investigation. It covered EEG telemetry (with or without ictal specific area/PET)

- **Stage 3**
  - to determine the safety and appropriateness of surgery. It covered Wada test, intracranial monitoring, and further EEG telemetry.

The analysis was from the perspective of the NHS, although it also included a qualitative discussion of the indirect costs associated with epilepsy. Costs are in UK 1998 pounds sterling. The cost-effectiveness analysis took a fifteen-year time horizon and discounted both costs and benefits at 6% per annum.
One-way and multi-way sensitivity analyses were included.

- The authors concluded that:
  - In a 'typical' health authority, between 3 and 14 surgical candidates would be identified per year. The cost per person going forward to surgery for assessment was estimated between £10k and £16k. The total cost per year for assessment and surgery for a healthy authority was estimated between £60k and £220k.

- The average cost per person per year of active epilepsy (at least one seizure in the last year) is £530 compared to £75 for inactive epilepsy.

- Surgery results in approximately 65% of individuals undergoing temporal lobe resection (TLR) and 45% of individuals undergoing extra temporal resection (ETR) becoming seizure free. 10% of those on medical management become seizure free.

- The base case model marginal cost per seizure free year compared to medical management is £2291 for TLR individuals, £4,096 for ETR individuals and £2,329 for all surgical cases.

The results were particularly sensitive to the time horizon used in the analysis.

Key parameters were the effectiveness of surgery and the proportion of those who proceed to surgery from neuropsychological testing.

The authors recognised that there was a lack of trial data, a likely referral bias in case series from the major centres, differences in practice between trial centres. The review also states that a NHI consensus statement recognised that there was a lack of evidence linking seizure control to quality of life and identified this as an area for research. For these reasons, the review should be viewed with caution.
11 The role of non-drug treatments in the management of the epilepsies

11.1 Introduction

Although the mainstay of treatment for individuals with epilepsy is pharmacological, non-drug treatments such as psychological interventions, the ketogenic diet and vagus nerve stimulation are also used.

Psychological interventions such as relaxation therapy, cognitive behaviour therapy and biofeedback have been used alone or in combination in the treatment of epilepsy, with the aim of reducing seizure frequency and improve the quality of life.

The ketogenic diet (KD) is a high-fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation when ketone bodies become the main fuel for the brain's energy demands (Hartman 2008) 342. It has long been used for treatment of refractory epilepsy in children, although the exact mechanism of action is unclear.

It can be difficult to treat individuals with drug resistant epilepsy who have been assessed as being unsuitable for surgery. Vagus nerve stimulation (VNS) is used as an adjunctive treatment in such cases.

11.2 Does the treatment of epilepsy in adults or children with psychological methods lead to a reduction in seizure frequency and/or a better quality of life?

Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]

Psychological interventions (relaxation, cognitive behaviour therapy, biofeedback) may be used in conjunction with AED therapy in adults where either the individual or the specialist considers seizure control to be inadequate with optimal AED therapy. This approach may be associated with an improved quality of life in some individuals. [2004]

Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children with drug-resistant focal epilepsy. [2004]

Evidence statement

There is no evidence that psychological interventions (relaxation, cognitive behavioural therapy, biofeedback) can affect seizure frequency. Understanding of epilepsy, adjustment to epilepsy, and concordance with medication may be improved. Evidence for other outcomes, including anxiety, adjustment, and depression is conflicting. (Ia)
Details

Secondary Evidence

One Cochrane review was identified that addressed the use of psychological methods in the management of the epilepsies.343

Ramaratnam 2003343

This review assessed the effectiveness of psychological or behaviour modification therapies in treating epilepsy. Types of interventions searched for included the use of relaxation therapy, cognitive behavioural therapy (CBT), biofeedback, counselling, suggestion, hypnotherapy, conditioning, systematic desensitisation, behavioural countermeasures at seizure onset applied by the individual or another person, physical therapies, massage, aromatherapy, music, or dance therapy. Randomised or quasi-randomised studies assessing one or more types of psychological or behaviour modification techniques for people with epilepsy were included.

Outcomes included reduction in seizure frequency, and psychosocial and educational measures.

Only studies assessing relaxation, CBT, biofeedback, and educational interventions were identified.

Results of two studies showed a non-significant advantage for relaxation therapy with regard to seizure frequency (Peto odds ratio, 2.56, 95% CI 0.45 to 14.44). Due to lack of information and methodological issues, no reliable conclusions of the effect of other therapies were drawn.

With regard to other outcomes, four studies indicated improvements in the understanding of epilepsy, adjustment to epilepsy, and compliance with medication. However, the results of other trials on outcomes including anxiety, adjustment, and depression were contradictory. The authors suggested that these results may be linked with the baseline functioning of the participants in the different studies.

In view of methodological deficiencies and limited number of individuals studied, the review found no reliable evidence to support the use of these treatments and the authors called for further trials.

Engelberts 2002344

Another systematic review aimed to investigate the contribution of psychologists in the management of relatively well-controlled epilepsy in adults.

The authors concluded that, although some positive results were found, most of the studies had methodological inadequacies that did not allow firm conclusions to be made and called for further research.344

This review was assessed as of lower quality than the Cochrane review above, but reached similar conclusions.
Primary evidence

Since the Cochrane review presented above, no further RCTs with seizure frequency as an outcome were identified.

11.3 Ketogenic Diet

The ketogenic diet should not be recommended for adults with epilepsy. [2004]

11.3.1 Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation when ketone bodies become the main fuel for the brain’s energy demands (Hartman 2008). It has long been used for treatment of refractory epilepsy in children, although the exact mechanism of action is unclear.

The KD diet was initially reported for use in epilepsy in 1921 (Wilder 1921). The initial diet used was the Classical Ketogenic diet, based on the ratio of fat to carbohydrate (with protein), of 3 or 4:1. Later an alternative was suggested using triglyceride oil as a supplement, the Medium Chain Triglyceride (MCT) Diet (Huttenlocher et al 1971). The diet has to be carefully administered with the aid of a dietician.

In this chapter we examine the effectiveness, adverse effects and cost effectiveness of the ketogenic diet compared to no change in diet (placebo) and to no diet (normal diet) in the treatment of childhood epilepsy. There have been two randomised controlled trials examining efficacy. One very small trial compared the ketogenic diet against placebo. The other trial compared the ketogenic diet (classical or MCT variant) with a control group (normal diet). Additional data from this second comparison included an analysis on the relative efficacy and tolerability between the classical and the MCT diet.

11.3.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with epilepsy. No data was found for adults.

11.3.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions myoclonic seizures. The following interventions were included in our search; ketogenic diet, ketogenic diet plus glucose, Medium Chain Triglycerides Diet (MCT). We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
### 11.3.3.1 Ketogenic Diet versus normal diet (without dietetic input)

#### Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

#### Health economic evidence

No studies were identified in the economic literature search.

#### Evidence statements

**Efficacy — statistically significant results**

The ketogenic diet is more effective than no change in treatment in the proportion of participants experiencing at least 50% reduction in seizures. However, there is uncertainty about the magnitude of the effect. (LOW QUALITY)

**Efficacy — statistically non significant results**

No significant difference between the ketogenic diet and the no change in treatment in the proportion of participants seizure freedom (VERY LOW QUALITY)

**Adverse events— statistically significant results**

The ketogenic diet has significantly greater incidence of the following adverse events compared to no change in treatment, however there is uncertainty of the magnitude of the clinical effect.

- Vomiting (LOW QUALITY)
- Constipation (LOW QUALITY)
- Medication needed for constipation (LOW QUALITY)
- Lack of energy (LOW QUALITY)
Cost-effectiveness
No economic evidence comparing ketogenic diet to no change in treatment was identified.

Outcomes with no evidence
There were no studies that reported:
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Time to first seizure,
- Time to exit/withdrawal of allocated treatment
- Cognitive outcomes
- Quality of life outcomes.

11.3.3.2 Ketogenic Diet versus ketogenic diet plus glucose
The authors of the trials believe that using a 60g solution of glucose over the course of a day in conjunction with a ketogenic diet negates urinary and serum ketosis so creating a placebo arm. The use of an artificial sweetener (saccharin, which tastes similar to glucose) does not add carbohydrate and therefore was used in the treatment arm. Ketosis was never lost by withdrawals in the glucose arm.

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
There was no significant difference between the ketogenic diet and placebo in the proportion of participants experiencing at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing ketogenic diet plus saccharin to placebo was identified.

Outcomes with no evidence
There were no studies that reported:
- Seizure freedom
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Time to first seizure,
• time to exit/withdrawal of allocated treatment
• incidence of adverse events,
• cognitive outcomes
• quality of life outcomes.

11.3.3.3 Ketogenic diet versus Medium-Chain Triglycerides Diet (MCT)
The classical ketogenic diet is based on a ratio of 4:1 or 3:1 fat to carbohydrate and protein. The fat component is provided by long-chain triglycerides. For the MCT diet, medium-chain triglycerides are used as an alternative fat source. MCT yields more ketones per kilocalorie than the classical ketogenic diet. It is absorbed more efficiently and is carried directly to the liver in the portal blood, thus less fat is needed and so more carbohydrate and protein can be included in the diet.

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
There was no significant difference between the ketogenic diet and MCT diet for the proportion of participants experiencing at least a 50% reduction in seizure frequency at 12 months. (VERY LOW QUALITY)

Adverse events – statistically non-significant
There was no significant difference between the ketogenic diet and the MCT diet for the incidence of:
• vomiting (VERY LOW QUALITY)
• constipation (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing ketogenic diet to MCT diet was identified.
Outcomes with no evidence

There were no studies that reported:

- Seizure freedom
- Withdrawal due to adverse events
- Withdrawal due to lack of efficacy
- Time to first seizure,
- Time to exit/withdrawal of allocated treatment
- Cognitive outcomes
- Quality of life outcomes.
### 11.3.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Refer children with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**

GDG considered efficacy based on 50% seizure reduction and adverse effects to be the most important outcomes.

**Trade off between clinical benefits and harms**

The ketogenic diet is more effective than no change in treatment in the proportion of participants experiencing at least 50% reduction in seizures but there is no evidence to recommend any specific variant of the ketogenic diet. Any benefit may be mitigated by the frequency of side-effects and difficulty in complying with the diet.

The diet may be associated with significant gastro-intestinal side-effects, including diarrhoea, constipation, vomiting and hunger. Side effects can be improved by dietary manipulation and may improve spontaneously after a few weeks.

Compliance with, and adherence to, the diet is generally more difficult than with compliance with antiepileptic medication. This is largely because the diet is unnatural, involves a complete change of eating habits, and frequently life-style, and this involves the whole family as well as the child. Compliance with the diet must be complete and consistent to optimise its efficacy.

According to GDG experience, a successful and sustained response to the ketogenic diet can allow for the successful withdrawal of some or all concomitant AEDs in some patients which may lead to a reduction in side effect experienced. Successful withdrawal of these drugs may not translate to an overall cost savings due to the high costs of diet initiation and follow-up.

**Economic considerations**

The GDG recognised that implementation of the ketogenic diet would represent an additional cost compared with no diet change, but based on the clinical evidence would also reduce seizure frequency for some patients. In the absence of a full economic evaluation to assess the potential cost-effectiveness of the ketogenic diet, the GDG considered some of the substantial costs of implementing the diet, particularly those related to initiation and follow-up. As initiation of the diet requires substantial dietetic input in terms of teaching families about the diet, following up and making adjustments during the first several weeks and months and liaising with other health professionals involved in the child’s care, it is essential that a thorough assessment be made prior to diet initiation to identify those patients for whom the diet is a suitable treatment option. The diet will most often be initiated as an outpatient, but there are some patients who will require initiation as an inpatient.
The majority of costs associated with the ketogenic diet come from initiation and follow-up within the first year, although ongoing costs will include regular contact with the ketogenic diet clinic staff to monitor and manipulate the diet, dietary supplementation and regular blood tests. The clinical and blood test-monitoring will be greater than that required for children taking anti-epileptic medication. It is possible that the longer the diet is successfully maintained and achieves the desired response, the more cost-effective it may be.

The GDG considered that because of the high initial costs and the potential difficulty in implementation of and adherence to the diet, it should be reserved for those children who have previously tried other AEDs but failed to achieve the desired level of seizure control.

Based on the clinical evidence, the MCT diet was not clearly more effective than the classical diet, yet the cost of administering it is greater due to the additional cost of Liquigen (£2.90 per 100mL). In the absence of evidence to indicate greater effect, the GDG felt that the classical ketogenic diet should be tried first and MCT reserved for those patients with special considerations, such as patients using a gastronomy tube or unable to tolerate the classical variant.

**Quality of evidence**

Very limited trial data. The evidence is mostly of low quality. There are a limited number of events and very wide confidence intervals.

**Other considerations**

There is currently variation in access to ketogenic diet across England and Wales which will be important when implementing this recommendation.

11.3.5 Deleted recommendations from the 2004 guideline

11.3.5.1 The ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy.
11.4 In people with drug resistant epilepsy, is vagus nerve stimulation (VNS) effective as an adjunctive treatment?

Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalised seizures. [2004]

Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalised seizures. [2004]

Evidence statement

The evidence shows that VNS appears to be an effective and well tolerated treatment for drug resistant partial seizures. Stimulation using the high stimulation paradigm is significantly better than low stimulation. (Ia)

Details

Secondary Evidence

One Cochrane review and one technology appraisal were identified that addressed the use of VNS in the management of partial seizures and drug resistant epilepsy respectively. In addition, guidance on the use of VNS as an interventional procedure in children was published by NICE in 2004. The guidance is included in the guideline recommendations above.

Privitera 2003

Privitera and colleagues reviewed the evidence on the effects of VNS high-level stimulation compared to low-level (presumed subtherapeutic dose) stimulation in people with drug resistant partial seizures. Randomised, double-blind controlled trials of VNS comparing high and low stimulation paradigms in adults or children were included.

The following outcomes were assessed:

a. 50% or greater reduction in total seizure frequency;

b. treatment withdrawal (any reason);

c. adverse effects.

Primary analyses were intention-to-treat. Sensitivity best and worst case analyses were also undertaken. Summary odds ratios (ORs) were estimated for each outcome.
The two included studies\textsuperscript{353,354} were parallel trials, sponsored by Cyberonics as part of their pre-
approval program for VNS. Each trial tested two stimulation paradigms for VNS. All
participants were implanted with a stimulator, but the control group received less frequent and
lower intensity stimulation. In addition, participants in the control group did not receive any
electrical current when the device was activated by the hand-held magnet. A total of 312
individuals were randomised to treatment.

Stimulation parameters in the E03 trial\textsuperscript{353} were: current 0.5 to 3.0 mA (active and control);
frequency 20 to 50 Hz (control 1 to 2); pulse width 500 (control 130); on time 30 to 90 seconds
(control 30 seconds); off time 5 minutes (control 90 minutes).

Stimulation parameters in the E05 trial\textsuperscript{354} were: current 3.5 mA (active and control); frequency 30
Hz (control 1); pulse width 500 (control 130); on time 30 seconds (active and control 30); off time
5 minutes (control 180 minutes). Inclusion criteria were as follows: age 12 to 60 years; zero to 3
concomitant AEDs; minimum 6 seizures per month.

People with peptic ulcers were excluded from the E05 trial. In the E03 trial, one person dropped
out prior to randomization. In the E05 trial, one participant dropped out and another was
excluded from the efficacy analysis because he did not keep a seizure diary; both participants
provided adverse event data. These two participants contributed to the best and worst case
scenarios.

Results of the overall efficacy analysis showed that VNS stimulation using the high stimulation
paradigm was significantly better than low stimulation. The overall OR (95\% confidence interval
(CI)) for 50\% responders across all studies was 1.93 (95\% CI 1.1 to 3.3). This effect did not vary
substantially and remained statistically significant for both the best and worst case scenarios
(Overall odds ratio for 50\% responders across all studies 1.99 (95\% CI 1.1 to 3.4) (best case)
and 1.84 (95\% CI 1.06 to 3.18) (worst case)).

Results for the outcome ‘withdrawal of allocated treatment’ suggested that VNS is well tolerated
as no significant difference was found between the high and low stimulation groups (overall odds
ratio 1.08 (95\% CI 0.07 to 17.51), and withdrawals were rare. Statistically significant adverse
effects associated with implantation (low versus baseline) were hoarseness, cough, pain, and
paresthesia (hoarseness 4.74 (99\% CI 2.12 to 10.60); cough 2.97 (99\% CI 1.48 to 5.94); and
paresthesia 6.36 (99\% CI 2.69 to 15.08)). Statistically significant adverse effects associated
with stimulation (high versus low) were hoarseness and dyspnea (hoarseness 4.50 (99\% CI 2.45 to
8.27) and dyspnea 2.65 (99\% CI 1.15 to 6.08)), suggesting the implantation is associated with
hoarseness, but the stimulation produces additional hoarseness.

The reviewers concluded that for partial seizures, VNS appeared to be an effective and well
tolerated treatment.\textsuperscript{350}

\textbf{Bryant 1998}\textsuperscript{355}

This technology assessment was published prior to the publication of the E05 trial so conclusions
about effectiveness are not presented. (See Cochrane review above)

\textbf{Corabian 2001}\textsuperscript{351}

The Alberta Heritage Foundation for Medical Research published a health technology report on
the use of vagus nerve stimulation for people with refractory epilepsy. This updated a previous
TechNote published in 1998. Corabian and Legget found:
No published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of generalized epilepsy;

No published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of specific types of epilepsy in children;

No results obtained from prospective controlled studies or other comparative studies using controls that have been published on the direct comparison between the use of VNS and the use of new AEDs as adjunctive therapies for seizure frequency reduction in refractory epilepsy; and

No prospective controlled studies or other comparative studies with controls designed and conducted to determine the effect of VNS on seizure control in refractory epilepsy in terms of reduced seizure intensity/duration and AED intake in individuals with refractory epilepsy or improved QOL.

However, the authors did review several uncontrolled trials. They concluded that VNS was safe and effective when added to the existing treatment regimen for some individuals (aged over 12 years) in terms of a reduction in seizure frequency.

Raeburn 2003

The cost utility of VNS in medically refractory epilepsy was estimated based on a meta-analysis of two RCTs. However, one of the publications used reported preliminary results from a trial published in full later. This meta-analysis was therefore excluded.

Fisher 1999

A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology assessed the effectiveness of VNS for epilepsy. The same two RCTs were evaluated as in the Cochrane review by Privitera and colleagues.

The report concluded that ‘the degree of improvement in seizure control remains comparable to that of new AEDs, but is lower than that of mesial temporal lobectomy in suitable resection candidates’. The committee recommended that VNS was indicated for adults and adolescents over the age of 12 years with medically refractory partial seizures who are not candidates for potentially curative surgical resections.

Primary evidence

No RCTs were identified as being published since the HTA (2000 onwards).
Health economics

Bryant 1998355

This technology appraisal assessed the health economic evidence related to VNS.

As long-term effectiveness is unknown, the cost effectiveness analysis was limited to the first year. The cost per seizure saved was in the range £246 to £410. One study of the cost benefit ratio of VNS concluded that the cost of VNS could be expected to be paid back by savings in direct medical costs after 2 years.

The authors concluded that there still remained questions on the cost benefit of VNS.

Boon 1999358

This was a cost effectiveness study in which 25 individuals were treated by VNS implantation, 20 of whom had sufficient follow-up data. The mean age was 30 (range: 12-45; sd=9.0) years and the mean duration of epilepsy was 17 years (range: 5-35 years; sd=8.0).

The study sample were part of a population of 150 who underwent an extensive pre-surgical evaluation that included scalp video-EEG monitoring, optimum magnetic resonance imaging (MRI), interictal fluoro-deoxyglucose positron emission tomography (FDG-PET) and neuropsychological assessment. After thorough pre-surgical evaluation, 105 of 150 (70%) were considered as the non-surgical candidates because a confined and resectable epileptogenic zone could not be identified. They were either offered continuing drug therapy with a re-matching of their standard AEDs (n=50), participation in phase-3 drug trials with novel AEDs such as topiramate, gabapentin or levetiracetam (n=30), or VNS (n=25). 25 individuals gave informed consent to have a vagus nerve stimulator implanted. This was a before-and-after study, carried out in a single centre. The mean post-transplantation follow-up time was 26 months (range: 6-50 months; SD: 14.4). Individuals were followed on an outpatient basis at regular intervals, usually every 2-4 weeks during ramping up and every 1 to 3 months thereafter. Loss-to-follow-up comprised 5 who lacked sufficient follow-up data.

Mean (SD) seizure frequency decreased from 14 seizures/month (range: 2-40) in the period before implantation to 9 seizures/month (range: 0-30) (p=0.0003) after implantation.

The mean number and dosage of AEDs remained unchanged in 14 individuals after implantation. For one individual, two AEDs were tapered, for another, only one AED was tapered. In 4 individuals, an additional AED was administered.

Regarding the side effects, 10 individuals reported hoarseness, voice change, paresthaesias in the throat or in the area around the stimulator. Dysphagia and persistent coughing during stimulation were reported in 10 individuals during stimulation. In three cases, these side-effects required a temporary reduction of output current but stimulation did not have to be interrupted.

At the time of maximum follow-up six individuals reported side effects. These side effects did not require any change of stimulation output and subsided over time.

In conclusion, the study experience confirmed the efficacy rate (50% reduction in seizure frequency in about 25% of individuals) observed in the literature that compares favourably with new AEDs such as lamotrigine, topiramate, and gabapentin. Results in the study suggested that VNS remains effective in the long-term, offering a favourable safety profile, acute side-effects...
being related to initial stimulation and resolving spontaneously without the need to stop the stimulation.

The cost analysis considered epilepsy related direct medical costs. It included the costs of AEDs, clinic visits, hospital admissions, laboratory tests, and the VNS stimulator and implantation procedure. For each individual, the yearly cost of AEDs was calculated on the basis of the mean number and type of AEDs in the years before and follow-up time after the implantation. The yearly cost of clinic visits was calculated in the years prior to implantation and during the follow-up time after implantation. The cost analysis did not cover the costs associated with hospital admissions due to conditions unrelated to epilepsy or epileptic seizures and admissions scheduled solely in the context of the pre-surgical evaluation. For each individual, a comparison was made between the mean yearly sum of these costs in the years before and the available follow up time after the implantation. The paired student's t-test was used for statistical analysis.

The main results were that the mean yearly epilepsy related direct medical costs per individual dropped from $6,682 (range: $829 - $21,888) in the period before implantation to $3,635 (range: $684 - $12,486) (p=0.0046), after the VNS implantation.

The authors concluded that VNS is an efficacious and safe treatment for medically refractory epileptic seizures during the first years after implantation. It appeared to be equally effective and safe in the long-term and lacked the common side effects of AEDs. VNS has a favourable cost-benefit.358
12 Information needs of individuals, families, and carers

12.1 Introduction

Having a first seizure is a very traumatic and worrying event for the individual and their family and/or carers. If epilepsy is diagnosed, then the diagnosis can have wide ranging physical and psychological and social consequences which may be as difficult to deal with as the seizures themselves. The management of epilepsy in individuals may require long-term drug treatment and regular review of their condition is essential.

It is therefore crucial that appropriate information and support for the individual with epilepsy and their family and/or carers is provided at each stage of the care pathway. Individuals with epilepsy, their families, and professionals involved in their care need information appropriate to the individual’s developmental age, gender, culture, and stage of life. Potential positive outcomes of information giving and support include reduced mortality and morbidity, individual empowerment and the means to make informed decisions to achieve the best possible quality of life.

12.2 Information needs of the individual with epilepsy, the family, the carer, and special groups

Individuals with epilepsy and their families and/or carers should be given, and have access to sources of, information about (where appropriate):

- epilepsy in general
- diagnosis and treatment options
- medication and side effects
- seizure type(s), triggers and seizure control
- management and self-care
- risk management
- first aid, safety and injury prevention at home and at school or work
- psychological issues
- social security benefits and social services
- insurance issues
- education and healthcare at school
- employment and independent living for adults
- importance of disclosing epilepsy at work, if relevant (if further information or clarification is needed, voluntary organisations should be contacted).
- road safety and driving
- prognosis
- sudden death in epilepsy (SUDEP)
- status epilepticus
- life style, leisure and social issues (including recreational drugs, alcohol, sexual activity and sleep deprivation)
- family planning and pregnancy
- voluntary organisations, such as support groups and charitable organisations, and how to contact them. [2004]

The time at which this information should be given will depend on the certainty of the diagnosis, and the need for confirmatory investigations. [2004]

Information should be provided in formats, languages and ways that are suited to the individual's requirements. Consideration should be given to developmental age, gender, culture and stage of life of the individual. [2004]

If individuals and families and/or carers have not already found high-quality information from voluntary organisations and other sources, healthcare professionals should inform them of different sources (using the Internet, if appropriate: see, for example, the website of the Joint Epilepsy Council of the UK and Ireland, www.jointepilepsycouncil.org.uk). [2004]

Adequate time should be set aside in the consultation to provide information, which should be revisited on subsequent consultations. [2004]

Checklists should be used to remind both individuals and healthcare professionals about information that should be discussed during consultations. [2004]

Everyone providing care or treatment for individuals with epilepsy should be able to provide essential information. [2004]

The person with epilepsy and their family and/or carers as appropriate should know how to contact a named individual when information is needed. This named individual should be a member of the healthcare team and be responsible for ensuring that the information needs of the individual and/or their family and/or carers are met. [2004]

Evidence statements

Individuals with epilepsy require information on:

- epilepsy in general
- diagnosis and treatment options
- medication and side effects
- seizure type(s), triggers and obtaining optimal seizure control
- prognosis
- safety, risk and injury prevention
psychological issues (especially stress)

social security benefits, driving regulations and insurance

employment; life style and social issues. (III)

Counselling issues are anxiety, depression, emotional support and information. (III)

People with epilepsy prefer verbal and written information that is personally relevant. (III)

Details

There is extensive literature on the general information needs of the individual with epilepsy and their families or carers.

It was agreed with the individual patient representatives on the GDG that the recommendations on information needs should be mapped to key points on the care pathway rather than summarised in a separate section of the guideline.

As far as the evidence base is concerned the focus was on published studies that reported the information needs of people with epilepsy and their families or carers. Published studies that have surveyed or interviewed people with epilepsy and/or their carers/family and reported specifically on information needs were included. Evidence that reported healthcare professionals’ views as to what individuals’ information needs are and studies looking more generally at the experience of adults and children living with epilepsy were excluded.

In 2001, Lynette Couldridge and colleagues published a systematic review on the information and counselling needs of people with epilepsy. All the papers referenced in the Couldridge review were reviewed, and a similar strategy was used to identify any relevant papers published since. The knowledge and experience of the GDG were used to help in the identification of ‘grey literature’ and surveys that contributed to the evidence base.

In this review the findings of the Couldridge review were presented with research identifying specific information needs at specific points on the care pathway was summarised.

Secondary evidence

Couldridge 2001

This paper reviewed key primary research on the information needs of people with epilepsy published between 1990 and 2000. Forty primary research papers were reviewed. The following questions relevant to this key clinical question were addressed by the review:

What are the information and counselling needs of people with epilepsy?

Individuals require information on:
Counselling issues identified were:

- Anxiety, depression, emotional support and information.

What is the preferred format, timing and delivery of epilepsy information?

- Little evidence was found to identify the best timing of education programmes or whether needs changed over time, although some researchers highlighted a need for counselling at the time of diagnosis.\textsuperscript{360}

- There is evidence to suggest that information tailored to individual needs and circumstances is the preferred method. Individuals prefer verbal and written information that is personally relevant.

\textbf{12.3 What information is required at different stages of the care pathway}

\textbf{First Seizure}

This should relate to information given in primary care or Accident and Emergency departments to individuals before they are referred for a specialist opinion.

The possibility of having seizures should be discussed, and information on epilepsy should be provided before seizures occur, for people at high risk of developing seizures (such as after severe brain injury), people with a learning disability, or people who have a strong family history of epilepsy. [2004]

Essential information on how to recognise a seizure, first aid, and the importance of reporting further attacks should be provided to a person who has experienced a possible first seizure and their family/carer/parent as appropriate. This information should be provided while the individual is awaiting a diagnosis and should also be provided to family and/or carers. [2004]

\textbf{Evidence statement}

Information is needed on managing the condition in children with new onset seizures. (III)
The Child Report of Psychosocial Care Scale was used to measure children’s satisfaction with healthcare received, need for information and support and seizure-related concerns and fears in children with new-onset seizures. The sample of 63 children (33 girls and 30 boys), 8-14 years, completed the scale two times, 3 months and 6 months after their first seizure. Results indicated that children wanted information related to the seizure condition, especially managing their condition, and support, in the form of talking to other children with seizures.

Investigations

This should relate to initial outpatient appointment with the appropriate specialist/epilepsy specialist nurse and any subsequent follow up appointments

Information should be provided to individuals and families and/or carers as appropriate on the reasons for tests, their results and meaning, the requirements of specific investigations, and the logistics of obtaining them. [2004]

Evidence statement

Adults want information about the reasons for tests, the results and meaning of these results. (III)

Details

Dilorio 1993

A US study of 59 adults with epilepsy (mean 39.3 years, range 19 to 60 years) found that individuals, nurses, and doctors similarly ranked major areas of learning need. However there were differences in the ranking of individual learning needs. Although this study did not relate the learning need to timing, both the results of tests and the reasons for such tests were ranked higher by individuals than by healthcare providers, and it could be argued that this information would be best provided when tests are ordered/ performed and results are discussed.

Ridsdale 2002

A UK RCT of a nurse intervention recruited 90 adults with newly diagnosed epilepsy (mean age 40 years, range 17 to 83 years). A sub group of 31 individuals were identified for interview in the qualitative arm of the trial, 24 agreed to participate. Some found a diagnosis of epilepsy when test results were normal confusing.
Diagnosis

This should relate to initial outpatient appointment with specialist / epilepsy specialist nurse and any subsequent appointments as appropriate

People with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). [2004]

Individuals and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. [2004]

Evidence statements

Adults want the diagnosis to be confirmed and counselling to be available. (III)

Adults want basic information on epilepsy (what it is, causes, how common it is etc.) and some want more extensive information (education, employment, leisure, benefits, social implications etc). (III)

Younger and middle aged people want information on epilepsy and driving. (III)

Older people with epilepsy want to learn about their new condition in addition to managing current ones, including the complications of adding new drugs to the current regime. (III)

There is a need for information to be given to carers to enable them to help the individual with epilepsy manage their condition, as well as to intervene effectively when they are unable to help themselves. (III)

Bereaved relatives would like information on epilepsy to be provided automatically to the individual with epilepsy either on or soon after diagnosis. (III)

Individuals with epilepsy and their families should be informed about the risks of sudden death, but there is uncertainty about making this information more generally available. (III)

Children want an explanation of the diagnosis. (III)

Families want provision of information, addressing concerns and concerns and fears, and providing emotional support as soon as possible after diagnosis. (III)

Details

Averis 1996\textsuperscript{364}

In an Australian questionnaire survey of 200 adults with epilepsy who attended a specialist clinic, confirmation of the diagnosis was rated as the second most important factor in the management of epilepsy (after availability of the doctor at time of need). The staff of the clinic believed that education should begin at diagnosis and cover topics as they become relevant to the individual.
The CSAG report stated that many older people would have liked counselling and more time with
the doctor or nurse at the time of diagnosis.

Goldstein 1997

In a UK survey of 94 adults with epilepsy attending a tertiary clinic, 73% of the 70 respondents
at diagnosis were told what epilepsy was, but only 42% properly understood the explanation.
31.4% of respondents would have liked basic information on epilepsy (what it is, causes etc) -
40% would have liked extensive information (education, employment, leisure, benefits etc) and
17.1% would have liked both. 4.3% did not want to know more about epilepsy.

May 2002

In an RCT to evaluate the use of an educational package to improve adults' knowledge and
understanding of their epilepsy, there was no difference in the levels of improvement between
those with a long and short duration of epilepsy (<=5 years vs >5 years). However, the authors
suggested that it was reasonable to offer an educational program as soon as possible after
diagnosis.

Buck 1996

In a UK community based survey of 677 adults with epilepsy, the duration of epilepsy influenced
the likelihood that individuals would discuss social implications; 79% of those with a reported
duration of less than one year compared with only 59% of those with a duration of more than 10
years (difference in proportions 11, 95% CI 2 to 20). The authors suggested that this may be
because individuals come to accept the social implications of epilepsy in time, or that doctors
assume this to be the case. Another reason offered was that individuals believe that it is less
appropriate to discuss social issues (as opposed to clinical issues) when there are time constraints
in the consultation.

Ridsdale 2002

A UK RCT to evaluate the effect of a nurse intervention on knowledge of epilepsy, satisfaction,
and well-being recruited 90 adults with newly diagnosed epilepsy (mean age 40 years, range
17 to 83 years). A sub group of 31 individuals were identified for interview in the qualitative
arm of the trial, 24 agreed to participate. Younger and middle aged people reported more
difficulty in dealing with the diagnosis, particularly with respect to driving. Older individuals
frequently had other medical problems and in this context, a new diagnosis of epilepsy seemed
to disturb them less. The main challenge for this group was to learn about their new condition in
addition to managing current ones, including the complications of adding new drugs to the current
regime. Many individuals reported being able to accept the diagnosis more after a nurse
explained how common epilepsy is. Safety information was appreciated, and many reported
receiving written information on request. Other issues raised were treatment (taking the pills,
what to do when forgotten, interactions, side effects, free prescriptions etc). The authors
concluded that challenges of coming to terms with the diagnosis and self-management were
different for individuals of different ages. In this context, nurses provided time and an approach
which allowed individuals to remember their own questions and remember the specific information
they required. The hypothesis of the nurse intervention (allied to information provision) being
valued by individuals most when they are first diagnosed was supported.
In an interview study of adults with epilepsy (mean age 47 years, range 18 to 75 years) individuals felt that information about the diagnosis was extremely important. Specifically 3 individuals who had been children when they were diagnosed reported that explanations were given to their parents, but not to them.

Austin 2002

In a before and after study of an psychoeducational intervention study, comments from the 10 participant families of children with epilepsy indicated that the intervention would be most effectively administered early in the course of the disorder. The tailored intervention included provision of information, addressing concerns and concerns and fears, and providing emotional support.

Kennelly 2002

In an interview study of 78 semi-structured interviews with the bereaved relatives of individuals with epilepsy who had died of SUDEP, several issues around the provision of information were identified. The relatives wanted ‘information on epilepsy to be provided automatically to the individual either on or soon after diagnosis’. They also stressed the need for information to be given to carers as well as the individual with epilepsy to ‘enable them to help them manage their condition, as well as to intervene effectively when they are unable to help themselves’.

Elwyn 2003

Focus group interviews with 19 individuals with epilepsy identified both a lack of support at diagnosis and a lack of time and encouragement to express their concerns, which was particularly important at diagnosis.

Information needs and SUDEP

Information on SUDEP should be included in literature on epilepsy to show why preventing seizures is important. Tailored information on the individual’s relative risk of SUDEP should be part of the counselling checklist for people with epilepsy and their families and/or carers. [2004]

The risk of SUDEP can be minimized by:

- optimising seizure control
- being aware of the potential consequences of nocturnal seizures. [2004]

Tailored information and discussion between the individual with epilepsy, their family and/or carers (as appropriate) and healthcare professionals should take account of the small but definite risk of SUDEP. [2004]

Where families and/or carers have been affected by SUDEP, healthcare professionals should contact families and/or carers to offer their condolences, invite them to discuss the death, and offer referral to bereavement counselling and a SUDEP support group. [2004]
Evidence statements

Bereaved relatives would like individuals with epilepsy to be presented with information on the risk of SUDEP during a face-to-face consultation by the responsible medical professional, either at or soon after diagnosis. (III)

Bereaved relatives need information from medical professionals to help them come to terms with the death of a person from SUDEP. (III)

Details

Kennelly 2002370

In an interview study of 78 semi-structured interviews with the bereaved relatives of individuals with epilepsy who had died of SUDEP, several issues around the provision of information were identified. There was an expressed dissatisfaction with the level of information provided either to them or to their carers.

There was some uncertainty about whether information about SUDEP should be more generally available. They felt that people with epilepsy and their families should be informed about the risks of sudden death. They also felt that information on the risks were vital as they themselves sometimes trivialised the seriousness of the condition. Information on SUDEP in epilepsy literature would have allowed them to take preventative measures, or at least be better prepared when the sudden death occurred. However, other relatives felt that SUDEP should not be over-emphasised as the risks are relatively low and people with epilepsy might live in greater fear than necessary.

Most relatives thought that the most effective way to present individuals with information on the relatively rare risk of sudden death was during a face-to-face consultation by the responsible medical professional, either at or soon after diagnosis.

Bereaved relatives needed information from medical professionals to help them come to terms with the death. However they reported difficulties in accessing medical professionals, particularly the specialist responsible for managing the care of the person with epilepsy. The authors recommended that

‘it should be standard practice after a sudden death from epilepsy for the medical professional in charge to offer an appointment to the bereaved relatives to discuss the case. This would offer families the opportunity to ask questions to which they want answers and to gain greater understanding of why the death occurred. This could greatly help in the grieving process.’370

Many relatives said that they needed additional support during the months after a sudden death. Suggestions included the establishment of a local support network in which local health services offer bereaved families a needs assessment and provide a named contact for regular checks and reviews of their situation. Relatives felt that the most appropriate people to take responsibility for providing this service were local primary care staff or support group staff.
Drug treatment

Information that is provided about anti-epileptic drugs (AEDs) needs to be in the context of that provided by the manufacturer, for example, indications, side effects and licence status. [2004]

Details

As could be expected, there was considerable evidence on the information needs of individuals with epilepsy and others with regard to drug treatment, side effects, etc. However, no mention of preferred timing was given.

Other treatment

No evidence on the information needs of individuals on non-drug treatments could be found.

Remission

Mills 1997

A UK questionnaire survey found that in 394 adults with epilepsy, people who had had an attack in the past 12 months were more likely to want discussion of topics (causes, side effects, laws etc), significantly so for hospital attenders but not for GP attenders. However, the perceived adequacy of information was similar for both settings.

Refractory Epilepsy and Surgery

Information should be provided to individuals and families and/or carers as appropriate about the reasons for considering surgery. The benefits and risks of the surgical procedure under consideration should be fully explained before the individual's informed consent is obtained. [2004]

Evidence statement

Individuals want accurate and balanced information on surgery. (III)

Swarztrauber 2003

Focus group interviews were conducted with adults, including a sub-group of African Americans, and adolescents with refractory epilepsy, and their parents. The aim of the interviews was to determine how individuals felt about current treatments for refractory epilepsy and to describe their experiences.
Adults wanted more information on the surgical treatment of epilepsy. They also had perceptions of exaggerated risks of surgery, and many participants felt that surgery was a ‘last ditch effort’ and ‘experimental’. Many adults felt that physicians portrayed surgery in a negative way.

Parents wanted their children to be able to take part in the decision about surgery when the child was old enough.

Special groups – see relevant sections
12.4 What is the risk of SUDEP in individuals with epilepsy

Evidence Statement

For those with severe epilepsy, a death rate of 1:200 per year can be estimated, whereas on a population basis the rate is between 1:500 and 1:1000 per year implying that for mild idiopathic epilepsy the rate is less than 1:1000. For those in remission the risk appears to be negligible. (III)

Details

A summary of the risk of death from SUDEP in key groups of people with epilepsy was requested by the GDG. This information could be used in recommendations on individual information and advice.

A systematic review of the literature relating to the incidence and prevalence of SUDEP and its possible risk factors was not done for reasons presented in Chapter 2.

The literature review on SUDEP from the SUDEP Report19 is presented and a further review article was identified that summarized the available evidence on the mortality associated with epilepsy up to 1996.374

Secondary evidence

The National Sentinel Clinical Audit of Epilepsy-Related Death19

In chronic epilepsy, SUDEP is the main cause of excess mortality, and in this group of people the mortality rate has been found to be 4.5 times higher than expected, with more than half attributed to SUDEP.18 In the UK it is estimated that 500 deaths per annum are SUDEP. Young people with severe epilepsy and learning disability may be at even higher risk of SUDEP, with one recent study showing a death rate 15.9 times greater than expected.375

SUDEP is defined376 as: ‘sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in individuals with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomic cause for death.’

Case-control studies have been used to determine possible risk factors for SUDEP. Reported risk factors 377 for SUDEP include:

- young age
- generalised tonic-clonic seizures
- uncontrolled epilepsy
- learning disability
- seizures occurring during sleep
unwitnessed seizures and poor adherence to antiepileptic drug regimen.

The most significant risk factor shown by case-controlled studies, however, is the occurrence of seizures, and the risk of SUDEP appears to be directly related to the frequency of seizures.\textsuperscript{378} Indeed, most of the excess mortality of epilepsy is related to seizure frequency. In a recent case control study, Nilsson and colleagues reported that people who had not been seizure free during the year had a 23-fold increased risk of SUDEP compared to people with fully controlled seizures.\textsuperscript{378} Tomson,\textsuperscript{379} in a review of published studies, concluded that the risk of SUDEP is 40 times higher in people who continue to have seizures. Sperling and colleagues found that elimination of seizures after surgery reduced the mortality rate in people with epilepsy to a level indistinguishable from that of the general population.\textsuperscript{380} They suggested that uncontrolled seizures are a major risk factor for excess mortality in epilepsy. The reason for this relationship seems to be that most SUDEPs are seizure-related.\textsuperscript{377,378,381,382}

In line with other studies of risk it is important that the relative risk is not used alone as this does not indicate how common or uncommon the condition is in the population under study. It is important that an indication of the absolute risk of SUDEP is given in different population groups with epilepsy.

O'Donoghue 1997\textsuperscript{374}

This narrative review clearly sets out the methodological problems associated with the epidemiology of epilepsy mortality. Three strategies have been used to study the incidence of SUDEP:

1) rates of death in large population using death certificates and coroners' reports;

2) antiepileptic drug prescription as a surrogate for the diagnosis of epilepsy and

3) follow up of a cohort of people with epilepsy for a defined period of time.

Approaches 1 & 2 have particular problems relating to the accuracy and completeness of ascertainment of the number of deaths and the size of the population studied. Approach 3 is prone to selection bias as the cohort studied may be attendees at specialist tertiary centers rather than the whole population of people with epilepsy.

The authors discussed the evidence in relation to different groups of people with epilepsy, identifying that those with refractory epilepsy awaiting surgery have the highest risk of SUDEP and those in remission the lowest rate. They drew the following conclusions from their review:

- Comparison of population-based and cohort studies revealed that for those with severe epilepsy, a death rate of 1:200 per year can be estimated, whereas on a population basis the rate is between 1:500 and 1:1000 per year implying that for mild idiopathic epilepsy the rate is less than 1:1,000. For those in remission the risk appears to be negligible.\textsuperscript{374}
13 Women of childbearing age with epilepsy

13.1 Introduction

Most women with epilepsy who are receiving optimal treatment for their epilepsy, and who are well-informed, supported and fully counselled have uncomplicated pregnancies, normal deliveries, and healthy children.

However, there are a number of important health-related issues relating to the diagnosis of epilepsy and the use of AEDs in women of child-bearing age. First, both the disease and its treatment may alter the menstrual cycle and fertility. Second, there are problems with drug interactions, particularly with hormonal contraceptives. Some methods of hormonal contraception may not be as effective in women taking AEDs. The effectiveness will depend on which AED(s) are being taken. Effective contraception has an additional importance in women with epilepsy because of the risks associated with an unplanned pregnancy to the women and the developing fetus. Third, AEDs are associated with teratogenic effects. Fourth, AEDs and uncontrolled seizures can cause adverse effects during pregnancy. Conversely, pregnancy and the menstrual cycle can affect seizure control due to hormonally induced alteration of the seizure threshold.383

13.2 What information and counselling should be given and when?

In order to enable informed decisions and choice, and to reduce misunderstandings, women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause. [2004]

Information about contraception, conception, pregnancy, or menopause should be given to girls and women in advance of sexual activity or pregnancy, or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with girls and women with epilepsy. These may include an individual’s family and/or carers. [2004]

All healthcare professionals who treat, care for, or support women with epilepsy should be familiar with relevant information and the availability of counselling. [2004]

Evidence statements

Women with epilepsy want, and need, information and counselling about issues relating to AED therapy and its effects, contraception, pregnancy, the risk of inheritance, and the menopause. (III)

Information is preferred before the time it is needed. (III)

Details

Secondary evidence

No systematic reviews of RCTs of information provision for women with epilepsy were identified.
One systematic review of other evidence was found. Couldridge and colleagues reviewed the primary evidence (including non-RCT studies) on the information and counselling needs of people with epilepsy, the preferred format, timing, and delivery of information and counselling, and the outcomes of information giving and counselling.359

None of the 40 included studies reported the role or effects of information or counselling in women with epilepsy as a group, although some studies did have women in the study population.

Primary evidence

No RCTs on the effectiveness of information giving or counselling were identified.

Since the publication of the systematic review described above359, two large surveys of women with epilepsy were found.

Crawford and Lee reported the results of a questionnaire survey of female members of the British Epilepsy Association. 1855 questionnaires (from a total of 6000) were included in the results (response rate 31%).

47% (n=89) of women taking oral contraception felt they had not been given enough information about the oral contraception pill and their AED(s). 43% (n=637) reported receiving no information about pregnancy, and 25% (n=459) had discussed pregnancy with no-one. Many women intending to have children in the subsequent two years felt they still had unanswered questions (see Figure 11-1).
Figure 11-1: Concerns about pregnancy\textsuperscript{384} Modified from Seizure, 8, Crawford P and Lee P, Gender difference in management of epilepsy - What women are hearing, pages 135-9, Copyright (1999) with permission from BEA Trading Ltd.

Overall, women felt there was a need for more information about epilepsy and pregnancy. The survey concluded that women with epilepsy wanted, and needed, more information and counselling about issues relating to contraception, pregnancy, and the menopause.\textsuperscript{384}

Crawford 2003\textsuperscript{385}

In 2001, the Ideal World survey aimed to assess the quality of current treatment information provision to women with epilepsy at different life stages, and to identify the information needs and wants with a view to ensuring that all women with epilepsy are counselled appropriately, in a timely manner, and are able to make informed choices about their treatment.

Approximately 12,000 female members of Epilepsy Action were surveyed, and the questionnaire was also posted on the Epilepsy Action website. 2,600 questionnaires and 90 web responses were completed, and 2000 responses randomly selected for analysis.

The most important issues for women aged 19 to 44 years who were considering having children were:

1. risk of epilepsy/medication affecting the unborn child (87%)
2. effect of pregnancy on seizure control (49%)
3. risk of a child developing epilepsy (42%)
For women aged 45 years or more, the most important issues were:

1. epilepsy medication and osteoporosis (63%)
2. epilepsy medication as you get older (57%)
3. changes in seizures during the menopause (44%).

Most women (84%) wanted to be better informed about treatment decisions, and 41% wanted to take a more proactive role in discussions around treatment. 43% wanted more information so they could ask for a review of their medication. 57% wanted the latest information on epilepsy treatment and the risk of birth defects on an ongoing basis, even if the data were incomplete.

The preferred timing of receiving information can be seen in 13.2.

Table 11-1: Preferred time to receive information Modified from Seizure, 12, Crawford P and Hudson S, Understanding the information needs of women with epilepsy at different lifestages: results of the 'Ideal World' survey, pages 502-7, Copyright (2003) with permission from BEA Trading Ltd.

<table>
<thead>
<tr>
<th>Effect of Epilepsy on:</th>
<th>Diagnosis (%)</th>
<th>Before Puberty (%)</th>
<th>At Puberty (%)</th>
<th>Before considering pregnancy (%)</th>
<th>When considering pregnancy (%)</th>
<th>Approaching menopause (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periods</td>
<td>35</td>
<td>32</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td>25</td>
<td>6</td>
<td>30</td>
<td>15</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>17</td>
<td>2</td>
<td>10</td>
<td>42</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Risk of child developing epilepsy</td>
<td>19</td>
<td>1</td>
<td>5</td>
<td>41</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>AEDs and pregnancy fetal development</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>43</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58</td>
</tr>
</tbody>
</table>

The survey showed consistently that information is preferred before the time it is needed. 59% wanted information in a written format, and 28% through conversation with a healthcare professional.
13.3 What issues should be considered in women who may become pregnant or who are breast feeding?

Women should be reassured that an increase in seizure frequency is generally unlikely in pregnancy or in the first few months after birth. [2004]

The clinician should discuss with the woman the relative benefits and risks of adjusting medication to enable her to make an informed decision. Where appropriate, the woman’s specialist should be consulted. [2004]

Generally, women may be reassured that the risk of a tonic-clonic seizure during the labour and the 24 hours after birth is low (1-4%). [2004]

All women with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that best suits her and her family. [2004]

Prescribers should consult Appendix 5 of the British National Formulary when prescribing AEDs for women who are breastfeeding. The decision on whether to continue AED therapy should be made between the woman and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. [2004]

Evidence Statements

Generally, seizure frequency does not change during pregnancy or in the early puerperium in women with epilepsy. (IIb)

In a minority there may be an increase in seizure frequency (15% to 37%). The explanation of an increase in seizure frequency is uncertain, but potential factors may include poor adherence with treatment, altered AED pharmacokinetics and sleep deprivation. (IIb)

1-2% of women with active epilepsy will have a tonic-clonic seizure during labour, and a further 1-2% in the following 24 hours. (III)

All the older antiepileptic drugs have been associated with malformations, with sodium valproate being associated with a significantly higher risk of malformations than carbamazepine. (Ia NICE)

Multiple drug therapy is associated with a greater risk, although this may be related to the severity of the mother’s epilepsy. (Ia NICE)

No high quality evidence on the possible effects of AED therapy while breastfeeding was found.

Details

Issues are:

- increased risk of seizures
- teratogenic effects of AEDs
Evidence statements, recommendations and reviews are presented for each of the four areas above. (For side effects, see Section on Pharmacological treatment)

13.4 Increased risk of seizures during pregnancy or whilst breastfeeding

Secondary evidence

No systematic reviews of seizure control during pregnancy were identified.

Primary evidence

Prospective cohort studies that assessed seizure frequency during pregnancy in women with epilepsy were included.

Five studies were identified that measured changes in seizure frequency during pregnancy (see 13.3). For each study different inclusion criteria were applied to participants, different time periods and different definitions of 'increased' or 'decreased' seizure rates were used. If no definition of seizure rate change was given, the study was excluded.
### Table 11-2: Seizure frequency during pregnancy and puerperium

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Number of participants</th>
<th>Definition of seizure rate change(s)</th>
<th>Increased</th>
<th>Unchanged</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardy 1987386</td>
<td>Women who had at least 2 epileptic seizures fulfilling the criteria of the WHO Dictionary of Epilepsy, with the first seizure occurring before pregnancy</td>
<td>154 pregnancies in 140 women</td>
<td>Increased if the number of seizures was 200% or more during pregnancy and 3 months after than in the 12 months before Decreased if the number of seizures was 50% or less during pregnancy and 3 months after than in the 12 months before</td>
<td>32%</td>
<td>54%</td>
<td>15%dd</td>
</tr>
<tr>
<td>Gjerde 1988387</td>
<td>Women who had epilepsy and used one or more AEDs for at least one year prior to pregnancy</td>
<td>78 pregnancies in 66 women</td>
<td>Increased if there was at least one more seizure during pregnancy than in the 9 month before pregnancy Decreased if there was at least one less seizure during pregnancy than in the 9 month before pregnancy</td>
<td>17%</td>
<td>67%</td>
<td>17%</td>
</tr>
<tr>
<td>Schmidt 1983388</td>
<td>Women who had three or more verified epileptic seizures who completed the pregnancy</td>
<td>136 pregnancies in 122 women</td>
<td>Increased or decreased if the actual seizure frequency changed, rather than a percentage (ie one more or one less seizure) during pregnancy and 3 months following delivery compared with the 9 months before pregnancy</td>
<td>37%</td>
<td>50%</td>
<td>13%</td>
</tr>
<tr>
<td>Tanganelli 1992389</td>
<td>Women with epilepsy</td>
<td>138 pregnancies in 97 women</td>
<td>Increased or decreased frequency defined as a 10% or more change during pregnancy when compared with the 9 months prior to pregnancy</td>
<td>17%</td>
<td>80%</td>
<td>3%</td>
</tr>
<tr>
<td>Tomson 1994390</td>
<td>Women who were treated with AEDs for epilepsy since the beginning of pregnancy</td>
<td>93 pregnancies in 70 women</td>
<td>Change in seizure frequency was defined as a movement from one frequency category to another (five categories ranging from seizure free to one seizure a week or more) when the rate during pregnancy was compared with the 9 months prior to the pregnancy</td>
<td>15%</td>
<td>61%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**dd** Percentages may not add to 100% due to rounding errors
Schmidt and colleagues assessed the factors associated with increased seizures and found that non-adherence to medication, sleep deprivation, and inadequate therapy influenced seizure rate.

Three studies\(^{386,388,389}\) reported seizure frequency in the first 3 months after the birth.

Bardy found a statistically significant increase in complex partial seizures during the early puerperium (\(p<0.001\)).\(^{386}\)

Increased seizures were seen in six pregnancies in the Schmidt study\(^{388}\) and non-adherence and sleep deprivation were associated with five of these.

Tanganelli and Regesta\(^{389}\) reported that during the puerperium, seizure frequency returned to pre-pregnancy levels in all but two women (2%, \(n=2/97\)).

Two studies reported seizures in labour. In 97 women with epilepsy, no seizures during labour occurred. In the other study,\(^{386}\) seizures occurred during labour in 10 cases, an incidence nine times greater than the average.

Bardy\(^{391}\) also reported that a generalised tonic-clonic seizure occurred in labour in approximately 1-2% of women with epilepsy, and within 24 hours of delivery in another 1-2%.

There are two main sources of possible bias in all of the trials above:

1. because the history of seizure frequency before pregnancy relies on recall by the woman and her family (and in some studies, from medical records) there may be an underestimate of seizure frequency before pregnancy.

2. because none of the studies compare seizure rates in pregnant women with those in women who are not pregnant, some of the changes in rate may be due to random fluctuations in the epilepsy, rather than the effect of pregnancy.
13.5 Teratogenic effects of AEDs whilst pregnant

13.5.1 Introduction

It is recognised that an unborn child may be put at risk if exposed to toxins, of which alcohol and
drugs, including prescribed medication are examples. Exposure to anti-epileptic drugs (AEDs)
during pregnancy is associated with an increased risk of congenital malformations, and may have
an adverse effect on foetal growth and psychomotor development. Although data on older AEDs
and risk of congenital malformation has been evident, that on newer agents is only just being
accumulated through pregnancy registries. Further, data on longer term affects on
neurodevelopment of children exposed in utero can only be obtained through prospective study
design. It is important that appropriate accurate information is made available to women so that
informed choices can be made.

13.5.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included children of pregnant women with epilepsy who were exposed to one or
more AEDs. Comparison groups included children of women with epilepsy who were not exposed
to AEDs and non exposed children of women from the general population (without epilepsy). We
looked for data specifically on the proportion of children born with major malformations, the
proportion of children born with minor malformations, the incidence of miscarriage and
developmental/cognitive outcomes. We found several systematic reviews for this review and
therefore did not perform a review for individual studies. The systematic reviews included
prospective controlled cohorts and case control studies.

Where the systematic reviews provided information on the individual included studies then the
results of each study were presented separately in this review. However, when the systematic
reviews presented pooled data and a meta-analysis could be performed then the results were
presented in this way. This evidence review is divided in two sections based on the types of
outcomes reviewed:

The first section presents evidence for minor/major malformations and miscarriage: We used a
systematic review and meta-analysis (Meador, 2008) of published pregnancy registries and
cohorts to pro on minor malformations, major malformations and miscarriage. This systematic
review included studies with at least 100 total pregnancies or births.

The second section presents evidence for developmental/cognitive outcomes: We used a
Cochrane review (Adab, 2004) and a meta-analysis of cohort studies (Banach, 2010) for
information on the developmental/cognitive outcomes. Adab (2004) included phenobarbitone,
phentoin, carbamazepine, oxcarbazepine, sodium valporate, lamotrigine, topiramate,
gabapentin, vigabatrin, tiagabine and zonisamide. These AEDs were either taken as monotherapy
or polytherapy. The Banach (2010) review included sodium valproate. The Meador (2008) review included carbamazepine, lamotrigine, phenobarbital, phenytoin and valproate, taken as
monotherapy or polytherapy.

Table 11-3: Cognitive scales

<table>
<thead>
<tr>
<th>Full name of the scale</th>
<th>Scales abbreviations</th>
<th>Brief description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley scales of development</td>
<td>An age standardised test of infant development between one month to 42 months. Measure development in 3 domains;</td>
<td>Significant delay for scores with 2 SD below the mean, e.g. score&lt;70.</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griffiths child development scale</td>
<td>Assess 5 areas of children development; locomotor, personal, social, hearing and speech, eye and hand co-ordination, performance. 2 scales for children 0-2 years and 2-8 years. Each scale scored independently and summating all the subscales given the total DQ. Global delay is a DQ&lt;70.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Intelligence scale for children WISC</td>
<td>A measure of general intellectual functioning for children aged 6-16 years. 12 subsets assessing 2 areas of intelligence: verbal IQ (VIQ) and performance (PIQ), summated provide a composite score (FSIQ).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler preschool and primary scale intelligence WIPPSI</td>
<td>A measure of general intellectual functioning for children aged 6-16 years.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbia Mental Maturity scale CMMS</td>
<td>Assess general reasoning ability in children aged 3-9 years. Raw score, age deviation score, percentile rank, stanine and maturity index.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illinois test of psycholinguistic abilities ITPA</td>
<td>A measure of used and acquisition of language for children aged 4-8 years. 10 subsets and 2 supplementary subsets. Raw scores used to derive a composite score, psycholinguistic age scores and psycholinguistic quotients for subtests and composite.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frostig test of visual perception FTVP</td>
<td>Assess visual perception skills in children aged 4-8 years. 5 subsets. Raw scores obtained for each subset and converted to age equivalents or perceptual ages (Pas) and Scale Scores (SS); total score expressed in Perceptual Quotient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincoln Oseretzy test of Motor Performance LOS</td>
<td>A measure of motor performance for children 6-14 years. 36 subscales. Scores presented as percentile ranks for each age level.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCarthy Scales McC</td>
<td>A measurement device to assess the abilities of preschool children 2.5-8.5 years. Six scale scores: verbal, perceptual-performance, quantitative, general cognitive, memory, motor.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiter international performance scale LIPS</td>
<td>Non verbal test of intelligence. Assess intellectual ability, memory and attention for those whom traditional test could not be used between 2-20 years. 2 main batteries; visualisation and reasoning (VR) and attention and memory (AM). Each battery provides a measure of IQ SCORES.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychological test battery adapted from Luria NEPS</td>
<td>A standardized test battery used in the screening and evaluation of neuropsychologically impaired individuals 13 years old and older. It consists of 269 items in 11 clinical scales. Scores for three summary scales can also be calculated: pathognomonic, right hemisphere, and left hemisphere.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School career</td>
<td>Being in inappropriate class for age and learning disorders Frequency (proportion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch test</td>
<td>3 subtests; reading, spelling, arithmetic. Proportion of children with score&lt; 10th centile</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
13.5.2.1 Incidence of malformations

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Congenital malformations - statistically significant results

Significantly more children of women taking the following AEDs had congenital malformations compared to general population:

- Valproate
- Phenobarbital and one other AED
- Phenytoin and one other AED
- Valproate and one other AED
- Phenobarbital and two other AEDs
- Phenytoin and two other AEDs
- Valproate and two other AEDs

Significantly more children of women taking the following AEDs were born with malformations compared to general population:

- Carbamazepine
- Valproate

Cost-effectiveness
No economic evidence comparing exposure to any AED to non-exposure in the general population was identified.

13.5.2.2 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to monotherapy compared to general population

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Congenital malformations/other pregnancy outcomes - statistically significant results

The incidence of stillbirth was significantly higher in children exposed in utero to monotherapy compared to children in general population, however there is uncertainty over the magnitude of its effect. (VERY LOW QUALITY)^

The incidence of spontaneous abortions was significantly higher in children in general population compared to children exposed in utero to monotherapy. (VERY LOW QUALITY)^

The incidence of elective abortions was significantly higher in children in general population compared to children exposed in utero to monotherapy. (VERY LOW QUALITY)^
The incidence of births with congenital malformation was significantly higher in children exposed in utero to monotherapy compared to children in general population. (VERY LOW QUALITY) ^

The incidence of perinatal deaths was significantly higher in children exposed in utero to monotherapy compared to children in general population. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any monotherapy to non-exposure in the general population was identified.

13.5.2.3 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to polytherapy compared to general population

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Congenital malformations/other pregnancy outcomes- statistically significant results

The incidence of spontaneous abortions was significantly higher in children in general population compared to children exposed in utero to polytherapy. (VERY LOW QUALITY) ^

The incidence of elective abortions was significantly higher in children in general population compared to children exposed in utero to polytherapy. (VERY LOW QUALITY) ^

The incidence of elective abortions due to malformations was significantly higher in children exposed in utero to polytherapy compared to children in general population, however there is uncertainty over the magnitude of its effect. (VERY LOW QUALITY) ^

The incidence of births with congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY) ^

The incidence of congenital malformations (total events) was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY)

The incidence of perinatal deaths was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY) ^

Cost-effectiveness
No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.2.4 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to monotherapy compared to polytherapy1
Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Congenital malformations/other pregnancy outcomes—statistically significant results
The incidence of births with congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in monotherapy. (VERY LOW QUALITY)
The incidence of congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in monotherapy. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any polytherapy to exposure to any monotherapy was identified.

13.5.3 Comparison between specific monotherapies on developmental/cognitive outcomes
13.5.3.1 Phenytoin versus carbamazepine
Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/Cognitive outcomes—statistically non-significant results
No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the following developmental/cognitive scales:
  • Bayley scale (mental, motor, language, cognitive) (VERY LOW QUALITY)
  • McCarthy scale of children's abilities (GCI T, verbal, perceptual, quantitative, memory, motor over 30 months) (VERY LOW QUALITY)
  • Reynell standard scores (comprehension, expressive) (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenytoin monotherapy to carbamazepine monotherapy was identified.
13.5.3.2 Phenytoin versus phenobarbitone

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes – statistically non significant results
No significant difference between phenytoin monotherapy and phenobarbitone monotherapy for the following developmental/cognitive scales:

- Gesell developmental schedules (VERY LOW QUALITY)
- Mental development (8 months) (VERY LOW QUALITY)
- Motor development (8 months) (VERY LOW QUALITY)
- IQ (4 years) (VERY LOW QUALITY)
- WISC/WPPSI (4-9 years) (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing phenytoin monotherapy to phenobarbitone monotherapy was identified.

13.5.3.3 Phenobarbitone versus carbamazepine

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes – statistically non significant results
No significant difference between phenobarbitone monotherapy and carbamazepine monotherapy for the Dutch test (non optimal school career, poor reading, poor arithmetic, poor spelling) (VERY LOW QUALITY).

Cost-effectiveness
No economic evidence comparing phenobarbitone monotherapy to carbamazepine monotherapy was identified.

13.5.3.4 Sodium valproate versus carbamazepine

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes - statistically significant results
Children exposed to sodium valproate monotherapy scored significantly lower compared to children exposed to carbamazepine monotherapy in utero for:
- WPPSI/WISC revised verbal IQ scale, however there is uncertainty over the magnitude of this effect. (VERY LOW QUALITY)
- Bayley scales – mental and differential ability scale, however there is uncertainty over the magnitude of this effect. (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of children with mild to severe developmental delay (4mths – 10 years)
No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the following developmental/cognitive scales:
- WPPSI/WISC revised non verbal IQ scale (VERY LOW QUALITY)
- WPPSI/WISC revised full scale (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing sodium valproate monotherapy to carbamazepine monotherapy was identified.

13.5.3.5 Sodium valproate versus phenytoin

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes
No significant difference on the Bayley scale in children exposed to sodium valproate and phenytoin. (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing sodium valproate monotherapy to phenytoin monotherapy was identified.

14.5.3.6 Sodium valproate versus lamotrigine

Clinical Evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes

Children exposed to valproate scored significantly lower on the Bayley scale compared to children exposed to lamotrigine. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to lamotrigine monotherapy was identified.

13.5.4 Any monotherapy exposure versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to monotherapy scored significantly lower compared to non exposed children in general population for:

- WPPSI (performance and total scale) (10-20 years) (VERY LOW QUALITY)
- LOS scale (4-6 years) (VERY LOW QUALITY)
- WISC performance IQ (10-19 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to monotherapy and non exposed children in general population for the proportion of children with borderline intelligence and children with learning disabilities (VERY LOW QUALITY)

No significant difference between children exposed to monotherapy and non exposed children in general population for the following developmental/cognitive scales:

- Bayley Scales (mental, motor) (15 months) (VERY LOW QUALITY)
Co
st-effectiveness
No economic evidence comparing exposure to any monotherapy to non-exposure in the general population was identified.

13.5.4.1 Carbamazepine exposure versus no exposure in general population
Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes - statistically significant results
Children exposed to carbamazepine scored significantly lower compared to non exposed children in general population for:

- McCarthy GCI, verbal, perceptual, quantitative, memory and motor scores (early years) (VERY LOW QUALITY)
- Bayley mental development index (early years) (VERY LOW QUALITY)\(^\)
- McCarthy Global development index (early to school years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to carbamazepine and non exposed children in general population for the following developmental/cognitive scales:

- Reynell Scales (comprehension, expressive) (early years) (VERY LOW QUALITY)
- Bayle Scales (mental, performance, cognitive, language, motor) (early years) (VERY LOW QUALITY)
- Griffiths child development scale (early years, early to school years) (VERY LOW QUALITY)
- McCarthy (early to school years) (VERY LOW QUALITY)
- Dutch test for poor outcomes (reading, spelling, arithmetic, school career) (early to school years) (VERY LOW QUALITY)

\(\)
• WPPSI-R/WISC-R (verbal, non verbal IQ, full scale) (early to school years) (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to carbamazepine to non-exposure in the general population was identified.

13.5.4.2 Phenytoin exposure versus no exposure in general population

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes - statistically significant results
Children exposed to phenytoin scored significantly lower compared to non exposed children in general population for:

• Bayley scale-language (early to school years) (LOW QUALITY)
• McCarthy scale (GCI, verbal, perceptual, quantitative) (early to school years) (LOW QUALITY)
• Reynell scale (comprehension, expressive) (early to school years) (LOW QUALITY)
• IQ (4 years) (LOW QUALITY)

Developmental/cognitive outcomes - statistically non significant results
No significant difference between children exposed to phenytoin and non exposed children in general population for the following developmental/cognitive scales:

• Griffiths child development index (VERY LOW QUALITY)
• Mental scale (specific tests not detailed) (8 months) (VERY LOW QUALITY)
• Motor scale (specific tests not detailed) (8 months) (VERY LOW QUALITY)
• Gesell development quotient (VERY LOW QUALITY)
• Bayley scales (MDI, PDI, cognitive, language, motor) (VERY LOW QUALITY)
• McCarthy scales (memory, motor) (VERY LOW QUALITY)
• WISC/WPPSI (VERY LOW QUALITY)


Cost-effectiveness
No economic evidence comparing exposure to phenytoin to non-exposure in the general population was identified.

13.5.4.3 Phenobarbitone exposure versus those no exposure in general population

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically significant results
Significantly more children exposed to phenobarbitone compared to non exposed children in general population had low scores (<10th centile) in:
- Dutch test for spelling (LOW QUALITY)
- Dutch test for arithmetic (LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to phenobarbitone and non exposed children in general population for the following developmental/cognitive scales:
- Mental development scale (specific tests not detailed) (VERY LOW QUALITY)
- Motor development scale (specific tests not detailed) (VERY LOW QUALITY)
- Gesell development quotient (VERY LOW QUALITY)
- IQ test (not specified) (VERY LOW QUALITY)
- Dutch test for reading (VERY LOW QUALITY)
- School career (VERY LOW QUALITY)
- WISC/WIPPSI (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to phenobarbitone to non-exposure in the general population was identified.

13.5.4.4 Sodium valproate exposure versus no exposure in general population

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically significant results
Children exposed to sodium valproate scored significantly lower than no exposed children in the general population in the WPPSI-R/WISC-R verbal IQ scale. (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non-significant results

No significant difference was found on either scale of IQ (verbal, performance and full scale) between children exposed to sodium valproate in utero and general population (non exposed children of non epileptic mothers) (VERY LOW QUALITY).

No significant difference was found on non verbal and full scale of WPPSI-R/WISC-R between children exposed to sodium valproate in utero and general population (non exposed children of non epileptic mothers) (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing exposure to sodium valproate to non-exposure in the general population was identified.

13.5.4.5 Comparison of any AED versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to any AED compared to non exposed children in general population had significantly low scores in:

- Bayley scale (motor, home inventory) (15 months) (VERY LOW QUALITY)
- Gesell development scale (18-36 months) (VERY LOW QUALITY)
- Enjohiji’s test (fundamental habits, human relationships, speech, language in infants < 24 months) (fundamental habits, body movement, hand movement, human relationships, speech, language in infants 24-53 months) (VERY LOW QUALITY)
- WPPSI scale (5.5 years) (VERY LOW QUALITY)
- LIPS scale (5.5 years) (VERY LOW QUALITY)
- Proportion of children with specific cognitive dysfunction (VERY LOW QUALITY)
- WPPSI scale (verbal, performance) (4-6 years) (VERY LOW QUALITY)
- CMMS scale (VERY LOW QUALITY)
- FTVP scale (VERY LOW QUALITY)
- LOS scale (VERY LOW QUALITY)
- WPPSI/WISC scale (proportion of children with IQ<90) (4-9 years) (VERY LOW QUALITY)
• WPPSI/WISC scale (proportion of children with language disability), however there is uncertainty over the magnitude of its effect (4-9 years) (VERY LOW QUALITY)
• WPPSI/WISC scale (full scale) (4-8 years) (VERY LOW QUALITY)
• WISC scale (verbal, performance) (4-8 years) (VERY LOW QUALITY)
• VMI scale (4-8 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to any AED and non exposed children in general population for the following developmental/cognitive scales:
• Griffiths development scale (VERY LOW QUALITY)
• Enjohiji’s test (body, hand movement in infants<24 months) (VERY LOW QUALITY)
• Proportion of children with mental deficiency, borderline intelligence (5.5 years) (VERY LOW QUALITY)
• ITPA scale (VERY LOW QUALITY)
• McCarthy scale (VERY LOW QUALITY)
• WPPSI/WISC scale (proportion of children with learning disabilities) (4-9 years) (VERY LOW QUALITY)
• WPPSI/WISC scale (proportion of children with special education needs) (4-9 years) (VERY LOW QUALITY)
• ITPA (auditory association, grammatic closure) (4-8 years) (VERY LOW QUALITY)
• Griffiths scale (locomotor function, personal and social behaviour, hearing and speech, eye and hand coordination, performance, practical reasoning) (VERY LOW QUALITY)
• Dutch test (reading, spelling, arithmetic) (7-13 years) (VERY LOW QUALITY)
• School career (7-13 years) (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any AED to non-exposure in the general population was identified.

13.5.4.6 Any polytherapy exposure versus those no exposure in general population

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes- statistically significant results
Children exposed to polytherapy compared to non exposed children in general population had significantly low scores in:
• Bayley Motor scale (15 months) (VERY LOW QUALITY)
• CMMS scale (4-6 years) (VERY LOW QUALITY)
• ITPA scale (4-6 years) (VERY LOW QUALITY)
• WPPSI scale (4-6 years) (VERY LOW QUALITY)
• Performance scale (4-6 years) (VERY LOW QUALITY)
• McCarthy scale (4-6 years) (VERY LOW QUALITY)
• WPPSI scale (verbal, performance, total scale) (10-20 years) (VERY LOW QUALITY)
• WPPSI-R/WISC-R verbal IQ scale (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:
• Bayley Mental scale (15 months) (VERY LOW QUALITY)
• Proportion of children with mild-severe developmental delay (early to school years) (VERY LOW QUALITY)
• FTVP scale (4-6 years) (VERY LOW QUALITY)
• LOS scale (VERY LOW QUALITY)
• WISC scale (verbal IQ, performance IQ, total IQ) (10-19 years) (VERY LOW QUALITY)
• Proportion of children with borderline intelligence (VERY LOW QUALITY)
• Proportion of children with learning disability (VERY LOW QUALITY)
• WPPSI-R/WISC-R scale (non verbal IQ, total scale) (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any polyherapy to non-exposure in the general population was identified.

13.5.4.7 Any AED exposure in utero versus no exposure in children of mothers with epilepsy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes- statistically significant results
Children exposed to polytherapy compared to non exposed children in general population had significantly low scores in:
• WPPSI Performance scale (4-6 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:
• Bayley scale (mental, motor, home inventory) (15 months) (VERY LOW QUALITY)
• WPPSI scale (5.5 years) (VERY LOW QUALITY)
LIPS scale (5.5 years) (VERY LOW QUALITY)
Dutch test (reading, spelling, arithmetic) (VERY LOW QUALITY)
School career (7-13 years) (VERY LOW QUALITY)
WPPSI Verbal scale (4-6 years) (VERY LOW QUALITY)
ITPA scale (4-6 years) (VERY LOW QUALITY)
FTVP scale (4-6 years) (VERY LOW QUALITY)
LOS scale (4-6 years) (VERY LOW QUALITY)
McCarthy scale (4-6 years) (VERY LOW QUALITY)
WPPSI scale (verbal, performance, total IQ) (10-19 years) (VERY LOW QUALITY)
Proportion of children with borderline intelligence (VERY LOW QUALITY)
Proportion of children with learning disability (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.4.8 Any monotherapy exposure versus no exposure in children of mothers with epilepsy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Developmental/cognitive outcomes – statistically non significant results
No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:
- Dutch test (reading, spelling, arithmetic) (7-13 years) (VERY LOW QUALITY)
- School career (7-13 years) (VERY LOW QUALITY)
- WISC scale (verbal, performance, total IQ) (10-19 years) (VERY LOW QUALITY)
- WPPSI scale (verbal, performance, total IQ) (VERY LOW QUALITY)
- Proportion of children with borderline intelligence (VERY LOW QUALITY)
- Proportion of children with learning disability (VERY LOW QUALITY)

Cost-effectiveness
No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.
13.5.4.9 Carbamazepine exposure versus no exposed children of women with epilepsy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically non significant results
No significant difference was found on any scale of WPPSI-R/WISC-R between children exposed to carbamazepine in utero and general population (non exposed children of non epileptic mothers) (VERY LOW QUALITY).

Cost-effectiveness
No economic evidence comparing exposure to carbamazepine to non-exposure in women with epilepsy was identified.

13.5.4.10 Sodium valproate exposure versus no exposed children of women with epilepsy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically significant results
Children exposed to sodium valproate scored significantly lower than non exposed children of women with epilepsy in:
- WPPSI-R/WISC-R verbal IQ (VERY LOW QUALITY).

Developmental/cognitive outcomes – statistically non significant results
No significant difference was found on WPPSI-R/WISC-R (non verbal, full scale) between children exposed to sodium valproate in utero and non exposed children of epileptic mothers (VERY LOW QUALITY).

No significant difference was found on either scale of IQ (verbal, performance and full scale) between children exposed to sodium valproate in utero and non exposed children of epileptic mothers (VERY LOW QUALITY).

Cost-effectiveness
No economic evidence comparing exposure to sodium valproate to non-exposure in women with epilepsy was identified.
### Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Discuss with women of childbearing potential the risk of AEDs causing malformations and neurodevelopmental delay to an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Risk of continued use of sodium valproate to the unborn child should specifically be discussed [new 2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The GDG placed greater importance on the incidence of major malformations, miscarriages and neurodevelopmental outcomes for the child of a mother with epilepsy.</td>
</tr>
<tr>
<td>Trade off between clinical benefits and harms</td>
<td>The risk of harm to mother and unborn child from seizures needs to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. Drugs and doses that may be cost-effective in the general epilepsy population, such as sodium valproate, may not be as cost-effective in this group due to its potential teratogenic effect.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Evidence comes from three systematic reviews; one review focused on incidence of malformation and the other two on child neurodevelopmental outcomes. No individual RCTs were reviewed. This recommendation was also based on GDG consensus opinion.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>This recommendation was updated from the first edition of this guideline (2004).</td>
</tr>
</tbody>
</table>
**Recommendation**

Discuss with girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) and their parents and/or carer the risk of AEDs causing malformations and neurodevelopmental delay to an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Risk of continued use of sodium valproate to the unborn child should specifically be discussed [new 2011]

<table>
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</tr>
<tr>
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<td>None</td>
</tr>
</tbody>
</table>

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3
<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th>Be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of childbearing potential. [2011]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative values of different outcomes</strong></td>
<td>Seizure freedom and adverse events in the mother and malformations and neurodevelopmental delay in the child were considered to be the most important outcomes.</td>
</tr>
<tr>
<td><strong>Trade off between clinical benefits and harms</strong></td>
<td>Risks of seizure exacerbation or relapse with reduction in dose of AED need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. The GDG felt that if health care professionals are aware of the most up to date data on the teratogenic risks of different AEDs, then well informed prescribing decisions can be made.</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>This recommendation was based on GDG consensus opinion.</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>This recommendation is unchanged from the 2004 edition of this guideline. The GDG considered this recommendation to be still valid in light of the reviewed evidence for the 2011 update.</td>
</tr>
</tbody>
</table>
Recommendation

Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalized tonic-clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of AED for each individual. [new 2011]

Relative values of different outcomes

Seizure freedom and adverse events in the mother and malformations and neurodevelopmental delay in the child were considered to be the most important outcomes.

Trade off between clinical benefits and harms

Risks of seizure exacerbation/relapse with reduction in dose of AED need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.

Economic considerations

No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. Drugs and doses that may be cost-effective in the general epilepsy population, such as sodium valproate, may not be as cost-effective in this group due to its potential teratogenic effect.

Quality of evidence

This recommendation was based on GDG consensus opinion.

Other considerations

None.

Recommendation

Discuss with women who are taking lamotrigine that taking the combined oral contraceptive pill with lamotrigine can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When a woman starts or stops taking oral contraceptives, the dose of lamotrigine may need to be adjusted. [new 2011]

Relative values of different outcomes

Seizure freedom, adverse effect and effective contraceptive were considered the most important outcomes.

Trade off between clinical benefits and harms

Interaction between lamotrigine and the oral contraceptive may reduce lamotrigine’s anticonvulsant effect because of hepatic metabolism.

Economic considerations

There was no economic evidence available and this type of scenario was not incorporated into the original economic models undertaken for the guideline. However, the GDG considered that the likely extra resource use and costs associated with adjusting dosage (extra medical appointments and/or increased or decreased daily dose) was likely to be cost-effective if it helps to maintain seizure control.

Quality of evidence

This recommendation was based on GDG consensus opinion.

Other considerations

None.
Recommendation

Follow guidance in the ‘British national formulary’ (available at www.bnf.org) on the interactions between AEDs and hormonal contraception. [new 2011]

Relative values of different outcomes

Seizure freedom, adverse effect and effective contraceptive were considered the most important outcomes.

Trade off between clinical benefits and harms

The risks of unplanned pregnancy caused by drug interaction between AEDs and hormonal contraceptives must be considered, but the risks of seizures require that, when possible, the most effective antiepileptic medication be prescribed.

Economic considerations

There was no economic evidence available and concomitant use of AEDs and hormonal contraceptives was not incorporated into the original economic models undertaken for the guideline. However, the GDG considered that interactions between AEDs and hormonal contraceptives should be borne in mind to reduce the risk of unplanned pregnancies that could require changes to treatment and thus the risk of reduced seizure control and/or possible harm to the unborn child.

Quality of evidence

This recommendation was based on GDG consensus opinion.

Other considerations

None.

13.5.6 Research recommendations (for full list see section 2.11)

13.5.6.1 AEDs and pregnancy

What is the outcome (malformation rate and longer-term neurodevelopmental outcome) of children born to mothers who have taken the AEDS in pregnancy?

Why is this important

Pregnancy registers are increasing the data that are available on established AEDS; however, these registers may give malformation rates but do not provide controlled long-term data on neurodevelopmental outcome.

Research should include:

- Measures of maternal outcome, including seizure frequency and quality of life.
- Major and minor rates of congenital malformations.
- Prospective neurodevelopmental (including cognitive) and behavioural outcomes in children born to women with epilepsy; these should be undertaken on a long-term basis and ideally using a cohort study, followed from birth and until adult life.

13.5.7 Deleted recommendations from 2004 guideline

13.5.7.1 In women of childbearing potential, the risk of the drugs (see 1.8.13A) causing harm to an unborn child should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive
assessments of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.

13.5.7.2 In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs (see 1.8.13C) causing harm to an unborn child should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.

13.5.7.3 In all women with epilepsy, seizure freedom during pregnancy should be sought.

13.6 Do AEDs interact with contraceptives?

In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. [2004]

In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the possibility of interaction with oral contraceptives should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. [2004]

In women of childbearing potential, the risks and benefits of different contraceptive methods, including hormone-releasing IUDs, should be discussed. [2004]

If a woman taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, a minimum initial dose of 50 micrograms of oestrogen is recommended. If breakthrough bleeding occurs, the dose of oestrogen should be increased to 75 micrograms or 100 micrograms per day, and 'tricycling' (taking three packs without a break) should be considered. [2004]

The progesterone-only pill is not recommended as reliable contraception in women taking enzyme-inducing AEDs. [2004]

Women taking enzyme-inducing AEDs who choose to use depot injections of progesterone should be informed that a shorter repeat injection interval is recommended (10 weeks instead of 12 weeks). [2004]

The progesterone implant is not recommended in women taking enzyme-inducing AEDs. [2004]

The use of additional barrier methods should be discussed with women taking enzyme-inducing AEDs and oral contraception or having depot injections of progesterone. [2004]

If emergency contraception is required for women taking enzyme-inducing AEDs, the dose of levonorgestrel should be increased to 1.5 mg and 750 micrograms 12 hours apart. [2004]
Evidence statements

Carbamazepine, phenytoin, oxcarbazepine, topiramate and barbiturates reduce the effectiveness of oral contraceptives, necessitating the use of alternative methods, or special high-dose regimens of oral contraceptives. Even with this precaution, the effectiveness of the oral contraceptive is reduced. (Ia NICE)

Hormone-releasing IUDs are effective as a method of contraception in women taking AEDs. (III)

There is limited evidence that progesterone implants (specifically levonorgestrel) are ineffective in women taking enzyme-inducing AEDs. (III)

There is no evidence on the effectiveness of emergency contraception in women taking enzyme-inducing AEDs.

Details

The NICE technology appraisal stated that oxcarbazepine and topiramate interact with oral contraceptives whilst lamotrigine, gabapentin, levetiracetam, and tiagabine do not. Details of interactions for vigabatrin were not reported. Of the older drugs, sodium valproate does not interact with the oral contraceptive, but must be used with caution in women of child bearing age.41,395

No systematic reviews of RCTs or RCTs were identified that compared different methods of contraception or different doses of oral contraception. In addition, no cohort studies of women with epilepsy and contraception failure rates were identified. The evidence presented below is therefore non-experimental describing failure rates of different contraceptive methods in women with epilepsy who are taking AEDs and drug interactions between AEDs and hormonal contraception, or reviews of the interactions between AEDs and hormonal contraception.

Hormonal contraception (general)

Crawford 2002396

In a review on AEDs and hormonal contraception, Crawford reviewed the literature on drug interactions between AEDs and oral contraceptives and other hormonal contraceptive methods. Recommendations on contraception for women taking AEDs were then presented. These were:

- Women taking phenobarbital, phenytoin, carbamazepine, felbamate, topiramate, or oxcarbazepine should take an oral contraceptive pill containing at least 50mcg of oestrogen.
- Women taking other AEDs can take a normal dose oral contraceptive pill.
  (Based on 17 studies and other references such as the BNF)
- The progesterone-only pill is likely to be unreliable in women taking enzyme-inducing AEDs.
  (Based on the BNF)
- The frequency of injection for depot progesterone should be increased to every 10 weeks (compared with the usual 12 weeks) in women taking enzyme-inducing AEDs.
  (Based on expert opinion only)
- Progesterone implants (specifically levonorgestrel implants) should be not used as a method of contraception in by women taking enzyme-inducing drugs.
  (Based on case reports and a small case series of 19 women)

These recommendations were similar to those previously reached by the Women with Epilepsy Guidelines Development Group based on available evidence and expert judgement and experience.397

**Oral contraception ('The pill')**

**Coulam 1979**398

In 1979, Coulam and Annegers presented the results of a record review of 82 women with epilepsy who were also taking oral contraception.398 In total, there were 3,233 woman-months of oral contraception use in three subgroups of women:

- 41 women used AEDs and oral contraceptives for 955 months
- 30 women were taking oral contraceptives only for 828 months
- 31 women who had been seizure free and had not been taking AEDs for 5 years were taking oral contraception for 1,450 months.

The expected and observed rates of contraceptive failure were then calculated. Three contraceptive failures occurred, compared to the expected number of 0.12 (relative risk 25, 95%CI 5 to 73). All three of the women in whom oral contraception failed were taking AEDs; two of the women with were taking combined oral contraception and one was taking sequential contraception.

**Back 1988**399

The Committee on Safety of Medicines (CSM) monitors adverse drug reactions in the UK. Back and colleagues searched the CSM adverse reactions register for 1968 to 1984 to identify pregnancies reported in women taking oral contraceptives and AEDs.

43 pregnancies were reported in women taking AEDs; of these, 25 were taking phenytoin, 20 phenobarbitone, 7 primidone, 6 carbamazepine, 4 ethosuximide, and 1 taking sodium valproate. Some of the women were taking more than one drug.

Of these 43 pregnancies, 25 were taking high oestrogen contraception (50mcg), 13 were taking medium oestrogen contraception (30mcg to 35 mcg) and 5 were taking other types of oral contraceptive, including progesterone only, biphasic and triphasic preparations.

The authors suggested that due to the low levels of reporting of adverse events (less than 10%), the reported failures were a fraction of the actual number.
No evidence was found on the most effective dose of oral contraception, or the most effective regimen. A recent guideline on the management of women with epilepsy recommended, on the basis of evidence and consensus, that

- For women on enzyme-inducing AEDs (phenytoin, phenobarbitone, primidone, carbamazepine, topiramate) wishing to take the combined oral contraceptive pill:
  - Start on a 50mcg ethinyl oestradiol dose
  - If breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75mcg or 100mcg per day, or consider giving three packs of the pill without a break (tricycling).

**Hormone-releasing intrauterine devices**

**Bounds 2002**

The authors of this study aimed to document the contraceptive effectiveness of the hormone-releasing IUD Mirena® in women taking AEDs and other enzyme-inducing drugs.

65 women were recruited to the study, of which 56 were included in the analysis. Of these 56 participants, 49 (87.5%) were taking medication for epilepsy. Drugs included carbamazepine, phenytoin, phenobarbitone, primidone, and topiramate.

During the 1,075 months of exposure to the risk of pregnancy, two accidental pregnancies were reported, both to women taking AEDs (primidone and phenytoin, and phenytoin only). Only one of these was assessed as being a true failure event; the other failure may have been due to a non-protected period after removal of the IUD. The failure rate was calculated to be 1.1 per 100 woman-years (95% CI 0.03 to 6.25) based on the true failure only, and 2.2 per 100 woman-years (95% CI 0.27 to 8.07) based on both failures.

The authors stressed that this was a pilot study only, but that the failure rate of 2.2 per 100 woman-years compared well with failure rates for women on oral contraception and AEDS (approximately 7 per 100 woman-years, and was better than rates for barrier methods (15 to 20 per 100 woman-years).383,400

**Progesterone implants**

**Haukamaa 1986**

Nine women with epilepsy aged 16 to 35 years participated in this study to assess the efficacy of progesterone implants in women taking AEDs. The control group was 10 women aged 28 to 44 years without epilepsy who were taking no medication.

No pregnancies occurred in the control group in the 12 months of the study. Two pregnancies occurred in the epilepsy group; both women were taking phenytoin and their plasma levels of levonorgestrel were low at the time of conception. In addition, nine of the control group continued to use the implant after 12 months. Of the women with epilepsy, only six of the nine women continued to use the implant at 12 months.
Emergency contraception

FFPRHC 2003

The Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit produced evidence-based guidance for the use of emergency contraception in primary and secondary care.

Drug interactions relevant to emergency contraception were reviewed and no evidence was cited around the interaction between levonorgestrel and enzyme-inducing AEDs. The guidance recommended that:

- two tablets (1.5mg) are followed 12 hours later by a single tablet (0.75mg), although this is outside the product license.

The use of an increased dose was also proposed in another review of emergency contraception, although again the lack of evidence was highlighted. Similarly, the guidelines on the management of women with epilepsy stated that ‘there are no data on whether a change in dose of the morning-after contraceptive pill is required in women taking AED medication; some practitioners use a slightly higher dose in those women taking enzyme-inducing drugs’.

13.7 Does epilepsy increase the risk of complications in pregnancy?

Women with epilepsy should be informed that although they are likely to have healthy pregnancies, their risk of complications during pregnancy and labour is higher than for women without epilepsy. [2004]

Care of pregnant women should be shared between the obstetrician and the specialist. [2004]

Pregnant women who are taking AEDs should be offered a high-resolution ultrasound scan to screen for structural anomalies. This scan should be performed at 18-20 weeks’ gestation by an appropriately trained ultrasonographer, but earlier scanning may allow major malformations to be detected sooner. [2004]

All pregnant women with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to the UK Epilepsy and Pregnancy Register (www.epilepsyandpregnancy.co.uk). [2004]

Evidence statements

Most women with epilepsy have healthy pregnancies however they may have an increased risk of complications. (IIa)

Prenatal screening can identify some abnormalities. (Ia NICE)
13.7.1 Are women with epilepsy at increased risk of complications during the pregnancy and labour?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Fairgrieve 2000

One prospective, population based study was identified. 400 notifications of pregnancies in women with epilepsy were included. Of the 359 (90%) known pregnancy outcomes, the obstetric complication rate was similar to that of the background population, except for an excess of premature deliveries (8.2%). No statistical significance was given.

Tanganelli 1992

Another prospective controlled study compared 138 pregnancies in 97 women with epilepsy with 140 control pregnancies in 88 women who did not have epilepsy. Slightly more complications occurred in women with epilepsy compared with controls (23.4% vs 15.6%) but the difference was not statistically significant. However, induced labour and prolonged labour were approximately twice as likely in women with epilepsy (9.0% vs 4.7% and 5.7% vs 2.3%).

Olafsson 1998

Complications of pregnancy, delivery, and outcome in women with active epilepsy were compared with women without epilepsy in a retrospective population study. Active epilepsy was defined as treatment with AEDs during pregnancy or during the 5 year period preceding the pregnancy. In the 19 year study period, the number of live births was 82,483 (from 81,473 pregnancies) of which 268 children were born to 157 women with active epilepsy (from 266 pregnancies).

Although the frequency of adverse events in pregnancy were similar in both groups, caesarean section was performed twice as frequently in women with active epilepsy (13%, 35 of 266 compared with 8.8%, 7,139 of 81,473). Perinatal mortality (11.2 in 1000 compared with 8,7 in 1000, OR=1.5, 95% CI 0.3-4.1) and mean birth weight (3,601g compared with 3,647g, p=0.2) were not significantly different for the offspring of women with active epilepsy.

13.7.2 When should screening for structural fetal anomalies be performed in pregnant women with epilepsy?

A recent NICE guideline reviewed the evidence on the detection of structural fetal abnormalities in healthy pregnant women. A systematic review assessed the overall prevalence of fetal anomaly to be 2.09%, ranging from 0.76% to 2.45% in individual studies and including major and minor anomalies. Overall, 44.7% of these anomalies were detected using screening, with a range of 15.0% to 85.3% as different anomalies are more or less likely to be correctly identified.

They found that variation in detection rate occurred with:

- the type of anomaly being screened
13.8 When should folic acid be started?

All women on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. [2004]

Evidence statement

There is limited evidence to show that folic acid supplementation reduces the risk of NTD and other congenital malformations in women taking AEDs. (IV)

Details

This was not subject to a full evidence review for reasons given in Chapter 2.

Folates and folic acid have a major role to play in the prevention of neural tube defects.407

It is already recommended that all women who are planning pregnancy should be advised to take 400mcg of folic acid from when they begin trying to conceive until the 12th week of pregnancy and that those who suspect they are pregnant and who have not been taking supplements should start folic acid supplements immediately and continue until the 12th week of pregnancy.407

No RCTs of different levels, or different timing of folic acid supplementation in women with epilepsy were identified.

A narrative review408 on neural tube defects and folic acid supplementation in women with epilepsy concluded that:

'The value of periconceptional folic acid supplementation for women in the general population is accepted. However, it is unclear whether folic acid supplementation protects against the embryotoxic and teratogenic effects of AEDs because animal and human studies and case reports have shown variable results. Nevertheless, folic acid supplementation is recommended for women with epilepsy as it is for other women of childbearing age. However, the dose of 400mcg per day may not be high enough for many women who do not metabolise folate effectively.'408
13.9 What are the dangers of seizures in women who are pregnant or post-natal?

Women with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women who plan to stop AED therapy (see Section on withdrawal). [2004]

Women with generalised tonic-clonic seizures should be informed that the foetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency. [2004]

Women should be re-assured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing foetus adversely unless they fall and sustain an injury. [2004]

The risk of seizures during labour is low, but it is sufficient to warrant the recommendation that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures. [2004]

Advanced planning, including the development of local protocols for care, should be implemented in obstetric units that deliver babies of women with epilepsy. [2004]

Parents should be reassured that the risk of injury to the infant caused by maternal seizure is low. [2004]

Parents of new babies or young children should be informed that introducing a few simple safety precautions may significantly reduce the risk of accidents and minimise anxiety. An approaching birth can be an ideal opportunity to review and consider the best and most helpful measures to start to ensure maximum safety for both mother and baby. [2004]

Information should be given to all parents about safety precautions to be taken when caring for the baby (see Appendix D). [2004]

Evidence statements

There is no evidence that simple partial, complex partial, absence and myoclonic seizures adversely affect the pregnancy or developing fetus. (IV)

Generalised tonic-clonic seizures are likely to result in more profound hypoxia than in the non-gravid state due to increased maternal oxygen requirements. This may have adverse affects for the fetus. (IV)

Indirect deaths from medical conditions exacerbated by pregnancy were greater than those deaths from conditions directly arising from pregnancy. Some of these deaths were attributed to epilepsy. (III)

Babies of mothers with active epilepsy, particularly if the mother has juvenile myoclonic epilepsy, are at risk of injury. The risk of injury is related to seizure type and severity. In particular, the pattern of seizures is crucial. (III)
Details

This KCQ was not subject to a full evidence review for reasons set out in chapter 2.

Effects of maternal seizures on the fetus

An expert workshop convened by the Epilepsy Research Foundation considered both published evidence and expert opinion and concluded that:

- Partial seizures and non-convulsive generalised seizures are unlikely to expose the fetus to immediate risks in utero.
- Generalised tonic-clonic seizures may reduce blood flow to the uterus, but that evidence was lacking. If the woman falls, then there is a risk of uterine contraction and subsequent placental abruption.
- The evidence suggested that increased rate of teratogenesis is due to AEDs rather than to seizures in pregnancy.
- It seems unlikely that maternal seizures during pregnancy have important long-term developmental effects on fetal development.

Effect of maternal seizures on the woman

The Confidential Enquiries into Maternal Deaths in the United Kingdom found that:

- Indirect deaths (n=136) were greater than direct deaths (n=106).
- Of those indirect deaths, nine were related to epilepsy.

The Enquiry recommended that women need specialist advice in pregnancy, and that the possibility of SUDEP should be discussed with all women who plan to stop AED therapy.

Effect of maternal seizures during labour

The expert workshop recommended that, as seizures during labour can affect the fetus, delivery for women with epilepsy should take place at obstetric units with sufficient facilities. No details of what ‘sufficient facilities’ were given.

Effect of maternal seizures in the post natal period

An audit of 187 women with epilepsy seen in a preconception clinic was undertaken to assess the risk posed to a baby born to a mother with active epilepsy. The experience of the 187 women...
(Group 1) seen in the clinic and given counselling and information about safety was compared with 38 women (Group 2) who were given no counselling about safety precautions. There were 3 minor incidents recorded in Group 1 compared with 8 serious and 4 minor incidents in Group 2. Of the 15 women recording an incident, 7 had JME. Apart from one mother who had her first seizure whilst carrying her child, all the incidents were preventable.411

13.10 What is the role of drug monitoring in pregnant women with epilepsy?

Routine monitoring of AED levels in pregnancy is not recommended. If seizures increase, or are likely to increase, monitoring of AED levels may be useful to plan or anticipate the extent of change of dose adjustment needed. [2004]

Evidence statements

There is no clear-cut relationship between serum levels of AEDs and seizure control in non-pregnant and pregnant women with epilepsy. (IV)

No evidence to support the use of routine blood monitoring of AED levels was found.

Details

No systematic reviews or RCTs were identified. (see What is the role of monitoring in adults and children with epilepsy?).

In 1993, the ILAE Commission on Antiepileptic Drugs published guidelines for therapeutic monitoring of AEDs. They highlighted three areas of concern:

- the lack of strict correlation between efficacy and/or toxicity of AEDs and their blood levels for individuals.
- blood levels judged on an individual sampling may be misleading where there exists wide diurnal variation.
- accuracy of measurements must be considered.

In conclusion, the Commission recommended that

- indiscriminate use of blood level determinations is not recommended, but that tailored determinations with specific purposes such as pregnancy may be helpful.328

13.11 Should oral or parenteral vitamin K be used?

All children born to mothers taking enzyme-inducing AEDs should be given 1 mg of vitamin K parenterally at delivery. [2004]
Evidence statement

There is limited evidence to show that the risk of haemorrhagic disease of the newborn is not increased in women taking enzyme-inducing AEDs provided that infants receive the standard treatment of 1mg vitamin K parenterally (intra-muscular or intra-venous) at birth. (III)

Details

This was not subject to a full evidence review for reasons given in Chapter 2.

No systematic reviews or RCTs comparing oral and parenteral vitamin K were identified. Only one prospective study was identified.

Kaaja 2002

The occurrence of bleeding complications in newborns exposed to maternal enzyme-inducing AEDs in utero was examined in 662 pregnancies (452 women and 667 offspring). A group of 1,324 pregnancies (1,334 neonates) served as the control group. None of the exposed group or the control received vitamin K supplementation during pregnancy or labour. All newborns of mothers with epilepsy and control newborns received a standard dose of 1mg vitamin K intramuscularly at birth.

Five exposed (0.7%) and five control (0.4%) newborns suffered a bleeding complication. Bleeding was associated with birth at less than 32 weeks (OR=13, 95%CI 2.7-64) and alcohol abuse (OR=17, 95%CI 1.8 to 162). No association was found with exposure to enzyme-inducing AEDs (OR=1.1, 95%CI 0.3-4.6, p=0.8).

Limitations described by the authors included the low incidence of neonatal bleeding in both groups. Also, the results cannot be extrapolated to women on polytherapy (only 21.3% of fetuses were exposed to polytherapy) or on primidone or phenobarbital, as these were seldom used by the included women.

13.12 What is the risk of inheriting epilepsy?

Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has idiopathic epilepsy and a positive family history of epilepsy. [2004]

Although there is an increased risk of seizures in children of parents with epilepsy, individuals with epilepsy should be given information that the probability that a child will be affected is generally low. However, this will depend on the family history. [2004]

Evidence statements

For idiopathic generalized epilepsy, the risk of a child developing the condition is 5–20% if there is one affected first degree relative (including the mother), and over 25% if two first degree relatives are affected. Thus the risk of a individual with idiopathic generalized epilepsy having an affected child is about 9–12%, and the risk is 3% in children of those with cryptogenic (partial) seizures. (IV)

There is a higher risk in those families who have many affected members. (IV)
Details

This was not subject to a full evidence review for reasons given in Chapter 2.

For idiopathic generalized epilepsy, the risk of a child developing the condition is 5–20% if there is one affected first degree relative (including the mother), and over 25% if two first degree relatives are affected. Thus the risk of an individual with idiopathic generalized epilepsy having an affected child is about 9–12%, and the risk is 3% in children of those with cryptogenic (partial) seizures.383
13.13 What is the role of joint epilepsy and obstetric clinics in the care of women with epilepsy who are pregnant?

Joint epilepsy and obstetric clinics may be convenient for mothers and healthcare professionals but there is insufficient evidence to recommend their routine use. [2004]

It is, however, important that there should be regular follow up, planning of delivery, liaison between the specialist or epilepsy team and the obstetrician or midwife. [2004]

Evidence statement

No evidence for the effectiveness of joint epilepsy and obstetric clinics could be found.

Details

No systematic reviews or RCTs were identified.
14 People with learning disabilities and epilepsy

14.1 Introduction

The prevalence of learning disabilities in the population is approximately 18 per 1000. Thus, a GP with a list size of 2000 has approximately 36 individuals with learning disabilities, of whom about six will have severe learning disabilities. Epilepsy and learning disabilities commonly co-exist and most often develop in childhood. It is estimated that epilepsy has a prevalence of 15% in people with mild learning disabilities and 30% in those with severe learning disabilities.

People with mild learning disabilities (IQ 50 to 70) and no other concomitant conditions are at lowest risk (5-7%) of developing epilepsy. Up to 75% of those with additional disabilities such as cerebral palsy or postnatal brain injury have epilepsy. Severe learning disability (IQ 20 to 50) is more likely in individuals with early seizure onset. People with Down’s syndrome and other chromosomal conditions commonly have epilepsy; approximately 8-10% of such people have a history of seizures. Many children with epilepsy do not have associated learning disabilities, but some childhood onset epilepsies, such as Lennox-Gastaut syndrome, are associated with learning disabilities.413

There are particular challenges in providing information and support for this group as there may be occasions where people with learning disabilities and epilepsy cannot make their own decisions due to a lack of mental capacity. It is important that decisions are made with appropriate advocacy for the individual, as outlined in recent guidance from the Department of Health.414

Problems in conducting an evidence-based review

The KCQs identified by the GDG were converted into EBQs and systematic literature searches were carried out. In common with other reviews in the field415 large gaps in the available evidence were identified and much of what was identified was of poor methodological quality. The lack of placebo-controlled double blind drug trials in this population is singled out for comment.

Where there is a lack of evidence, the key recommendations from a recent consensus guideline on the management of epilepsy in adults with an intellectual disability are summarized.415

14.2 Who should manage and treat epilepsy in people with learning disabilities?

Evidence statements

No studies were identified that compared outcomes for people with epilepsy and learning disabilities managed by different groups of clinicians. In particular, there was no comparison of ‘specialist’ versus ‘non-specialist’ care.

There was one study that suggested that specialists may be better at managing learning disabilities with epilepsy. (III)
14.2.1 Do people with learning disabilities and epilepsy who receive care from a specialist in learning disabilities and epilepsy compared with care from a non-specialist have differences in processes and outcomes of care?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Collacott 1989

A cohort of 215 people (mean age 38 years±14 years) with learning disabilities and epilepsy was followed-up for four years. The participants were all residents of a mental handicap unit in the UK. The anticonvulsant regimes were reviewed by a specialist in mental handicap and a specialist in clinical pharmacology. Of the 172 who remained in the study, 41% were seizure free compared with 37% on the initial review (p<0.005). Overall, seizure frequency was reduced in 48%, increased in 33% and unchanged in 19%. At the final review, the mean number of AEDs per individual was reduced from 1.41 to 1.05 (p<0.005).

Although this study suggests that specialists are better at managing PLD and epilepsy, there was no description of who managed the individuals prior to the assessment.

DeToledo 2002

Video-EEGs of 824 institutionalised adults with epilepsy were studied to identify ‘new seizure types’ identified by staff (caregivers, teachers, therapists, LPNs, RNs). Of the 63 requests for an evaluation of newly identified seizure types, epilepsy was confirmed in 4 events (6.3%).

This study compares specialists with non-clinical staff, not general physicians.

14.3 Is making a diagnosis more difficult in people with learning disabilities?

It can be difficult to diagnose epilepsy in people with learning disabilities, and so care should be taken to obtain a full clinical history. Confusion may arise between stereotypic or other behaviours and seizure activity. [2004]

It is important to have an eye witness account supplemented by corroborative evidence (e.g. a video account), where possible. [2004]

Clear, unbiased reporting is essential. Witnesses may need education to describe their observations accurately. [2004]

Evidence statements

Stereotypic behaviour and other abnormal movements may be confused with seizures. (III)
14.3.1 Are the rates of misdiagnosis higher for people with learning disabilities and epilepsy when compared with people with epilepsy who do not have learning disabilities?

This question has already been considered in Chapter 7.2 and no primary studies were identified that answered this question.

14.3.2 What are the practical difficulties in establishing the diagnosis in this group?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

DeToledo 2002

‘New seizure types’ in institutionalised adults with epilepsy were identified by staff, who then requested video-EEGs for evaluation. Of the 63 requests for video-EEG, epilepsy was confirmed in 4 events (6.3%). Episodes likely to be confused with seizures in those with severe learning disabilities were stereotypic, repeated blinking or swallowing, buccolingual movements, spontaneous smiling or grimacing, periods of apparent psychomotor arrest, and dystonic posturing. In less impaired individuals, the most common diagnoses were stereotypic self-stimulation and self-abusive behaviours, ataxia with falls, and simulation of convulsions.

14.4 Are there difficulties in doing investigations in this group?

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<th>Evidence statements</th>
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<tr>
<td>Those with learning disabilities may require particular care and attention to tolerate investigations. [2004]</td>
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<tr>
<td>Facilities should be available for imaging under anaesthesia, if necessary. [2004]</td>
</tr>
<tr>
<td>In the child presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. [2004]</td>
</tr>
</tbody>
</table>

No studies were found that compared either the conduct or interpretation of investigations done in people with learning disabilities and epilepsy with people with epilepsy who do not have learning disabilities.
14.4.1 Are there a) difficulties in conducting investigations (EEG; neuroimaging); b) difficulties in interpreting investigations (EEG; neuroimaging) in people with learning disability and epilepsy when compared with people with epilepsy who do not have learning disabilities?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Brodtkorb 1994

An EEG recording could not be made in 10 of 63 institutionalised individuals with learning disabilities due to 'co-operation problems'.

Consensus guideline recommendations

Working group of the International Association of the Scientific Study of Intellectual Disability 2001

Kerr and colleagues recommended that:

- Facilities should be available for imaging under general anaesthesia.

14.5 What are the main factors to assess when making a management plan for an individual with learning disabilities and epilepsy?

In making a management plan for an individual with learning disabilities and epilepsy, particular attention should be paid to the possibility of adverse cognitive and behavioural effects of AED therapy. [2004]

The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for those with learning disabilities as for the general population. [2004]

Evidence statements

There is no evidence to suggest that different antiepileptic drugs should be used for those with learning disabilities than for those without learning disabilities. (NICE)

People with learning disabilities and epilepsy are at increased risk of adverse cognitive or behavioural side effects from AEDs. (IV)
14.6 Pharmacological management of people with epilepsy and learning disabilities

14.6.1 Introduction

Up to 50% of individuals with epilepsy are likely to have a specific, or more global learning disability. Those with very early onset epilepsy are particularly at risk. Further, those who have learning disability per se are at a higher risk of developing epilepsy in the longer term. There is no evidence to suggest that epilepsy in the learning disabled population requires any different consideration with regard to treatment compared to those without learning disability. One could argue however, they may be more susceptible particularly to cognitive side effects of anticonvulsant medication. Further, they may be disadvantaged in their management by lack of self advocacy.

14.6.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with learning disabilities and epilepsy. People with Lennox-Gastaut syndrome were excluded from this evidence review and were reported in a separate evidence review (see section 10.7).

14.6.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for adults and children with epilepsy and learning disabilities. The following interventions were included in our search; pregabalin, zonisamide, lacosamide, lamotrigine, gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbital, clobazam, felbamate, acetazolamide, sodium valproate, primidone and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
<table>
<thead>
<tr>
<th>Placebo (Pla)</th>
<th>Pregabalin (PRE)</th>
<th>Zonisamide (ZNS)</th>
<th>Lacosamide (LCS)</th>
<th>Lamotrigine (LTG)</th>
<th>Gabapentin (GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine (OXC)</td>
<td>Tiagabine (TGB)</td>
<td>Levetiracetam (LEV)</td>
<td>Topiramate (TPM)</td>
<td>Vigabatrin (VGB)</td>
<td>Phenytoin (PHT)</td>
</tr>
<tr>
<td>Phenobarbitone (PBT)</td>
<td>Clobazam (CLB)</td>
<td>Felbamate (FBM)</td>
<td>Acetazolamide (ACT)</td>
<td>Sodium valproate (VPA)</td>
<td>Primidone (PRM)</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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14.6.3.1 Topiramate as adjunctive therapy versus Placebo

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results
For adults and children with epilepsy and learning disabilities, there was no significant difference for the proportion of participants achieving at least 50% reduction in seizure frequency between topiramate adjunctive therapy and placebo. (VERY LOW QUALITY)

Adverse events – statistically significant results
For people with epilepsy and learning disabilities, significantly more patients had the following adverse events with topiramate adjunctive therapy compared to placebo:
- anorexia, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)
- somnolence, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results
There was no significant difference for the proportion of participants that withdrew due to adverse events between topiramate adjunctive therapy and placebo. (VERY LOW QUALITY)

There was no significant difference between topiramate adjunctive therapy and placebo for the incidence of:
- accidental injury (VERY LOW QUALITY)
- asthesia (VERY LOW QUALITY)
- hostility (VERY LOW QUALITY)
- infection (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- abnormal gait (VERY LOW QUALITY)
- convulsions (VERY LOW QUALITY)
- nervousness. (VERY LOW QUALITY)

Quality of life- statistically non-significant results
No significant difference was found between topiramate adjunctive therapy and placebo on the following domains of quality of life:
- seizures (VERY LOW QUALITY)
- drugs (VERY LOW QUALITY)
- daily life (VERY LOW QUALITY)
• severity (VERY LOW QUALITY)
• side effects (VERY LOW QUALITY)
• behaviour (VERY LOW QUALITY)
• mood (VERY LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:
• seizure freedom
• time to first seizure
• time to exit

Cost-effectiveness
No economic evidence comparing adjunctive topiramate to placebo in a population of patients with learning disabilities was identified.

14.6.3.2 Gabapentin adjunctive therapy versus Lamotrigine adjunctive therapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economics
No studies were identified in the economic literature search.

Evidence statements
Efficacy – statistically non-significant results
No significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No statistically significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events-statistically non-significant results
For people with learning disabilities, no statistically significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:
• withdrawal due to lack of efficacy
• time to first seizure,
• time to exit/withdrawal of allocated treatment
• incidence of adverse events
• cognitive outcomes.
• quality of life outcomes
**Cost-effectiveness**

No economic evidence comparing adjunctive gabapentin to adjunctive lamotrigine in a population of patients with learning disabilities was available.

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**14.6.4 Recommendations and link to evidence**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Enable adults and children who have learning disabilities, and their family and/or carers where appropriate, to take an active part in developing a personalised care plan for treating their epilepsy. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**
The objective of epilepsy treatment in this patient group is no different than from a general epilepsy population. As for adults and children without learning disabilities, seizure freedom, reduction of seizures and avoidance of adverse effects are important outcomes. There was no evidence to suggest that efficacy of drugs differs for this population.

**Trade off between clinical benefits and harms**
Given the individual’s complex co morbidities, adults and children with learning disabilities and their family/carers could contribute actively on setting priorities personalised to individual needs.

**Economic considerations**
The GDG considered that extra time may be required to implement this recommendation, but that personalised care plans for this group of patients may help improve the long term outcomes of treatment and may ultimately reduce some need for hospital admissions, outpatient appointments and GP consultations. Outcomes may be improved as choice of drug and dose can be tailored to the patient more successfully, thus reducing risk of discontinuation due to intolerable side effects. The GDG considered it likely to be a cost-effective use of resources, although no evidence is available.

**Quality of evidence**
This recommendation was based on GDG expertise.

**Other considerations**
GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist services.
**Recommendation**

Allow additional time for consultation to achieve effective management of epilepsy in adults and children with learning difficulties. [new 2011]

**Relative values of different outcomes**

The objective of epilepsy treatment in this group of patients is no different than from a general epilepsy population. As for adults and children without learning disabilities, seizure freedom, reduction of seizures and adverse effects are important outcomes. There was no evidence to suggest that efficacy of drugs differs for this population, however, the GDG opinion was that importance is placed on cognitive and behavioural effects of AEDs as it may be more difficult to assess and treat in this population.

**Trade off between clinical benefits and harms**

Communication with the patient and the carer may be more challenging and it may take longer during the consultation to monitor any side effects and optimise drug management, particular considering issues that may arise under the Mental Capacity Act (2005).

**Economic considerations**

The GDG considered that extra time may be required to assess and manage this group of patients, but that it is likely to represent a cost-effective use of resources. Optimising their treatment is likely to improve their outcomes and may result in fewer hospital admissions, outpatient appointments and GP consultations.

**Quality of evidence**

This recommendation was based on GDG expertise.

**Other considerations**

GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist services.

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**Recommendation**

Do not discriminate against adults and children with learning difficulties and offer the same investigations and therapies as for the general population. [new 2011]

**Relative values of different outcomes**

The objective of epilepsy treatment in this group of patients is no different than from a general epilepsy population. As for adults and children without learning disabilities, seizure freedom, reduction of seizures and adverse effects are important outcomes.

**Trade off between clinical benefits and harms**

GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist services.

**Economic considerations**

This recommendation was based on GDG expertise.

**Quality of evidence**

GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist services.

**Other considerations**

GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist services.
14.6.5 Deleted recommendations from 2004 guideline

14.6.5.1 People with learning disabilities should receive the same support and care for their epilepsy as the general population. In addition, those with learning disabilities need the care of the learning disabilities team.

14.6.5.2 Learning disabilities are a common association with epilepsy. The management and treatment of the epilepsy should be undertaken by a specialist, working within a multidisciplinary team.
14.6.6 Is epilepsy more difficult to treat in people with learning disabilities?

Every therapeutic option should be explored in individuals with epilepsy in the presence or absence of learning disabilities. [2004]

Evidence statements

Remission rates for people with learning disabilities and epilepsy are lower than those for people with epilepsy who do not have learning disabilities. (IIb)

In community based studies of children with epilepsy and learning difficulties a significant (39-40%) proportion achieve remission. (IIb)

14.6.7 Likelihood of remission of seizures

Details

Only studies of prognosis that used a community sample of participants were included so as to avoid referral bias.

Secondary evidence

No systematic reviews were identified.

Primary Papers

Airaksinen 2000

151 children with learning disabilities were identified at the ages of 8 or 9 years from four birth cohorts in Finland. By the age of 22 years, 32 (21%) of the children had defined epilepsy. Four people with epilepsy had died by age 22, but the causes of death were not directly related to epilepsy. The cumulative probability of remission from seizures (defined as for 5 or more years) at the ages of 10, 17, and 22 years was 8, 25, and 32%. In addition to the 8 (29%) children in remission, 14% of the living 28 children had been seizure free for at least 12 months. So, although 71% of the children had active epilepsy (defined as having seizures in the past 5 years) at age 22 years, 43% had been seizure-free for at least 12 months.

Annegers 1979

In a study of 618 individuals with a diagnosis of epilepsy (at least two seizures with no apparent cause), 457 were followed-up for at least 5 years, 328 for at least 10 years, and 141 at least 20 years. 49 of these had neurologic dysfunction (spasticity, hemiparesis, mental retardation) from birth. The percentage of those with neurologic dysfunction had a 46% probability of remission (seizure free for 5 years) at 20 years after diagnosis compared with 74% for those who had no neurologic dysfunction and idiopathic epilepsy. The probability for individuals with neurologic deficits being in remission and off medication 10 years after diagnosis was less than 15% compared
with 36% for the idiopathic group and less than 20% for the symptomatic group. The probability for those with neurologic deficits being in remission and off medication 20 years after diagnosis was 30% (47% for the idiopathic group and 54% for the symptomatic group).422

Brorson 1987423

A follow-up study of 195 children (aged 0 to 19 years) with active epilepsy (at least one seizure in the past 3 years) in Uppsala, Sweden was undertaken. Of the 194 children that agreed to participate, 74 had some neurodeficit. After 12 years, 29 of the 74 children (39%) were in remission, defined as being seizure free for 3 consecutive years. The annual remission rate was high (12%) only in the first few years after onset, but then fell to 3%.423

Goulden 1991424

A prospective study of children with mental retardation (MR) was undertaken to assess the risk of seizures in this population. Of the 221 children included, 11 died prior to age 22, none as a result of seizures. By age 22 years, 33 (15%) had repeated, unprovoked seizures. 39% of these were in remission (defined as seizure free for 5 years). Rates of remission differed by group: 56% MR only, 47% MR and cerebral palsy, 11% postnatal injury.424

Sillanpaa 1975425

244 people with epilepsy aged under 16 years with recurrent epileptic seizures were followed-up for a mean period of 10.5 years (minimum 7 years). 94 (28%) were classified as having some degree of motor handicap (clumsiness, cerebral palsy, severe secondary hypotonia). The risk of persistent seizures was 2 times, five times, and ten times that for those with no motor handicap for people with clumsiness, cerebral palsy, and severe secondary hypotonia respectively.425
14.7 What are the additional management issues in people with learning disabilities?

Healthcare professionals should be aware of the higher risks of mortality for people with learning disabilities and epilepsy and discuss these with individuals, their families and/or carers. [2004]

All individuals with epilepsy and learning disabilities should have a risk assessment including:

- bathing and showering
- preparing food
- using electrical equipment
- managing prolonged or serial seizures
- the impact of epilepsy in social settings
- SUDEP
- the suitability of independent living, where the rights of the individual are balanced with the role of the carer. [2004]

Evidence statements

Mortality rates are higher in people with learning disabilities and epilepsy than those for people with epilepsy who do not have learning disabilities. However, epilepsy is not the major cause of death in this group. (IIb)

Management issues that are viewed as important by healthcare professionals and carers are:

- Concerns about seizures and their impact on individuals with epilepsy and learning disabilities and their carers;
- Concerns about treatment and its impact on individuals with epilepsy and learning disabilities and their carers;
- Concerns about how both the carer(s) and an individual with epilepsy and learning disabilities can achieve a ‘care balance’;
- Concerns about the social impact for individuals with epilepsy and learning disabilities.(III)

14.7.1 Is there increased mortality in people with learning disabilities and epilepsy?

Details

Secondary evidence

No systematic reviews were identified.
Primary evidence

**Brorson 1987**

A follow-up study of 195 children (aged 0 to 19 years) with active epilepsy (at least one seizure in the past 3 years) in Uppsala, Sweden was undertaken. Of the 194 children that agreed to participate, 74 had neurodeficit. After 12 years observation, 8 of the children with neurodeficit died, significantly more than children without (p<0.05). All had active epilepsy. One child died suddenly and unexpectedly, and without any witnesses. One child died due to seizures (in SE), three died due to infections, and three had unexplained deaths in institutions.

**Forsgren 1996**

A cohort of 1,478 people with mental retardation living in a Swedish province was followed for 7 years to study the pattern of mortality. 296 people had epilepsy (defined as recurrent, unprovoked seizures) and mental retardation (MR). During the observation period, 124 people died, of whom 30 (10.1%) had epilepsy. The increased death rate was highly significant for people with MR and epilepsy, (SMR 5.0, 95% CI 3.3 to 7.5) and people with MR, epilepsy and CP (SMR 5.8, 95% CI 3.4 to 9.8). Epilepsy was reported as the cause of death in 1 of the 30 cases, and as a contributing cause in 6. Examination of medical files, death certificates, and necropsy (11 cases) found two deaths to be probably seizure related (one after a fall probably after a seizure, one found dead in bed with no obvious cause) and 28 deaths not related to the epilepsy.

**Forssman 1970**

Mortality and sudden death rates were studied in a cohort of 310 children attending a school specialising in the education of people with epilepsy and learning disability. Children were included if they attended at any time between 1970 and 1993. Total duration of follow-up was 4,135 person years. There were 28 deaths (mean age 19 years, range 10 to 28); 14 were classified as sudden death.

**Nashef 1995**

Mortality and sudden death rates were studied in a cohort of 12,903 individuals cared for in institutions for the mentally deficient was undertaken in 1955 to 1959. 12,873 (99.8%) were followed-up until they died or to January 1st 1968. Standard mortality was calculated from the life tables for the standard population in 1960-1965. 1,784 people died during the period of observation, of whom 445 had epilepsy. The overall reduction in life expectancy was 5% compared with 14% for people with epilepsy. Of the 1,682 with epilepsy, 26% (445) died and the relative mortality rate was 7.9 times the standard (compared with 3.2 overall).

**14.7.2 What management issues in people with learning disabilities do healthcare practitioners and carers view as important?**

Secondary evidence

No systematic reviews were identified.
Primary papers

Espie 2001

The 2001 paper reported the development and validation of the Glasgow Epilepsy Outcome Scale (GEOS): a health measurement scale developed specifically for use with adults with epilepsy and learning disabilities. In the initial scale development work a convenience sample of 48 carers and 46 health practitioners participated in focus group discussions to determine issues of concern in the management of adults with epilepsy and learning disabilities. This led to the development of four subscales which are summarised here:

1) Concerns about seizures
   - Seizure pattern
   - Seizure severity
   - Emergency risks
   - Injury risks
   - After effects of seizures

2) Concerns about treatment
   - Diagnostic issues
   - Treatment decisions
   - Medication for epilepsy
   - Drug side effects
   - Dependence on medication

3) Concerns about caring
   - Achieving a care balance (e.g., freedom versus supervision)
   - Care dependency (e.g., carers lose their own independence)
   - Care expertise (e.g., do not know how to help the person during a seizure)

4) Concerns about social impact for person with epilepsy
   - Loss of independence
   - Social attitudes
   - Personal skills (e.g., dangerous for person to use kitchen, use stairs)
15 Young people with epilepsy

15.1 Introduction
Adolescence is a period of transition from dependence to independence, when adolescents begin to adopt a multitude of new social and emotional roles and learn to cope with altered bodily functions. Adolescents with a chronic illness such as epilepsy are constantly struggling for independence. At the same time, their illness often keeps them tied physically, emotionally and financially to their families. Good management of this transition period by healthcare professionals is vital to develop and maintain the self-esteem and confidence of the adolescent with epilepsy.429

15.2 Is a different approach to management required in adolescence?
The physical, psychological, and social needs of young people with epilepsy should always be considered by healthcare professionals. Attention should be paid to their relationships with family and friends, and at school. [2004]
Healthcare professionals should adopt a consulting style that allows the young person with epilepsy to participate as a partner in the consultation. [2004]
Decisions about medication and lifestyle issues should draw on both the expertise of the healthcare professional and the experiences, beliefs and wishes of the young person with epilepsy as well as their family and/or carers. [2004]
During adolescence a named clinician should assume responsibility for the ongoing management of the young person with epilepsy and ensure smooth transition of care to adult services, and be aware of the need for continuing multi-agency support. [2004]

Evidence statement
No studies were identified which tested the effectiveness of interventions (e.g., educational interventions) designed to increase adherence with healthcare professional’s advice in young people with epilepsy.

Details
No systematic reviews of RCTs or RCTs of different processes of care for adolescents with epilepsy were identified.

15.3 What are the factors that affect adherence to treatment in adolescents with epilepsy?
Secondary evidence
One systematic review of adherence with medication in people with epilepsy was identified. Although this review did not focus only on adolescents, it found that being a
teenager was associated with poor adherence with medication (see What influences AED treatment concordance in adults and children?).\textsuperscript{331}

The authors then considered the existing literature on adherence to medication in adolescents as a group. Studies suggested that poor adherence to prescription regimens may be influenced by:

- feelings of isolation,
- feelings of stigma,
- threats to independence and ability to join in with peers,
- perceived lack of understanding of their condition, and
- denial of their epilepsy.

Conversely, good adherence with treatment regime was found to be linked with:

- support from parents,
- support from the doctor,
- good motivation,
- feelings of epilepsy not being a threat to social well-being, and
- [good] family environment.

The authors concluded that the needs of adolescents require special attention.\textsuperscript{331}

15.4 Is there any evidence of effectiveness for any given strategies proposed to improve outcomes for adolescents?

The studies reported in the above systematic review\textsuperscript{331} are reported as showing an association between certain healthcare professional behaviours and self-reported adherence with medication. It should be noted that association does not in itself prove that the relationship is causal, that is, having regular healthcare professional input leads to improved adherence to the treatment plan.

Multidisciplinary services provided jointly by adult and paediatric specialists have a key role in the care of the young person with epilepsy. This can facilitate the transition from paediatric to adult services and aid in the dissemination of information. [2004]

Before the transition to adult services is made, diagnosis and management should be reviewed and access to voluntary organisations, such as support groups and epilepsy charities, should be facilitated. [2004]

Evidence statement

No studies were identified which compared outcomes for young people attending specialist teenage epilepsy as opposed to those attending ‘routine’ child or adult clinics.
Details

Appleton 1999\textsuperscript{430}\textsuperscript{

In this personal practice paper, the authors proposed that a specialist service should be provided because teenagers feel uncomfortable or may feel it inappropriate to continue to attend paediatric services, and they are likely to remain on medication for a long period of time. They suggested that this could be sited within a specific clinic for teenagers.

Smith 2002\textsuperscript{431}\textsuperscript{

This paper reports the experience of one specific teenager epilepsy clinic. It does not compare outcomes for adolescents attending specialist teenage epilepsy as opposed to those attending ‘routine’ child or adult clinics.

15.5 What are the special needs or information requirements of this group?

The information given to young people should cover epilepsy in general and its diagnosis and treatment, the impact of seizures and adequate seizure control, treatment options including side effects and risks, and the risks of injury. Other important issues to be covered are the possible consequences of epilepsy on lifestyle and future career opportunities and decisions, driving and insurance issues, social security and welfare benefit issues, sudden death and the importance of adherence to medication regimes. Information on lifestyle issues should cover recreational drugs, alcohol, sexual activity and sleep deprivation. [2004]

Evidence statements

There is little research available on the specific information needs of young people. (III)

Individuals with epilepsy require information on: Epilepsy in general; Diagnosis and treatment options; Medication and side effects; Seizures and seizure control; Injury prevention; Psychological issues; Social security; Driving and insurance; Employment; Prognosis; Life style and social issues. (III)

Secondary evidence

Couldridge 2001\textsuperscript{359}\textsuperscript{

This UK paper systematically reviewed the information and counselling needs of people with epilepsy. It aimed to locate, appraise and synthesise evidence from key primary research in this area between 1990 and 2000. The review did not focus specifically on the needs of adolescents and epilepsy. Fifteen papers identified specific information needs of people with epilepsy. Results from these studies suggest that people with epilepsy require information on:
1. epilepsy in general
2. diagnosis and treatment options
3. medication and side effects
4. seizures and seizure control
5. injury prevention
6. psychological issues
7. social security
8. driving and insurance
9. employment
10. prognosis
11. lifestyle and social issues

The review identified one paper that dealt specifically with the experiences of young people with epilepsy.

Wilde 1996

This qualitative study was set in the East Midlands (Leicester) and involved in-depth interviews with 24 young people (15 females, 9 males), aged between 13 and 25 years, all of whom had epilepsy and attended outpatient clinics.

The important issues raised included the finding that a large proportion of the sample (71%) reported having been the victims of prejudice, especially bullying and teasing while they were at secondary school. Additionally, many subjects were critical of the medical profession and support services for people with epilepsy, complaining that they were not meeting their needs appropriately. Most subjects reported feelings of apprehension about telling others about their epilepsy, especially members of the opposite sex, and potential employers. Most described supportive, positive relationships with their families and close friends, and parental overprotection was rarely reported by them as being a significant problem. In addition, an estimate of subjects' adjustment to epilepsy was obtained which appears to indicate that the majority were coping well with their condition, even though it may have been resented by some of them.

15.6 Should the diagnosis of epilepsy be revisited in this group?

The diagnosis and management of epilepsy should be reviewed during adolescence. [2004]
Evidence statements

No studies were identified which compared outcomes for young people having their diagnosis reviewed/revisited at their outpatient clinic appointment as opposed to those who did not have their diagnosis reviewed/revisited.

One uncontrolled case review found that 10% of young people attending such a clinic did not have a diagnosis of epilepsy and 22% were on an inappropriate AED. (III)

It is the opinion of respected authorities that the diagnosis and management of epilepsy should be revisited in this group. (IV)

A revisit is indicated on the following grounds: the differential diagnosis of a seizure in young people is wide and can include non-epileptic attack disorder, vasovagal attacks and migraine. (IV)

There is a need to classify the epilepsy syndrome to ensure optimum treatment and accurate prognosis. The choice and side effects of antiepileptic drugs (AEDs) need to be considered in the short and long term. (IV)

Secondary evidence

No systematic reviews of the literature that addressed the above question were identified.

Primary evidence

Appleton 1997

This UK-based study reported a case series from adolescents attending a dedicated clinic for teenagers with epilepsy.

In 1991, a specific clinic for teenagers with epilepsy was established in Liverpool to address the unique needs and concerns of this age group and, importantly, to facilitate a smooth hand-over of specialist epilepsy care from paediatric to adult services. An additional and crucial benefit of this clinic has been to provide a further, and hopefully final, screen to confirm (or refute) the diagnosis of epilepsy, to corroborate, or correctly identify, the specific epilepsy syndrome and to ensure that the most appropriate antiepileptic drug (AED) is being prescribed and when, if possible, the drug can be withdrawn.

Of 120 consecutive individuals referred to the teenager clinic, 12 (10%) did not have epilepsy, and 26 (22%) were being treated with an inappropriate AED. The main issues and concerns voiced by the teenagers included choices of further education and career, the possibility and risks of withdrawing anticonvulsants, driving regulations, the inheritance of epilepsy and pregnancy/contraception.
They identified the following reasons why the diagnosis of epilepsy should be revisited in this group:

- The differential diagnosis of a seizure in adolescents is wide and can include non-epileptic attack disorder, vasovagal attacks and migraine;

- There is a need to classify the epilepsy syndrome given the prevalence of juvenile myoclonic epilepsy in this group;

- Poor seizure control during adolescence can affect maturation due to disruption of endocrine systems;

- The choice and side effects of antiepileptic drugs (AEDs) need to be considered: for boys and girls: the cosmetic side effects of AEDs; for girls: pregnancy and AEDs.

The authors recommended that ‘adolescence is an important time to review the diagnosis of epilepsy’.433

Expert evidence

Appleton 1999430

Appleton and Neville stated that the adolescent period was an important time to review the diagnosis of both epilepsy and the epilepsy syndrome, and to consider any underlying cause. Reasons included previous misdiagnosis, and particularly the potentially serious implications of misdiagnosis for employment, driving, and psychosocial health.
16 Older people

16.1 Introduction

16.2 Pharmacological management of epilepsy in older people

16.2.1 Introduction

The elderly are a rapidly growing population. As a consequence, an increasing number are presenting with epilepsy, many the result of cerebrovascular disease. There is no evidence to suggest that seizures are any more resistant to medication than the younger population. However, the high rate of other illness and comedication, as well as the aging brain, suggest they may require very specific consideration with regard to treatment choice.

16.2.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included older people taking anti-epileptic drugs. We looked for data specifically on the incidence of adverse events (10% or above), cognitive effects and quality of life. Only validated measures of cognitive effect and outcomes relating to quality of life have been investigated for the purposes of this evidence review. The GDG decided that evidence on the effectiveness of the various drugs at reducing number of seizures was better examined by considering the data from general epilepsy population. This data can be found in other sections of the guideline.

16.2.3 Matrix of the evidence

We searched for RCTs comparing the tolerability of different pharmacological interventions for epilepsy in an older population. The interventions we included in our search were pregabalin, zonisamide, lacosamide, lamotrigine gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenyoin, phenobarbitone, clobazam, clonazepam, felbamate, acetazolamide, primidone, sodium valproate and carbamazepine. We searched for any RCT studies that compared the tolerability of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.
16.2.3.1 Lamotrigine monotherapy versus carbamazepine monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements
Adverse events – statistically significant
Significantly more participants on lamotrigine monotherapy compared to carbamazepine monotherapy had:

- Incidence of tremor (LOW QUALITY)
- Incidence of weight loss (MODERATE QUALITY)

Significantly more participants on carbamazepine monotherapy compared to lamotrigine monotherapy had:

- Incidence of death (LOW QUALITY)
- Incidence of somnolence (MODERATE QUALITY)
- Incidence of rash (MODERATE QUALITY)
Adverse events – statistically non-significant

There was no significant difference between lamotrigine monotherapy and carbamazepine monotherapy for incidence of:

- Incidence of poor co-ordination (VERY LOW QUALITY)
- Incidence of dizziness. (VERY LOW QUALITY)
- Incidence of headache. (VERY LOW QUALITY)
- Incidence of sedation. (VERY LOW QUALITY)
- Incidence of GI problems. (VERY LOW QUALITY)
- Incidence of weight gain > 4lbs. (VERY LOW QUALITY)
- Incidence of water retention. (VERY LOW QUALITY)
- Incidence of nystagmus. (VERY LOW QUALITY)
- Incidence of dysarthria. (VERY LOW QUALITY)
- Incidence of gait problems (VERY LOW QUALITY)
- Incidence of change in mood or affect. (VERY LOW QUALITY)
- Incidence of cognitive disturbances. (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:

- quality of life outcomes

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to carbamazepine monotherapy was identified.

16.2.3.2 Lamotrigine monotherapy versus sustained-release carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Adverse events – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy for:

- Withdrawal due to adverse events (VERY LOW QUALITY)
- Incidence of dizziness (VERY LOW QUALITY)
- Incidence of rash/skin reaction (VERY LOW QUALITY)
• Incidence of headache (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results
There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy on the changes in SEALS score.

Outcomes with no evidence
There were no studies that reported:
• Quality of life outcomes

Cost-effectiveness
No economic evidence comparing lamotrigine monotherapy to sustained-release carbamazepine monotherapy was identified.

16.2.3.3 Sodium valproate monotherapy versus phenytoin monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Adverse events – statistically non-significant
There was no significant difference between sodium valproate monotherapy and phenytoin monotherapy for:

• Incidence of unsteadiness. (VERY LOW QUALITY)
• Incidence of Sleepiness. (VERY LOW QUALITY)
• Incidence of Tremor. (VERY LOW QUALITY)
• Incidence of Edema. (VERY LOW QUALITY)
• Incidence of Alopecia. (VERY LOW QUALITY)
• Incidence of Depression. (VERY LOW QUALITY)
• Incidence of Weight gain. (VERY LOW QUALITY)
• Incidence of Cognitive function. (MODERATE QUALITY)

Cognitive events – statistically significant
There was significant improvement in cancellation time test scores for phenytoin monotherapy compared to sodium valproate monotherapy at 6 months only.

Cognitive events – statistically non-significant
There was no significant difference between sodium valproate monotherapy and phenytoin monotherapy for all other cognitive tests at 6 weeks, 3 months, 6 months and 1 year.

Outcomes with no evidence

There were no studies that reported:

- quality of life outcomes

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to phenytoin monotherapy was identified.

16.2.3.4 Gabapentin monotherapy versus carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Adverse events – statistically significant

Significantly more participants on gabapentin monotherapy compared to carbamazepine monotherapy had:

- Incidence of weight gain > 4lbs. (MODERATE QUALITY)
- Incidence of water retention. (MODERATE QUALITY)

Adverse events – statistically non-significant

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for:

- Incidence of GI problems. (VERY LOW QUALITY)
- Incidence of weight loss. (VERY LOW QUALITY)
- Incidence of nystagmus. (VERY LOW QUALITY)
- Incidence of dysarthria. (VERY LOW QUALITY)
- Incidence of gait problems. (VERY LOW QUALITY)
- Incidence of tremor. (VERY LOW QUALITY)
- Incidence of sedation. (VERY LOW QUALITY)
- Incidence of change in mood or affect. (VERY LOW QUALITY)
- Incidence of cognitive disturbances. (VERY LOW QUALITY)
• Incidence of dizziness. (VERY LOW QUALITY)
• Incidence of headaches. (VERY LOW QUALITY)

Outcomes with no evidence
There were no studies that reported:
• quality of life outcomes

Cost-effectiveness
No economic evidence comparing gabapentin monotherapy to carbamazepine monotherapy was identified.

16.2.3.5 Lamotrigine monotherapy versus gabapentin monotherapy

Clinical evidence
For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence
No studies were identified in the economic literature search.

Evidence statements

Adverse events – statistically significant
Significantly more participants on lamotrigine monotherapy compared to gabapentin monotherapy had a higher incidence of weight loss. (MODERATE QUALITY)
Significantly more participants on gabapentin monotherapy compared to lamotrigine monotherapy had:
• Incidence of weight gain > 4 lbs. (MODERATE QUALITY)
• Incidence of water retention. (MODERATE QUALITY)

Adverse events – statistically non-significant
No significant difference between lamotrigine monotherapy and gabapentin monotherapy for:
• Incidence of GI problems. (VERY LOW QUALITY)
• Incidence of Hyponatremia. (VERY LOW QUALITY)
• Incidence of Nystagmus. (VERY LOW QUALITY)
• Incidence of Dysarthria. (VERY LOW QUALITY)
• Incidence of Gait problems. (VERY LOW QUALITY)
• Incidence of Tremor. (VERY LOW QUALITY)
• Incidence of Sedation. (VERY LOW QUALITY)
• Incidence of Change in mood or affect. (VERY LOW QUALITY)
• Incidence of Cognitive disturbances. (VERY LOW QUALITY)
• Incidence of Dizziness. (VERY LOW QUALITY)
• Incidence of Headaches. (VERY LOW QUALITY)

**Outcomes with no evidence**

There were no studies that reported:

• quality of life outcomes

**Cost-effectiveness**

No economic evidence comparing lamotrigine monotherapy to gabapentin monotherapy was identified.

### 16.2.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not discriminate against older people and offer the same investigations and therapies as for the general population. [new 2011]</th>
</tr>
</thead>
</table>

**Relative values of different outcomes**

Adverse effects of drugs and quality of life were considered the most important outcomes for this review as older people are more susceptible to side effects of drugs. Effectiveness of the drugs at reducing numbers of seizures is also important but is dealt with in the other sections of this guideline.

**Trade off between clinical benefits and harms**

AED are associated with significantly more adverse effects. The reduction in seizures found in our other reviews is assumed to be similar for older people. The GDG considered that the benefit of reduction in seizures outweighed the adverse effects associated with drug treatment in the same way as it does for other people with epilepsy.

**Economic considerations**

There was no economic evidence but the GDG considered that treatment with AEDs would be cost effective for older people just as it is for other people with epilepsy.

**Quality of evidence**

This recommendation was based on outcome data that was moderate to very low quality and GDG expertise.

**Other considerations**

The GDG wished to ensure that older people had optimal treatment and had the same opportunities as other adults to access treatments and specialist services. The GDG were concerned that sometimes currently this did not happen. The GDG wished to ensure that older people.
Pay particular attention to pharmacokinetic and pharmacodynamics issues with polypharmacy and comorbidity in older people with epilepsy. Consider using lower doses of AEDs and if using carbamazepine, offer modified-release carbamazepine preparations. [new 2011]

Relative values of different outcomes
Incidence of adverse events and cognitive outcomes were clinically important outcomes for this recommendation.

Trade off between clinical benefits and harms
Carbamazepine had significantly higher incidence of death, somnolence and rash compared to lamotrigine but there was no significant difference between the two drugs when carbamazepine was in sustained-release formulation. Significantly more participants on lamotrigine had weight loss when compared to gabapentin and carbamazepine and tremor when compared to carbamazepine. Significantly more participants on gabapentin had weight gain and water retention when compared to lamotrigine and carbamazepine. The GDG considered that older people may have equivalent reduction in seizures with lower doses of AEDs and by reducing the dose, adverse can be minimalised.

The GDG considered that older people are more likely have additional comorbidities and be taking drugs for their treatment than other adults. Drug interactions and comorbidities may cause undesirable pharmacokinetic and pharmacodynamic issues. Whilst it will take some extra time during the consultation for health care professionals to consider co morbidities and polypharmacy, the GDG considered that the benefits outweighed the risk of not doing this.

Economic considerations
No economic evidence was available to inform cost-effectiveness of AEDs in older people specifically. The GDG thought that the effectiveness of AEDs in this group is likely to be similar to other epilepsy populations and therefore cost-effectiveness was likely to be driven by the incidence of intolerable side effects causing withdrawal of treatment. The GDG also considered that the population may respond to lower doses of various AEDs which could reduce the burden of some side effects as well as reduce costs overall. The extra consultation time taken to consider co-morbidities and polypharmacy was considered to be worthwhile in order to reduce the risk of adverse effects of drug interactions. Finally, modified release formulations of carbamazepine are not more costly than non-modified release carbamazepine.

Quality of evidence
The quality of the studies was good with adequate reporting of randomisation, allocation concealment and blinding. However the drop-out rate was extremely high, with differences between groups which could bias results.
Other considerations

The GDG expertise supported this recommendation that carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations.

The GDG expresses the view that older people have not in general received adequate access to specialist services and there is a risk that they are receiving less than optimum treatment and poorer outcomes. They therefore thought it was important to make this recommendation to pay particular attention to choice of drug and dose for older people.

16.2.5 Deleted recommendations from 2004 guideline

The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for older people as for the general population.
17 People from black and minority ethnic groups

16.3 Introduction

The UK has a sizeable black and minority ethnic population. It is important that the health needs of individuals with epilepsy from black and minority ethnic groups are researched and the research findings disseminated to promote equity of care. To date published research in this area has been limited and has focused on small prevalence studies in particular ethnic groups.

Individuals who have epilepsy and who are black or from a minority ethnic group may encounter specific difficulties that have the potential to adversely affect their health outcomes. They may experience difficulties in communication and in accessing appropriate healthcare, including referral to a specialist to make a diagnosis of epilepsy and starting and continuing appropriate treatment. Different ethnic groups may have different health beliefs in relation to what it means to have a diagnosis of epilepsy, including the extent to which the condition is stigmatised. It is important that healthcare professionals are enabled to deliver culturally sensitive care to individuals with epilepsy from minority ethnic groups.

16.4 What are the information and service provision needs of people from black and minority ethnic groups?

People from black and minority ethnic groups may have different cultural and communication needs and these should be considered during diagnosis and management. The need for interpretation should be considered alongside other means of ensuring that an individual's needs are appropriately met. [2004]

An interpreter should have both cultural and medical knowledge. Interpreters from the family are generally not suitable because of issues such as confidentiality, privacy, personal dignity, and accuracy of translation. [2004]

Information, including information about employment rights and driving, should be available in an appropriate format or through other appropriate means for people who do not speak or read English. [2004]

Evidence statements

South Asians with epilepsy want information on all aspects of epilepsy, including treatment and side effects, and further sources of support, information, and advice. (III)

No other evidence was identified about the information needs of individuals with epilepsy and/or their carers in other black and minority ethnic groups in the UK.

eeThe Institute of Race Relations uses 'black' to refer to non-white groups - with heritages in Asia, Africa and the Caribbean - who share a common experience of British racism.
Details

No evidence was found in the Medicines Alliance review\textsuperscript{331} or the Couldridge review\textsuperscript{359} relating specifically to minority ethnic groups. One primary source of evidence was identified.\textsuperscript{441}

Ismail and colleagues 2003\textsuperscript{441}

This qualitative study aimed to explore the experiences of South Asians with epilepsy in relation to their health needs and beliefs and the role of health professionals in providing appropriate information and accessible services.

Individual in-depth interviews were conducted with a total of 56 people: 30 people with epilepsy and 16 family members (carers) and 10 health professionals. Two focus groups were conducted with 16 members of the wider South Asian community in Bradford.

The research findings covered perceptions of epilepsy, family support, impact on lifestyle and employment, traditional South Asian therapies and service provision. The impact of epilepsy on employment was reported negatively. Four themes were identified in relation to service provision:

- **Lack of information.** There was concern expressed about the lack of appropriate information and advice. The majority of respondents wanted more information from diagnosis onwards. Individuals and their families felt overwhelmed at diagnosis and would have liked more time and further explanations to help adjustment.

- **Language barriers.** One-third of the respondents with epilepsy were not fluent in spoken English. There was very limited use of official interpreters in consultations. Usually family members took on this role with the majority of people with epilepsy expressing a preference for this. However, some people felt embarrassed at the idea of discussing personal problems through family members. Also not all the carers interviewed were happy about interpreting; they admitted having difficulty in translating medical terminology. Also, health professionals expressed concerns about impartiality and confidentiality issues with such arrangements. Those who spoke little or no English wanted non-technical information in their own language. Written information was not always the preferred format as some individuals were unable to read, or felt that verbal communication would be more beneficial.

- **Interaction with healthcare professionals.** Epilepsy nurses were regarded as the most helpful health professionals due to their easy accessibility and holistic approach. Respondents were satisfied with their GPs with a special interest in epilepsy and hospital specialists (consultants) but more than half of respondents expressed dissatisfaction with the care provided by their own GP.

- **Support groups.** A large number of respondents were open-minded about the idea of attending support groups but faced practical difficulties with attendance (e.g., transport, childcare).
17 The care process for people with epilepsy

17.1 Introduction

It is outside the scope of this chapter to make recommendations on service delivery issues as they relate to the individual with epilepsy and/or their carers. It does not therefore directly address models of care, the roles or composition of primary or secondary healthcare teams and competencies, skill mix or training requirements.

The care process for individuals with epilepsy is, however, extremely important and needs to be considered in the guideline. This chapter makes recommendations on the process of care necessary for the individual with epilepsy and/or their carer to achieve the best possible health outcomes. It is thus specified what resources individuals with epilepsy should have access to at their consultation with a specialist (for example, written and visual information) but the guideline does not recommend what form of service configuration can best provide these resources (for example, a dedicated first seizure clinic).

17.2 What features of the care process in primary care/shared care lead to improved health outcomes for adults and children with epilepsy?

<table>
<thead>
<tr>
<th>Adults and children with epilepsy should have a regular structured review and be registered with a general medical practice. [2004]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults should have a regular structured review with their GP, but depending on the individual’s wishes, circumstances and epilepsy, the review may be carried out by the specialist. [2004]</td>
</tr>
<tr>
<td>For adults, the maximum interval between reviews should be 1 year but the frequency of review will be determined by the individual’s epilepsy and their wishes. [2004]</td>
</tr>
<tr>
<td>Epilepsy specialist nurses (ESNs) should be an integral part of the network of care of individuals with epilepsy. The key roles of the ESNs are to support both epilepsy specialists and generalists, to ensure access to community and multi-agency services and to provide information, training and support to the individual, families, carers and, in the case of children, others involved in the child’s education, welfare and well-being. [2004]</td>
</tr>
<tr>
<td>People with epilepsy should have an accessible point of contact with specialist services. [2004]</td>
</tr>
<tr>
<td>All people with epilepsy should have a comprehensive care plan that is agreed between the individual, family and/or carers where appropriate, and primary care and secondary care providers. This should include lifestyle issues as well as medical issues. [2004]</td>
</tr>
</tbody>
</table>

Evidence statements

There is a lack of good quality evidence of effectiveness for structured annual review in primary care. A high proportion of adults who died of epilepsy in the National Sentinel
Clinical Audit of Epilepsy-related Death had not had a structured review. Audits in primary care can improve the process of care for people with epilepsy. (IV)

There is evidence that epilepsy specialist nurses improve the process of care for people with epilepsy in primary care. (Ia)

There is some evidence to show that information recorded is improved and depression reduced with epilepsy specialist nurses. (Ia)

There is currently limited evidence that epilepsy specialist nurses improve clinically important outcomes for people with epilepsy in primary care. (Ia)

17.2.1 What evidence is there regarding the quality of care currently provided in primary care?

Details

Secondary evidence

There were no published high quality reviews identified of the quality of care for adults and children with epilepsy provided in primary care. One narrative review highlighted the limited evidence base in this area and the need for further research.442

Primary evidence

SUDEP 200219

In 2002, the National Sentinel Clinical Audit of Epilepsy was published. The audit reviewed the GP case notes of 285 individuals who died; 45 who received their care entirely within general practice and 241 who also received secondary care

After a first seizure most individuals (84%) were referred to secondary care. There was a low level of clinical information recording in relation to all those who died. Documented evidence of individual, written management plans was lacking. In the year prior to death, there had been no recorded review of 67% of people receiving all their care in general practice. 78% of those who were receiving combined care had been reviewed by either the specialist or the GP. Around 29% of individuals had been seen by their GP for non-epilepsy related problems in the month before death. Four individuals receiving only primary care had a change in seizure frequency, but were not referred. Of those receiving combined primary/secondary care, 68 individuals were considered to fulfil the criteria for re-assessment, but only 6 (9%) were re-referred.19

Clinical Standards Advisory Group (CSAG) 200012

Individuals’ perspectives on care

The CSAG postal survey of users’ views on epilepsy services was conducted across the UK and involved people recruited from both general practice (community sample) and secondary care (hospital sample). A response rate of 52% (2394/4620) was achieved.
Overall 91% were satisfied or fairly satisfied with GP care. There were no major
differences between adults and children, between community-based and hospital-
based samples, or between those who suffer from new-onset continuing epilepsy and
those who have controlled epilepsy. Many people did not consult their GP regularly
about their epilepsy and did not expect their GP to have a detailed knowledge of
epilepsy. In the 12 months before the survey, 58% of the community sample had not
visited a GP to consult about their epilepsy.

The majority of adults in the community sample, most of whom had controlled epilepsy
and were not attending hospital, considered their GP to be the main provider of care
(70%) and expressed a preference for GP care (61%). The majority of adults in the
hospital sample regarded their hospital doctor as the main provider of care (55%).
Only 17% of the overall sample considered their care to be shared between the GP
and hospital doctor. Children, in both samples, preferred care to be either shared
between primary and secondary care or provided by the hospital.

General practitioners perspectives on care

CSAG surveyed GPs in the UK with a 71% response rate (135/189).

The majority of GPs reported that they considered the care of people with epilepsy to be
shared with the hospital (57%). A minority saw their care as either hospital based
with little or no GP involvement (30%; of whom the majority of GPs, 59%, were not
happy with this situation) or GP led (GPs 'completely involved in management') (13%).
GPs felt that better shared care arrangements and communication and access to
hospital would improve clinical services. The most common suggestion (23%) by GPs
for improving primary care epilepsy services was the provision of an epilepsy
specialist nurse. However, only 16% of the GPs surveyed had access to epilepsy
specialist nurses (at either hospital or community level).

Primary care audits

Evidence is available on the quality of care provided in general practice through
published audits conducted in the last ten years. Several of these audits
reported findings from a small number of practices and/or relied on self-selecting
‘volunteer’ practices. One published audit addressed these problems by being region-
wide, randomly selecting the general practices and having a high participation rate
(87% participated, 31/36). They found that recording of information in the
medical notes was generally good, particularly in relation to information on date of
first seizure and AED therapy. It was, however, poor for some key items essential to
the effective management of the condition. A number of recommendations about
provision of care for epilepsy were not being met, in particular, there was little
evidence of any regular review of the care of people with epilepsy being undertaken
by general practitioners and counselling about the non-clinical aspects of epilepsy
often appeared inadequate.

It is difficult to report on the care specifically provided to children with epilepsy in
primary care. Although adults and children with epilepsy were included in a number
of the audits, only a minority of those reviewed were children under the age of 16 (for
example, 11% 444, 5%443) and the audit data were not disaggregated into adults and
children.
17.2.2 What process of care has been proposed to improve outcomes for adults and children with epilepsy in primary care?

- Structured annual review
- Shared care between primary and secondary care, for example facilitated by epilepsy specialist nurses or GPs with a special interest (GPSI) in epilepsy

17.2.2.1 Do adults and children with epilepsy attending primary care who receive structured annual review, when compared with those who do not, have better health outcomes?

Details

A consistent finding from a review of the evidence on the quality of care provided in primary care for people with epilepsy is that care is often reactive and of variable quality. The need for GPs to provide a structured management system for epilepsy, along the lines of that provided for diabetes and asthma, has been proposed by a number of authorities. This could be achieved by a structured annual review.

Secondary evidence

No systematic reviews were identified.

Primary evidence

No randomised controlled trials were found evaluating the effectiveness of structured review in the care of people with epilepsy.

The study by Thapar and colleagues was excluded as this evaluated the opportunistic use of a prompt and reminder card in general practice as opposed to structured annual review.

17.2.2.2 Do adults and children with epilepsy attending primary care who receive care from a specialist epilepsy nurse, when compared with those who do not, have better health outcomes?

Details

The need for shared care protocols between primary and secondary care has been proposed by a number of authorities. The deployment of nurses trained in epilepsy care (specialist epilepsy nurses) working in primary care who could liaise with secondary care has been proposed.
Secondary evidence

Bradley 2003\textsuperscript{450}

A Cochrane review assessed the effectiveness of specialist epilepsy nurses compared to routine care. Any RCTs or quasi-randomised trials that compared specialist nurse interventions compared to routine or alternative care were included.

Three trials were included, one in general practice and two in a neurology centre. The three trials only included individuals aged 15 years or older.

The findings from the trial based in general practice are summarised here.

The Ridsdale RCT\textsuperscript{451} (and the follow-up paper\textsuperscript{452}) was based in general practice and most of the participants had established epilepsy. The study included 251 adults (aged 15 years or over). The intervention involved an interview with a specialist epilepsy nurse followed-up by two specialist nurse interviews in addition to 'standard care'. A concern raised in the Cochrane review\textsuperscript{450} was that participants in the intervention group were told that they would attend a 'neurology clinic', which may have been interpreted as specialist care. Potentially this belief may have improved outcomes over and above the effects of the intervention from the epilepsy specialist nurse. The study key outcome variables were knowledge of epilepsy, and depression and anxiety scores at six months (assessed by validated questionnaires given before and after the intervention) and the recording of key variables (driving; drug compliance; adverse drug effects; alcohol, and self help groups) extracted from the clinical records.

The authors reported an increase of advice recorded in the notes of people with epilepsy ($p<0.001$). They also found a significant decrease in the risk for depression at six months ($p=0.024$) in those individuals who had not experienced an epileptic seizure in the last six months ($p=0.03$). However, there was no significant difference between control and intervention groups in those who had experienced a seizure in the last six months ($p=0.44$).

In conclusion, this study did not show an improvement in any clinically important outcomes\textsuperscript{453} for people with epilepsy managed in general practice by an epilepsy specialist nurse. As the authors of the study themselves noted ‘this study was small in size and scope, focusing on process rather than outcomes’ and the authors of the review called for further research in this area.\textsuperscript{450}

No systematic reviews of paediatric clinics were identified.

Primary evidence

No randomised controlled trials were found evaluating the effectiveness of epilepsy specialist nurses published after the date of the above Cochrane Review.

17.3 What features of the care process in secondary and tertiary care lead to improved health outcomes for adults and children with epilepsy?

Adults should have regular reviews. In addition, access to either secondary or tertiary care should be available to ensure appropriate diagnosis, investigation and treatment.
If the individual or clinician view the epilepsy as inadequately controlled. [2004]

Adults with well-controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist. [2004]

Children should have a regular structured review with a specialist. [2004]

For children, the maximum interval between reviews should be 1 year, but the frequency of reviews should be determined by the individual's epilepsy and their wishes and those of the family and/or carers. The interval between reviews should be agreed between the individual, their family and/or carers as appropriate, and the specialist, but is likely to be between 3 and 12 months. [2004]

At the review individuals should have access to: written and visual information; counselling services; information about voluntary organizations; epilepsy specialist nurses; timely and appropriate investigations; referral to tertiary services including surgery, where appropriate. [2004]

If the structured review is to be conducted by the specialist, this may be best provided in the context of a specialist clinic. [2004]

Evidence statements

There is a lack of good quality evidence of effectiveness of dedicated epilepsy clinics in secondary and tertiary care. (Ia)

There is some evidence that epilepsy specialist nurses improve clinically important outcomes such as knowledge, anxiety and depression for people with epilepsy in secondary and tertiary care. (III)

17.3.1 What evidence is there of the quality of care currently provided in secondary/tertiary care?

Details

Secondary evidence

No systematic reviews were identified that summarised the quality of care in the secondary and tertiary care settings.

Primary evidence

SUDEP report

In 2002, the National Sentinel Clinical Audit of Epilepsy was published. 180 cases were audited (158 adults and 22 children). Clinical review of these deaths suggested that 60% of epilepsy-related deaths were SUDEP and a further 7% were possible
SUDEP. However, these numbers were estimates because of concerns about information available to the audit on the circumstances of death, the events leading up to the death and the adequacy of post-mortem investigations.

Only 3% of people who died were recorded as seizure-free at their last hospital appointment. Most of the paediatric deaths occurred in individuals who had seizures that were difficult to control and/or had learning or physical disabilities. Although most adults (93%) were not recorded as seizure-free for at least a year before death, at least 37% of these people were not seen in the year before they died. The reasons for this were unclear in 50% of cases. Three individuals with learning disabilities had been ‘lost’ in the handover from paediatric to adult care. Around 15% of adults missed at least one appointment.

Access to appropriate specialist care was a particular problem in children and in adults with special needs. About 36% of children had inadequate access to a specialist in epilepsy care. Adults with learning difficulties were less likely to see a consultant.

In adults, seizure frequency was either not recorded or unclear in 47% of deaths. In children, there was inadequate documentation of classification of seizure type and syndrome and consideration of an underlying cause, and seizure frequency was either not recorded or unclear in 41% of deaths.

It appeared that appropriate investigation was poor in a significant percentage of people who died. For example, in adults, 32% did not have EEGs and of these 43% were under 25 years at diagnosis and should have had an EEG. Investigations were inadequate in 32% of children.

From a review of the audit findings, the expert panel raised concerns about therapeutic management and considered that it was deficient in 20% of adults and 45% of children. Six percent of adults and 18% of children had not been prescribed any antiepileptic drug (AED) at the time of death, in some cases despite ongoing seizures, and 14% of adults had documented drug adherence problems. Issues relating to therapeutic management included inappropriate choice or combinations of AED, sub-optimal or inappropriate doses, unsupervised or inappropriate management of AED treatment changes, little consideration of alternative or additional AEDs in cases of ongoing seizures and major drug errors.

The expert panel considered that secondary care had been inadequate (or contained at least one major error) in 85 adults (54%) and 17 children (77%). Most of these children and most adults had deficiencies in more than one aspect of care (and in addition to any finding on provision of information and support).

The main problems in adults and children with overall inadequate care were access to specialist care (66% of adults and 47% of children), lack of appropriate investigations (25% of adults and 41% of children) and therapeutic management (38% of adults and 59% of children). Overall, 39% of adult deaths and 59% of deaths in children were considered to have been potentially or probably avoidable.19
Clinical Standards Advisory Group (CSAG) report 2000\textsuperscript{12}

Users’ perspectives on care

The Clinical Standards Advisory Group was asked to advise on standards of NHS services for people with epilepsy. As part of the report, the experience of users was studied\textsuperscript{2454}. In all, 2,394 people with epilepsy took part in the postal survey; one in ten were newly diagnosed, 54% had continuing epilepsy and 37% had controlled epilepsy. In 54% of cases, epilepsy was classified as severe, and in 46% of cases, as mild.

There was little difference in overall experience between adults and children, or between those who had new-onset continuing epilepsy and those who had controlled epilepsy; the hospital-based sample of adults had a higher level of satisfaction with secondary care than the population-based sample (93% compared with 83%), but satisfaction was high for both groups of children (96%).

In the community-based sample, only 30% of all people had attended as an outpatient at a hospital in the preceding 12 months. For those attending hospital clinics, the levels of satisfaction were reasonably high: 87% found communication with their hospital doctors satisfactory or fairly satisfactory (85% adults and 93% children), and 80% felt that their hospital doctors took their views into account. However, 73% of respondents attending the hospital clinics reported seeing the same doctor repeatedly.

Most individuals (90% of the community-based sample and all of the hospital based sample) had been referred to a hospital doctor at the onset of symptoms. Approximately a third were waiting for six weeks or more before being seen. Individuals with established epilepsy had far longer waiting times for re-referral and longer intervals between follow-up appointments.\textsuperscript{12}

Clinicians’ perspectives on care

CSAG\textsuperscript{12} also surveyed neurologists (n=220), paediatricians running general paediatric clinics (n=64), general physicians (n=27), geriatricians (=27), and learning disability doctors(n=33) in the UK about the quality of secondary care for people with epilepsy.

Tertiary services were assessed by systematic telephone survey of all appropriate NHS Trusts in the UK.

All respondents thought that adults with newly diagnosed epilepsy should be referred to a hospital and those with continuing epilepsy should receive ongoing hospital care. There was concern about the lack of facilities in general clinics, long waiting times, the lack of clinic time for individuals and the paucity of links with other specialists. There was a widely held view that there were too few specialist staff, particularly neurologists, to meet the demand on hospital services. Hospital physicians supported the concept of shared care, as a means of improving efficiency and quality of care and ensuring that referrals are appropriate.

Most children were seen in general paediatric clinics; however, most of these clinics lacked staff who had a special interest in epilepsy. There was strong support for the view that some general paediatricians should be encouraged to take a special interest in epilepsy and to run special epilepsy clinics within general paediatric services. There was general agreement that clinics specialising in epilepsy could provide better care.
Access to and facilities for children in paediatric clinics were considered to be better than in adult neurology clinics. It was widely agreed that all children on medication for epilepsy should receive ongoing hospital care. The need for better access to specialist neurology and specialist epilepsy services was emphasised.

The evidence showed that there had been a marked expansion of neurology services in the UK during the last decade. There were general improvements in many aspects, although regional differences still existed. Examples of high-quality services were encountered, but the level of quality almost always depended on the exceptional activities of individuals. The hub and spoke model of neurology services however had a centrifugal momentum, and this did not generally engender the development of local services. Epilepsy is a common neurological condition, with a frequency and complexity that requires the facilities of both a regional centre and a local service. It requires services provided at primary, secondary and tertiary levels to be well integrated and co-ordinated. The poor correlation between severity of epilepsy and access to, or level of, specialist advice indicated both a lack of clear purpose in the patterns of referral and also possible wastefulness in the use of secondary and tertiary services.

The research team concluded that the requirement for a more integrated service would be best met by the development of a special epilepsy service (the Epilepsy Centre) within general neurology, situated at a local level which could take a local perspective but also have strong links to the regional NNC.12

Independent Review of Paediatric Neurology Services In Leicester 2003455

This review into the provision of paediatric neurology services in Leicester recommended:

- that formal appraisal of consultant medical staff operating on a single-handed basis should ensure that opportunities are in place for effective clinical networking incorporating peer review and that these opportunities are appropriately utilised.

- that the appropriate authorities consider clarifying the training requirements and qualifications needed for consultant medical staff practising in speciality areas, with particular reference to paediatric neurology.455

Other primary evidence

Bradley 1999456

Bradley and colleagues conducted a primary care based audit of epilepsy care, that evaluated the opinions of users and standards of care in both primary and secondary care. A user questionnaire was also analysed. The data from 395 clinical records and 211 questionnaires were included. Of the individuals who had hospital records (n=149), only 47% (n=70/149) were confirmed as seeing an appropriate specialist (defined as a neurologist, physician or psychiatrist with an interest in epilepsy, or paediatrician with an interest in epilepsy as relevant). 99% (n=147/149) had investigation by EEG, 22% (n=33/149) CT scan, with other investigations (MRI, video telemetry etc) being less common. 30% (n=63/211) of individuals reported having a blood test to check serum drug levels in the previous 12 months.
In general, the standard of record keeping in hospitals was lower than in general practice. In particular, the levels of recording of advice given were low, with those in hospital lower than general practice in most cases.556

Reynders 2002457

Reynders and Baker undertook a questionnaire survey to review the current practice of neuropsychologists working within epilepsy services in the UK. They found that although progress had been made towards fulfilling the recommended 1991 ILAE guidelines for services, not all had been implemented.

There was a need for appropriate and nationally recognised training for neuropsychologists and the establishment of centres of excellence. The review showed that meeting the full range of psychological needs of the individuals and their families remained underdeveloped.457

17.3.2 What process of care has been proposed to improve outcomes for adults and children with epilepsy in secondary/tertiary care?

- Specific epilepsy/seizure clinics
- Epilepsy Nurse Specialists

17.3.2.1 Do adults and children with epilepsy attending secondary care who receive care in a specialist clinic, when compared with those who do not, have better health outcomes?

Details

In the CSAG survey of clinicians, there was general agreement that clinics specialising in epilepsy could provide better care, and individuals expressed strong support for such services.12 Specialised clinics have also been proposed by many authorities.12,448

Secondary Evidence

Bowley 2000458

In a recent narrative literature review of epilepsy in people with learning disabilities, no evidence of research in service delivery was identified.

Bradley 2003459

One Cochrane review was identified that assessed the effectiveness of specialist epilepsy clinics compared to routine care. The selection criteria were any RCTs or quasi-randomised trials considering specialist clinic interventions compared to routine or alternative care. No trials of suitable quality were identified and the review concluded that it is not known whether such clinics improve outcomes for people with epilepsy459.
17.3.2.2 Do adults and children with epilepsy attending secondary care who receive care from a specialist nurse, when compared with those who do not, have better health outcomes?

Details

The role of the specialist nurse is supported by many authorities,\textsuperscript{12,448} and detailed descriptions of the role have been proposed.

Secondary evidence

Bradley 2003\textsuperscript{450}

A Cochrane review assessed the effectiveness of specialist epilepsy nurses compared to routine care. Any RCTs or quasi-randomised trials that compared specialist nurse interventions compared to routine or alternative care were included.

Three trials were included, one in general practice and two in neurology centres. The three trials only included adults aged 15 years or older. The two trials in neurology centres are presented below.

Ridsdale and colleagues assessed the effect of an epilepsy nurse specialist on newly diagnosed adults’ knowledge of epilepsy, satisfaction with the advice provided, and psychological well-being\textsuperscript{460}. The trial was assessed as of adequate quality. Individuals randomised to see the nurse specialist were significantly more likely to report that enough advice had been provided on most epilepsy-related topics compared with the control group. There were no significant differences in knowledge of epilepsy scores. However, there were significant differences in the group who, at baseline, had knowledge scores in the lowest quartile; those randomised to the nurse had higher knowledge scores (42.7 vs. 37.2; p<0.01). Compared with doctors, the nurse was highly rated for providing clear explanations.

The quality of the trial based in tertiary care\textsuperscript{461} was assessed as unclear. There was no significant difference between the intervention and control group for seizure frequency, levels of anxiety and depression, social functioning, overall health status, or absence from work. However, there was an increase in knowledge in the intervention group (p=0.035), although there is some concern about the reliability of the scale used (EKP-G scale). This trial reported a significant decrease in outpatient clinic hospital attendances (p<0.01) and a non-significant decrease in GP consultations (p=0.054). The economic evaluation suggested that specialist epilepsy nurse care is cheaper than standard care, but there were several flaws. However, the review stated that there was no evidence to suggest that specialist nurses were more expensive\textsuperscript{450}.

The review concluded that, for both primary and secondary/tertiary care, there was no convincing evidence that specialist nurse services improve outcomes for people with epilepsy, but low baseline knowledge in individuals with newly diagnosed epilepsy may be improved.

Meads 2002\textsuperscript{462}

Meads and colleagues reviewed the literature on both specialist epilepsy clinics compared to general neurology clinics and specialist nurses compared to usual care.
Unlike the Cochrane reviews described above, study designs other than RCTs were included.

For epilepsy clinics, the evidence was of poor quality with poorly designed studies and a different case-mix between specialist clinics and general neurology clinics.

For specialist nurses, the evidence was of a higher quality but showed no differences regarding seizure frequency or seizure severity between those receiving care from specialist nurses or usual care. However, there was some evidence that incidence of depression was decreased (one study of three). There was good evidence to show that the process of care was improved and that user satisfaction was improved. The one RCT that compared quality of life showed no difference between the groups.

The results were summarised as:

- Epilepsy clinics showed no evidence of reduced seizure frequency or severity, no quality of life information and were more expensive.
- Epilepsy nurse services showed no evidence of reduced seizure frequency or severity, no effect on quality of life but were less expensive.462.

Primary evidence

There were no RCTs identified as being published since the reviews presented above.

Health economics

Meads 2002462

The objectives of this paper were to systematically review two aspects of specialist epilepsy care provision:

- the evidence on the relative effectiveness and cost-effectiveness of specialist epilepsy clinics compared to general neurology outpatient clinics.
- the effectiveness on the relative effectiveness and cost-effectiveness of specialist epilepsy nurses in inpatient, outpatient or GP care compared to ‘usual care’ without a specialist epilepsy nurse.

Of the included studies on specialist clinics, only the RCT included an economic analysis, but it was poorly designed. The study estimates gave a total mean clinic cost per patient per year of £106.57 for the epilepsy clinic and £106.57 for the neurology clinic. The trial authors did not report any distribution information and the costs were not necessarily typical of all individuals.

In the RCT assessing the effectiveness of nurse specialists, the total mean NHS cost per patient per year was calculated to be £674 for the epilepsy nurse group and £858 for usual care; however, this was not a statistically significant reduction and was largely accounted for by the lower cost for an epilepsy nurses’ time compared to that for a doctor. The EUROQOL quality of life results showed that there were no
significant differences between the two groups on both weighted health status and self-rated health.

Meads and colleagues concluded that more research was needed to determine the most clinical effective model of service provision for people with epilepsy. The lower cost and the fact that user satisfaction and the process of care was superior with specialist epilepsy nurses suggested that, in the absence of better evidence, this could be an appropriate method of delivering care.462

17.4 What features of the care process in A&E lead to improved health outcomes for adults and children with epilepsy?

At the initial assessment for a recent onset seizure, the specialist should have access to appropriate investigations. [2004]

Individuals presenting to an Accident and Emergency department following a suspected seizure should be screened initially. This should be done by an adult or paediatric physician with onward referral to a specialist when an epileptic seizure is suspected or there is diagnostic doubt. [2004]

Protocols should be in place that ensure proper assessment in the emergency setting for individuals presenting with an epileptic seizure (suspected or confirmed). [2004]

Evidence statement

No evidence of effectiveness for components of the care process for people with epilepsy in an A&E setting was identified.

17.4.1 Quality of care currently provided in emergency departments (A&E)

Details

A&E departments often provide care to people with epilepsy for various reasons. In one study,463 43% of the study population (n=1,628) had attended an A&E department on account of epilepsy, and 47% required hospital admission.

Secondary evidence

No systematic reviews of the quality of care in A&E were identified.

Primary evidence

CSAG report12

The survey found that 15% of the community-based sample and 35% of the hospital-based sample had attended A&E during the previous 12 months because of their epilepsy. Of the community-based sample, 9% had been admitted overnight as an
emergency compared to 21% of the hospital-based sample. Of those admitted from
both groups, 80% stayed in hospital for 1–5 days.

Almost half of the individuals with first seizures presented to an A&E department
rather than to a GP.

Other areas of concern were identified from the research literature including poorly
controlled seizures, poor quality record keeping, wide variation in investigations done,
and hospital admissions.12

Other primary evidence

Ryan 1998464

In 1998, Ryan and colleagues published a comparative interdepartmental audit to
assess the quality and degree of completeness of documentation in A&E records and
to develop a proforma for the documentation of any case presenting with a seizure
which would incorporate management guidelines for use by A and E doctors. It was
carried out in 12 A&E departments in the South Thames region involving 1200 adults
who presented to A&E departments after a seizure (retrospective sample of 100 per
department).

Important aspects of the history and examination were frequently unrecorded in the
notes. The recording of vital signs was particularly poor, for example the
documentation rate of respiratory rate ranged from 34% to 92%, mean 63.4%. A
diversity of practice was shown between the departments that were audited and the
number of investigations performed in each department varied considerably, for
example glucose was measured in around 24% of the sample, range 10% to 39%.
Hospital admissions for people with first seizures varied widely between departments,
ranging from between 34.6% to 91.7% of cases. Of those admitted, 72.5% were
admitted to a general ward, and 27.5% to an A&E short stay ward. Documentation
of advice given to individuals about driving was recorded in 0.9% of cases.464

Reuber 2000465

Reuber and colleagues reviewed the A&E records of all adults attending the casualty
department at St James’s University Hospital with emergencies related to epilepsy
between 1 April and 30 September 1998. Out of a total of 36 024 adults attending,
190 were emergencies relating to epilepsy.

A problem relating to a previously recognized seizure disorder was the commonest
reason for attendance (see 18.1). Only 20% of attendances were for first seizures
(38/190). Care was highly variable and often suboptimal. Descriptions of seizure
semiology and examination findings were frequently deficient with only 59.4% (113
of 190) having a description recorded and 77.4% (147 of 190) having some form of
neurological examination. Most who attended did not require any treatment with
anticonvulsants in A&E. Only 19.5% (37 of 190) of cases received anticonvulsants
acutely. Intravenous or rectal diazepam was invariably used as first-line treatment.
Neurology Senior House Officers (SHOs) or registrars were only contacted about a
minority of cases (19.5%, 37 of 190). 59% (112 of 190) of all individuals seen with
emergencies relating to epilepsy were discharged home from A&E. 20% (3 of 15) of
adults fulfilling our definition of status epilepticus were sent home after receiving
emergency treatment with diazepam in A&E. Only a minority presenting with
emergencies related to epilepsy were referred for neurological follow-up, noted to be
under regular specialist follow-up, or admitted to the neurology ward (24.2%, 46 of
190).465

Figure 18.1 Causes of attendance465 Modified from Seizure, 9, Reuber M, Hattingh L and Goudling PJ,
Epileptological emergencies in accident and emergency: a survey at St James’s university hospital,
Leeds, pages 216-20, Copyright (2000) with permission from BEA Trading Ltd.

No evidence was found of the quality of care for children in A&E.

One audit was identified that audited the use of a specific treatment protocol rather
than any variation in care, so was excluded.466

17.4.2 What process of care has been proposed to improve outcomes for
adults and children with epilepsy in A&E?

No proposed process of care was identified for A&E departments.

17.5 How effective are individual/self management plans in adults and
children with epilepsy?

17.5.1 Introduction

There has been increasing interest in the use of self-management education to improve
the quality of life of people with long-term health conditions. Self-management
education programmes should employ a sound theoretical model of behaviour change
and employ strategies to empower people to build on their existing knowledge, skills
and self-efficacy (the confidence that one can carry out a behaviour necessary to
reach a desired goal). Their overall aim is to encourage individuals to take greater
control over their condition. Research from other chronic diseases such as asthma and
diabetes shows that self-management education can improve health outcomes.
Epilepsy self-management can be defined (or described) as a range of actions and skills that may help individuals with epilepsy feel more confident about making decisions about their condition, taking action about seizure control, using medication, and living with their condition. Good self-management includes working in partnership with healthcare professionals to decide the best treatment and care plan for their epilepsy. Self-management also involves developing strategies to manage the emotional and physical challenges of epilepsy, and ways to live life to the full, despite the condition.

17.5.2 Do adults and children with epilepsy who are educated in self-management, when compared with those who do not, have better health outcomes?

People with epilepsy and their families and/or carers should be empowered to manage their condition as well as possible. [2004]

Adults should receive appropriate information and education about all aspects of epilepsy. This may be best achieved and maintained through structured self-management plans. [2004]

In children, self management of epilepsy may be best achieved through active child-centred training models and interventions. [2004]

Healthcare professionals should highlight the Expert Patients Programme (www.expertpatients.nhs.uk) to individuals with epilepsy who wish to manage their condition more effectively. [2004]

Evidence statements

Self management education for adults with epilepsy can lead to an improvement in seizure frequency. It has also been shown to increase individuals' understanding of epilepsy and their adherence with medication and decrease individuals' fear of seizures and hazardous medical self-management strategies. (Ib)

Active education in children with epilepsy can lead to an improvement in seizure frequency. It has also been shown to decrease hospital emergency room attendance, school absenteeism and unnecessary restriction of activities. (Ib)

Secondary evidence

No systematic reviews were found that answered this KCQ.

Primary evidence

Four studies evaluated the use of self-management programs for people with epilepsy; two RCTs included adults only and two children.
Helgeson and colleagues assessed the effectiveness of the Sepulveda Epilepsy Education program (SEE) in adults. This individual/family programme used a psychoeducational treatment approach to deliver psychosocial help and health education. The underlying belief is that an adequate understanding of epilepsy leads to more effective coping strategies.

Thirty eight outpatients matched according to seizure type and frequency were assigned to treatment (n=20) or to a waiting list control group (n=18). The treatment group showed a significant increase in overall understanding of epilepsy (F(1,36)=39.74, p<0.0001), a significant decrease in fear of seizures (F(1,36)=7.49, p<0.009), and a significant decrease in hazardous self-management practices (F(1,36)=29.67, p<0.0001). The treatment group also showed a significant increase in medication compliance (F(1,24)=4.18, p<0.05).

The efficacy of the MOSES educational treatment programme for adults with epilepsy was evaluated by May and Pfafflin. 383 adults over the age of 16 years from 22 epilepsy centres were randomly allocated to either MOSES or a waiting list control group. Of the 242 that completed both questionnaires, 113 were allocated to the intervention group and 129 to the control group.

Although both groups showed improvements, the participants in MOSES showed significant improvements in knowledge (p<0.001), coping with epilepsy (p=0.004), seizure frequency (p=0.041), and were more satisfied with the therapy (better tolerability of AEDs, fewer side effects p=0.014) compared with the control group. The participants were also highly satisfied with the programme. However, there were many aspects of epilepsy measures that were not improved by the programme, including unnecessary restriction of activities, and epilepsy-related fears.

Lewis and colleagues assessed the impact of the Children’s Epilepsy Programme (CEP) on children with epilepsy and their parents. The CEP is a child-centred, family focused intervention based on decision making and communication.

252 children aged 7 to 14 years were randomised to either ‘active’ education (n=123) or to ‘passive’ education (n=113) where the same information was presented in a more traditional lecture format. The children and parents were assessed both before the intervention and 5 months after.

There was an increase in knowledge in both groups of children, but the knowledge of children in the intervention group increased significantly compared to the control group in areas related to management of seizures (during seizure no objects in the mouth p=0.002, during seizure do not restrain p=0.001, after seizure ER visit not required p=0.001) and unnecessary restriction of activities (p=0.001). There was a significant increase in the self-perception of social competency (p<0.05) in the intervention group (n=106) than the control group (n=92) and they also reported significantly better behaviour (p<0.002).

As for children, there was an increase in knowledge for both groups of parents. However, there was a significant decrease in knowledge related to seizure.
management (loss of sleep can trigger seizures $p=0.005$) in the intervention group (n=185) compared to the control group (n=180). Parents in the intervention group (n=175), and mothers particularly, were more likely to report that they were less anxious ($p<0.001$) and the levels of anxiety were decreased ($p<0.01$) when compared to the control group (n=176).469

An RCT of the ACINDES child-centred training model for children with chronic illnesses was conducted. This included 355 children aged between 6 and 15 years old, with moderate to severe asthma or epilepsy. 167 children with epilepsy were randomised to the intervention (n=103) or control (n=64) group.

Children in the intervention group showed significant improvements in knowledge, belief, attitudes, and behaviours compared with the control group (probability of experimental gain over control =0.69, $\sigma^2=0.007$). Parents of the children also had improved knowledge of epilepsy (increased from 22% to 56% c.f. control 8% to 15%, probability of experimental gain over control =0.62, $\sigma^2=0.0026$) and decreased fear of the child’s death (decreased from 69% to 30% c.f. control 74% to 65%, probability of experimental gain over control =0.63, $\sigma^2=0.0026$). The parents in the intervention group allowed their children to sleep at friend’s homes more often (probability of experimental gain over control =0.59, $\sigma^2=0.0026$). Rates of seizures ($p=0.026$), emergency visits ($p=0.046$), and school absenteeism ($p=0.011$) decreased significantly in the intervention group compared with the control group.470
18 References

1 National Collaborating Centre for Primary Care. *Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence.* London: Royal College of General Practitioners, 2009.


46 Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994; 271(9):703-707.


73 Sundaram M, Hogan T, Hiscock M et al. Factors affecting interictal spike
75(4):358-360.

74 Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting
the diagnosis of epilepsy: an operational curve. *Epilepsia.* 1987; 28(4):331-
334.

75 Ellingson RJ, Wilken K, Bennett DR. Efficacy of sleep deprivation as an
activation procedure in epilepsy patients. *J Clin Neurophysiol.* 1984; 1(1):83-
101.

76 Glick TH. The sleep-deprived electroencephalogram: evidence and practice.

77 Carpay JA, de Weerd AW, Schimsheimer RJ et al. The diagnostic yield of a
second EEG after partial sleep deprivation: a prospective study in children with

78 Schreiner A, Pohlmann-Eden B. Value of the early electroencephalogram after

79 Wassmer E, Quinn E, Seri S et al. The acceptability of sleep-deprived

80 Wassmer E, Carter PF, Quinn E et al. Melatonin is useful for recording sleep
EEGs: a prospective audit of outcome. *Dev Med Child Neurol.* 2001;

81 Cascino GD. Video-EEG monitoring in adults. *Epilepsia.* 2002; 43(SUPPL. 3):80-
93.

82 Krumholz A. Nonepileptic seizures: diagnosis and management. *Neurology.*

83 Kuyk J, Leijten F, Meinardi H et al. The diagnosis of psychogenic non-epileptic

84 Bye A, Lamont P, Healy L. Commencement of a paediatric EEG-video telemetry

85 Foley CM, Legido A, Miles DK et al. Diagnostic value of pediatric outpatient

86 Oldani A, Zucconi M, Smirne S et al. The neurophysiological evaluation of

87 Shihabuddin B, Abou-Khalil B, Fakhoury T. The value of combined ambulatory
cassette-EEG and video monitoring in the differential diagnosis of intractable


120 Buelow JM, McNelis A. Should every child with epilepsy undergo a neuropsychological evaluation? *Epilepsy & Behavior.* 2002; 3(3):1


156 Kwan P, Sperling MR. Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? Epilepsia. 2009; 50 Suppl 8:S7-62.


187 Shorvon SD, Lowenthal A, Janz D et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with


240 Kerr, M. *An open randomised comparison of add-on lamotrigine or valproate/carbamazepine withdrawing to monotherapy in patients with treatment resistant epilepsy.* (Report No. SCAB3001 (105-133)). Critchley Park: Glaxo Wellcome UK, 2001.


259 Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison. *Epilepsy and Behavior.* 2007; 10(4):547-552.


342 Hartman AL. Does the effectiveness of the ketogenic diet in different epilepsies yield insights into its mechanisms? Epilepsia. 2008; 49(Suppl 8):53-56.


Goldstein LH, Minchin L, Stubbs P. Are what people know about their epilepsy and what they want from an epilepsy service related? Seizure. 1997; 6:425-442.


Ridsdale L, Morgan M. Promoting selfcare in epilepsy: the views of patients on the advice they had received from specialists, family doctors and an epilepsy nurse. Patient Education & Counseling. 1999; 37:43-47.


413 Deb S. Epidemiology and treatment of epilepsy in patients who are mentally retarded. CNS Drugs. 2000; 13(2)


441 Ismail, H, Wright, J., Rhodes, P., and Small, N. South Asians and epilepsy. 

442 Thapar AK. Care of patients with epilepsy in the community: will new initiatives 


444 Jacoby A, Graham-Jones S, Baker G et al. A general practice records audit of 
the process of care for people with epilepsy. Br J Gen Pract. 1996; 
46(411):595-599.

445 Redhead K, Tasker P, Suchak K et al. Audit of the care of patients with 

446 Chappell B, Hall WW. Managing epilepsy in general practice: the 
dissemination and uptake of a free audit package, and collated results from 

447 Hodgson J, Beardmore G, Hall WW. Can district-wide audits improve primary 
care epilepsy management? An audit of seizure frequency recording. Br J Gen 

448 Frost, S., Crawford, P., Mera, S., and Chappell, B. National Statement of Good 
Practice for the treatment and care of people who have epilepsy. Joint Epilepsy 

449 Ridsdale L. The effect of specially trained epilepsy nurses in primary care: a 

450 Bradley P, Lindsay B. Specialist epilepsy nurses for treating epilepsy. Cochrane 
Database of Systematic Reviews. 2003; Issue 2:CD001907.

451 Ridsdale L, Robins D, Cryer C et al. Feasibility and effects of nurse run clinics 
for patients with epilepsy in general practice: randomised controlled trial. BMJ: 

452 Ridsdale L, Kwan I, Cryer C. The effect of a special nurse on patients' 
knowledge of epilepsy and their emotional state. Br J Gen Pract. 1999; 


454 Poole K, Moran N, Bell G et al. Patients' perspectives on services for epilepsy: 
A survey of patient satisfaction, preferences and information provision in 2394 

455 Independent review into paediatric neurology services in Leicester. London: 


459 Bradley P, Lindsay B. Epilepsy clinics versus general neurology or medical clinics. Cochrane Database of Systematic Reviews. 2003; Issue 2:CD001910.


