

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

October 2004

***National Collaborating Centre
for Primary Care***

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Foreword

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.

Preface

Dr Richard Roberts

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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.

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Abbreviations and glossary of terms

Abbreviations

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

Glossary of terms

Unless otherwise stated, taken from *Mosby's Medical, Nursing and Allied Health Dictionary 5th edition* and supplemented by the text of the full guideline.

Adherence	Acting in accordance with advice, recommendation or instruction. Compare with definition of concordance.
Aetiology	The cause or origin of a disease or disorder as determined by medical diagnosis.
Anti epileptic drug (AED)	Medication taken daily to prevent the recurrence of epileptic seizures. Refer to Appendix B concerning the choice of drug, side effects and suitability to syndrome.
Attack	An episode in the course of an illness.
Benign epilepsy syndrome*	A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae.
Clinical presentation	Refer to Appendix A for principal differential diagnoses for each presenting clinical scenario and their diagnostic features.
Concordance	Agreement between individual and clinical practitioner to follow a course of action. A mutual decision that is acted upon. Compare with definition of adherence.
Cryptogenic	A disease of unknown cause.
Dysmorphic	Abnormally formed.
Electroencephalography (EEG)	The process of recording brain wave activity. Electrodes are attached to various areas of the individual's head with collodion. Refer to 9.2 for the role of EEG in diagnosis of epilepsy and epilepsy syndromes.
Epilepsy	Recurrent epileptic seizures of primary cerebral origin.
Epileptic seizure*	An ictal event believed to represent a unique pathophysiologic mechanism and anatomical substrate. This is a diagnostic entity with aetiologic, therapeutic, and prognostic implications.
Epilepsy syndrome*	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 <i>per se</i> , for instance, do not constitute a syndrome. For example, 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.
Focal seizures and syndromes*	Replaces the terms partial seizures and localization-related syndromes.
Ictal phenomenology	Description or history of ictal events (seizures).
Idiopathic	Without known cause.
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.
Idiosyncratic	Physical or behavioural characteristic that is personal to that individual.
Ketogenic diet	A specific diet which is high in fats and low in carbohydrates and protein.
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.
Parasomnia	Any dysfunction associated with sleep. For example, headbanging/confusional arousal/REM sleep disorder – night terrors.
Pharmacokinetic interaction	The way, in which a drug is processed by the body, influencing absorption, metabolism, distribution and excretion.
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.
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.
Randomised controlled trial (RCT)	A study plan for a new treatment in which subjects are assigned on a random basis to participate either in an experimental group receiving the treatment or in a control group that does not.
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.
Seizure	A hyperexcitation of neurons in the brain which leads to changes in awareness or behaviour, for example involuntary movements, unusual sensations, and confused behaviour. Refer to Table 5 and Table 6.
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.
Status epilepticus (convulsive)	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. <i>Provided by Nashef L. Sudden unexpected death in epilepsy: Terminology and definitions. Epilepsia 1997;38:S20-S22.</i>
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.
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.

*Definitions from ILAE Task Force on Classification¹

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- Ashfield and Mansfield District PCTs
- Association of British Neurologists
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- 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
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- Cornwall Partnership NHS Trust

- CRISIS
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- 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
- National Centre for Young People with Epilepsy, The
- National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
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- North West Blackouts Group
- Nottinghamshire Healthcare NHS Trust
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- Sussex Ambulance Services NHS Trust
- Syncope Trust and Reflex anoxic Seizures (STARS)
- UCB Pharma Ltd
- UK Pain Society
- Vale of Aylesbury PCT
- Walton Centre for Neurology and Neurosurgery NHS Trust
- Welsh Assembly Government (formerly National Assembly for Wales)
- West Norfolk PCT
- West Sussex Health & Social Care NHS Trust
- Women's & Children's Collaborating Centre
- Worcestershire Mental Health Partnership NHS Trust
- Wyre Forest Primary Care Trust

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.²

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.³ 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 epileptic syndromes).⁴

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.¹ It can be difficult to make a diagnosis of epilepsy and misdiagnosis is common.⁵

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.^{2;6;7} 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.⁸

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.⁹ 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.¹⁰

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.⁶

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.¹¹

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).¹²

The incidence of epilepsy is about 50 per 100,000 per annum.¹³ The incidence is high in childhood, decreases in adulthood and rises again in older people.⁶ The usual prevalence figure given for active epilepsy in the UK is 5-10 cases per 1,000.¹¹

Epidemiological studies consistently report a standardised mortality rate (SMR) of 2-4 for epilepsy.^{14;15} 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).¹⁶ 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.¹⁷

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.¹¹ In addition, it is important to recognise that people with epilepsy may have co-morbidities. For example, children with epilepsy may have attentional difficulties, learning difficulties or cerebral palsy.¹⁸

1.4 Cost of epilepsy

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).¹⁹

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 literature²⁰ 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.²⁰

1.5 Health Services for people with epilepsy

Since 1953 six major reports^{11;17;21-24} have made recommendations to improve services for people with epilepsy in the UK, but these services remain patchy and fragmented.¹² The Department of Health has recently published an action plan²⁵ to improve services for people with epilepsy in response to the National Sentinel Clinical Audit (SUDEP report).¹⁷

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.

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.¹¹

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.¹⁷

1.5.2 Secondary care

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.¹⁷

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.

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*'.²⁶

This guideline offers best practice advice on the diagnosis, 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).

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 Scope

The guideline was developed in accordance with a specified scope prepared by the Institute. This scope set the remit of the guideline and specified those aspects of epilepsy to be included and excluded. The scope was published by the Institute in 2002 and is reproduced here:

1.11.1 Inclusions

Groups and categories of epilepsy that will be covered:

The guideline will address the diagnosis, treatment and management of epilepsy in children, adolescents, adults and older people. The guideline defines children as being aged 28 days to 18 years and adults aged 18 years and over. Young people are defined as being between 12 and 18 years of age.

The guideline will address the management of epilepsy during pregnancy, and in women of child-bearing age.

The guideline will address the management of epilepsy in people with learning disabilities.

The guideline will cover the following categories of epilepsy:

- focal/partial/localisation related epilepsies
- idiopathic generalised epilepsies
- status epilepticus.

The guideline will take note of the issues of patients who face social exclusion

Healthcare setting:

The guideline will cover the care received from healthcare professionals who have direct contact with, and make decisions concerning, the care of people with epilepsy.

The guideline will address care in primary, secondary and tertiary centres. The management of patients in accident and emergency departments will also be considered.

Clinical management:

As the management of epilepsy depends critically on an accurate diagnosis, recommendations regarding the process of diagnosis will be included in the guideline.

The recommendations will also cover the use of pharmacological interventions (those available in the UK according to the British National Formulary), including side effects of generic prescribing, potential withdrawal from drugs, polytherapy, drug interactions and side effects. These will take into account the recommendations from the Institute's appraisals of new drugs for adults and children with epilepsy. Advice on treatment options will be based on the best evidence available to the development group. When referring to pharmacological treatments, the guideline will normally recommend use within the licensed indications. Exceptionally, and only where the evidence supports it, the guideline may recommend use outside the licensed indications. It is recognised that in certain circumstances drugs may be prescribed to children with epilepsy outside the licensed indications. The guideline will expect that prescribers will use the Summary of Product Characteristics (SPC) to inform their prescribing decisions for individual patients.

The use of non-pharmacological interventions will be covered in the guideline; for example, the use of vagal nerve stimulation and surgery will be considered.

Issues relating to self-care and self-medication will be addressed in the guideline.

The issues surrounding symptom monitoring by the clinician, the patient and the parent/carer will be considered in the guideline.

Psychological therapies will be included.

Where there is evidence, ketogenic diet will be considered.

1.11.2 Exclusions

Groups and categories of epilepsy that will not be covered:

Neonates (infants aged 28 days or under) will not be included in the guideline.

The guideline will not cover the diagnosis or management of febrile convulsions.

Healthcare setting:

The guideline will also be relevant to the work, but will not cover the practice, of those working in the:

- occupational health services
- social services
- educational services
- voluntary sector.

The guideline will not develop advice on driving for those with the condition.

The guideline will not address the delivery of tertiary procedures (such as surgical techniques).

Clinical management:

Detailed recommendations regarding the use of different surgical techniques or nerve stimulation approaches will not be included but consideration will however be given to indications for referral for surgery and the discharge of patients from specialist care.

The guideline will not consider complementary or lifestyle approaches or interventions.

1.12 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.

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.

This 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 methodology team

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 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.

2.2.3 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.

2.3 *Developing key clinical questions (KCQs)*

The first step in the development of the guideline was to refine the guideline scope (see Section 1.11) 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.²⁷

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.

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.²⁸ 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.

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.

2.5 *Reviewing and grading the evidence*

2.5.1 General

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).²⁹ 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 inherent 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 Health economics

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 appraised by the health economist using a standard validated checklist.³⁰ 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.

2.6 *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.

2.7 *The relationship between the guideline and the Technology Appraisals for the newer antiepileptic drugs (AEDs)*

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 Wales³¹ (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.

2.8 *The relationship between the guideline and National Service Frameworks*

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*',³² 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.

2.9 *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.

2.10 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.

2.11 *Level of evidence table*

Hierarchy of evidence

1a	Systematic review or meta-analysis of randomised controlled trials
1b	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomisation
IIb	At least one well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, case-control studies, and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities
NICE	NICE guidelines or Health Technology Appraisal programme

2.12 *Grades of recommendation table*

Grading of recommendations

A	Based directly on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence
A (NICE)	Recommendation taken from NICE guideline or Technology Appraisal
GPP	Good practice point based on the clinical experience of the GDG

3 Key priorities for implementation

Diagnosis

- All individuals with a recent onset suspected seizure should be seen urgently^a by a specialist^b. This is to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.
- The seizure type(s) and epilepsy syndrome, aetiology and co-morbidity should be determined.

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.
- 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.
- The AED (anti-epilepsy 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.

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

a The Guideline Development Group considered that 'urgently' meant being seen within 2 weeks.

b 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.

between 3 and 12 months by arrangement) by a specialist. In adults, this review should be carried out at least yearly by either a generalist or specialist, depending on how well the epilepsy is controlled and/or the presence of specific lifestyle issues.

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

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.

^c The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

4 Executive summary

A – recommendation for adults C – recommendation for children

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.

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. **[D]**

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. **[GPP]**

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

4.2.2C In children, self management of epilepsy may be best achieved through active child-centred training models and interventions. **[A]**

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

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
- 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. **[C]**

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. **[GPP]**

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. **[GPP]**

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). **[GPP]**

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

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

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

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. **[GPP]**

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. **[GPP]**

4.3.10 People with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). **[C adults, GPP children]**

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. **[C]**

4.3.12 The risk of SUDEP can be minimized by:

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

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

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. **[C]**

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^d when an epileptic seizure is suspected or there is diagnostic doubt. **[GPP]**

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). **[D]**

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

4.4.3C The information that should be obtained from the child and/or parent or carer after a suspected seizure is contained in Appendix A.
[GPP]

^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.

^e Appendix A of the full guideline reviews the differential diagnosis in adults and children.

4.4.4A It is recommended that all people having a first seizure should be seen as soon as possible^f by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.

[A (NICE)]

4.4.4C It is recommended that all children who have had a first non-febrile seizure should be seen as soon as possible^e by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.

[A (NICE)]

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

4.4.6 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. **[C]**

4.4.7 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.

[GPP]

4.5 Diagnosis

4.5.1A The diagnosis of epilepsy in adults should be established by a specialist^g medical practitioner with training and expertise in epilepsy. **[C]**

4.5.1C The diagnosis of epilepsy in children should be established by a specialist^h paediatrician with training and expertise in epilepsy. **[C]**

^f The GDG considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.

^g For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy.

^h For children, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.

4.5.2C Individuals and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. **[GPP adults, C children]**

4.5.3 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. **[C]**

4.5.4 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. **[B]**

4.5.5 It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations (see Section on Investigations below) and/or referral to a tertiary centre (see Section on Referral below) should be considered. Follow-up should always be arranged. **[GPP]**

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

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

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. **[D]**

4.6.2C All investigations should be performed in a child centred environment. **[GPP]**

EEG

4.6.3 Individuals requiring an EEG should have the test performed soon after it has been requested.ⁱ **[GPP]**

4.6.4A 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. **[C]**

4.6.4C 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. **[C]**

4.6.5 An EEG should not be performed in the case of probable syncope because of the possibility of a false positive result. **[C]**

4.6.6 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. **[C]**

4.6.7 The EEG should not be used in isolation to make a diagnosis of epilepsy. **[C]**

4.6.8 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. **[C]**

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

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

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

- 4.6.11 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. **[C]**
- 4.6.12 Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. **[C]**
- 4.6.13 When a standard EEG has not contributed to diagnosis or classification a sleep EEG should be performed. **[C]**
- 4.6.14 In children, a sleep EEG is best achieved through sleep deprivation or the use of melatonin^j. **[GPP]**
- 4.6.15 Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG. **[C]**
- 4.6.16 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. **[C]**
- 4.6.17 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. **[GPP]**

Neuroimaging

- 4.6.18 Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. **[C]**
- 4.6.19 MRI should be the imaging investigation of choice in individuals with epilepsy. **[C]**

^j Melatonin is not currently licensed in the UK.

4.6.20 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. **[C]**

4.6.21 Individuals requiring MRI should have the test performed soon.^k

[GPP]

4.6.22 Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made. **[C]**

4.6.23 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. **[C]**

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

Other tests

4.6.25 Measurement of serum prolactin is not recommended for the diagnosis of epilepsy. **[C]**

4.6.26A 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. **[GPP]**

4.6.27A A 12 lead ECG should be performed in adults with suspected epilepsy. **[GPP]**

4.6.26C 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. **[GPP]**

4.6.27C In children a 12 lead ECG should be considered in cases of diagnostic uncertainty. **[GPP]**

^k The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

4.6.28 In cases of diagnostic uncertainty, a referral to a cardiologist should be considered. **[GPP]**

Neuropsychological assessment

4.6.29 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. **[D]**

4.6.30 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. **[D]**

4.7 Classification

4.7.1 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. **[D]**

4.7.2 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. **[C]**

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

4.8 Management

4.8.1 People with epilepsy should have an accessible point of contact with specialist services. **[GPP]**

4.8.2 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. **[GPP]**

4.8.3 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. **[D]**

4.8.4 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. **[GPP]**

Pharmacological treatment

(see Appendix B for further details of pharmacological treatment)

4.8.5 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. **[GPP]**

4.8.6 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 B¹). **[A]**

4.8.7 The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first line AED. **[GPP]**

¹ Appendix B provides details on prescribing for different seizure types and epilepsy syndromes. Significant side effects are also described.

4.8.8 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. **[D]**

4.8.9 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. **[A (NICE)]**

4.8.10 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. **[GPP]**

4.8.11 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. **[GPP]**

4.8.12 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. **[A (NICE)]**

4.8.13A 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. **[A (NICE)]**

4.8.13C 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. **[A (NICE)]**

4.8.14C Vigabatrin is recommended as a first-line therapy for the management of infantile spasms. **[A (NICE)]**

Initiation of pharmacological treatment

4.8.15 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. **[GPP]**

4.8.16A AED therapy should be initiated in adults on the recommendation of a specialist.

[GPP]

4.8.16C AED therapy in children should be initiated by a specialist.

[GPP]

4.8.17 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. **[GPP]**

4.8.18 Treatment with AED therapy is generally recommended after a second epileptic seizure. **[A]**

4.8.19 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. **[B]**

4.8.20 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. **[GPP]**

Continuation of pharmacological treatment

4.8.21 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. **[GPP]**

4.8.22 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. **[GPP]**

4.8.23 If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. **[GPP]**

4.8.24 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. **[GPP]**

4.8.25 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 above)
- using simple medication regimens
- positive relationships between healthcare professionals, the individual with epilepsy, and their family and/or carers. **[D]**

4.8.26A Regular blood test monitoring in adults is not recommended as routine, and should be done only if clinically indicated. **[C]**

4.8.26C Regular blood test monitoring in children is not recommended as routine, and should be done only if clinically indicated and recommended by the specialist. **[GPP]**

4.8.27 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. **[D]**

4.8.28A 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. **[GPP]**

4.8.29 Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication. **[GPP]**

Withdrawal of pharmacological treatment

4.8.30 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. **[A]**

4.8.31 Withdrawal of AEDs must be managed by, or under the guidance of, the specialist. **[GPP]**

4.8.32 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^m). **[A]**

4.8.33 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. **[D]**

4.8.34 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. **[GPP]**

4.8.35 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. **[GPP]**

Referral for complex or refractory epilepsy

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

4.8.37 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. **[C]**

^m Appendix H of the full guideline provides tables for the prognosis for remission of seizures in adults.

4.8.38 If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, individuals should be referred to tertiary services soonⁿ 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 **[D]**
- management is unsuccessful after two drugs **[GPP]**
- the individual is aged under 2 years **[GPP]**
- an individual experiences, or is at risk of, unacceptable side effects from medication **[GPP]**
- there is a unilateral structural lesion **[GPP]**
- there is psychological and/or psychiatric co-morbidity **[GPP]**
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. **[GPP]**

4.8.39C 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. **[D]**

4.8.40 Behavioural or developmental regression or inability to identify the epilepsy syndrome in an individual, should result in immediate referral to tertiary services. **[GPP]**

4.8.41 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. **[GPP]**

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

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

4.8.43 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. **[GPP]**

4.8.44 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. **[GPP]**

4.8.45 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. **[GPP]**

Psychological interventions

4.8.46A 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. **[A]**

4.8.46C Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children with drug-resistant focal epilepsy. **[A]**

4.8.47 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. **[A]**

Ketogenic diet

4.8.48A The ketogenic diet should not be recommended for adults with epilepsy. **[C]**

4.8.48C The ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy. **[C]**

Vagus nerve stimulation (VNS)

4.8.49A 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. **[A]**

4.8.49C 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. **[A]**

4.9 Prolonged or repeated seizures in the community

4.9.1 An individual who has prolonged convulsive (lasting 5 minutes or more) or serial seizures (three or more seizures in an hour) in the community should receive urgent care and treatment. **[A]**

4.9.2 Rectal diazepam is safe and effective in first-line treatment of prolonged seizures and is recommended in the majority of cases. **[A]**

4.9.3 For many individuals and in many circumstances, buccal midazolam^o 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. **[GPP]**

^o Buccal midazolam is currently unlicensed for the treatment of prolonged or repeated seizures.

4.9.4 Healthcare professionals should inform individuals, and their families and/or carers, that buccal midazolam is currently unlicensed. **[GPP]**

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

4.9.6 Care must be taken to secure the individual's airway and assess his or her respiratory and cardiac function. **[GPP]**

4.9.7 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. **[GPP]**

4.10 Treatment of status epilepticus

Convulsive status epilepticus

1.1.1 4.10.1 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 C^P):

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure intravenous (IV) access in a large vein. **[GPP]**

4.10.2 Lorazepam should be used as a first-line treatment in status epilepticus (see Appendix C). **[D]**

Refractory convulsive status epilepticus

4.10.3 Treatment of refractory status epilepticus in secondary care should follow the suggested guidelines (see Appendix C). **[D]**

^P Appendix C provides suggested treatment guidelines for status epilepticus

4.10.4A In adults, propofol or thiopental should be used to control refractory status epilepticus.

Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

4.10.4C In children, midazolam or thiopental should be used to control refractory status epilepticus.

Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

4.10.5 Regular medication should be continued at optimal doses and the reasons for status epilepticus should be investigated. **[GPP]**

4.10.6 As the treatment pathway progresses, the expertise of an anaesthetist/intensivist should be sought. **[GPP]**

4.10.7 If either the whole protocol or intensive care is required the tertiary centre should be consulted. **[GPP]**

4.10.8 An individual treatment pathway should be formulated for people who have recurrent convulsive status epilepticus. **[GPP]**

Non-convulsive status epilepticus

4.10.9 Non-convulsive status is uncommon and management is less urgent. A suggested guideline can be found in Appendix C. **[GPP]**

4.11 Women with epilepsy

4.11.1 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. **[C]**

4.11.2 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. **[C]**

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

4.11.4A In women of childbearing potential, the risk of the drugs (see Section on AEDs above) 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 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. **[A (NICE)]**

4.11.4C In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs (see Section on AEDs above) 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. **[A (NICE)]**

4.11.5 Prescribers should 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. **[GPP]**

4.11.6 All women on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. **[D]**

Contraception

4.11.7A 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.

[A (NICE)]

4.11.7C 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.

[A (NICE)]

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

4.11.9 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. **[D]**

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

4.11.11 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). **[D]**

4.11.12 The progesterone implant is not recommended in women taking enzyme-inducing AEDs. **[D]**

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

4.11.14 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. **[D]**

Pregnancy

4.11.15 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 above). **[C]**

4.11.16 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). **[GPP]**

4.11.17 In all women with epilepsy, seizure freedom during pregnancy should be sought. **[GPP]**

4.11.18 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. **[GPP]**

4.11.19 Women with generalised tonic-clonic seizures should be informed that the fetus 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. **[D]**

4.11.20 Women should be re-assured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury. **[D]**

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

4.11.22 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%). **[C]**

4.11.23 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.

[D]

4.11.24 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. **[B]**

4.11.25 Care of pregnant women should be shared between the obstetrician and the specialist. **[GPP]**

4.11.26 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. **[GPP]**

4.11.27 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. **[GPP]**

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

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

4.11.30 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. **[GPP]**

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

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

4.11.33 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. **[GPP]**

Breastfeeding

4.11.34 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. **[GPP]**

4.11.35 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. **[GPP]**

After the birth

4.11.36 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. **[GPP]**

4.11.37 Information should be given to all parents about safety precautions to be taken when caring for the baby (see Appendix D^q). **[C]**

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

^q Appendix D provides a checklist for the information needs of women with epilepsy and practical information for mothers with epilepsy

4.12 People with learning disabilities (see Sections 4.11 and 4.13)

4.12.1 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. **[GPP]**

4.12.2 Learning disabilities are a common association with epilepsy. The management and treatment of the epilepsy should be undertaken by a specialist, working within a multi-disciplinary team. **[C]**

Diagnosis (see also Section 4.5)

4.12.3 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. **[C]**

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

4.12.5 Clear, unbiased reporting is essential. Witnesses may need education to describe their observations accurately. **[GPP]**

Investigations (see also Section 4.6)

4.12.6 Those with learning disabilities may require particular care and attention to tolerate investigations. **[GPP]**

4.12.7 Facilities should be available for imaging under anaesthesia, if necessary. **[D]**

4.12.8C In the child presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. **[GPP]**

Management

4.12.9 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. **[D]**

4.12.10 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. **[A (NICE)]**

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

4.12.12 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. **[GPP]**

4.12.13 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. **[C]**

4.13 Young people with epilepsy (see also Section 4.11)

4.13.1 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. **[C]**

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

4.13.3 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.

[GPP]

4.13.4 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. **[GPP]**

4.13.5 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. **[D]**

4.13.6 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. **[D]**

4.13.7 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). **[D]**

4.13.8 The diagnosis and management of epilepsy should be reviewed during adolescence. **[D]**

4.14 Older people with epilepsy

4.14.1 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. **[A (NICE)]**

4.15 People from black and minority ethnic groups

4.15.1 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. **[D]**

4.15.2 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. **[D]**

4.15.3 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. **[D]**

4.16 Review

4.16.1 Adults and children with epilepsy should have a regular structured review and be registered with a general medical practice. **[D]**

4.16.2A 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. **[D]**

4.16.2C Children should have a regular structured review with a specialist. **[D]**

4.16.3A 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. **[D]**

4.16.3C 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. **[GPP]**

4.16.4A 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. **[D]**

4.16.5A 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. **[D]**

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

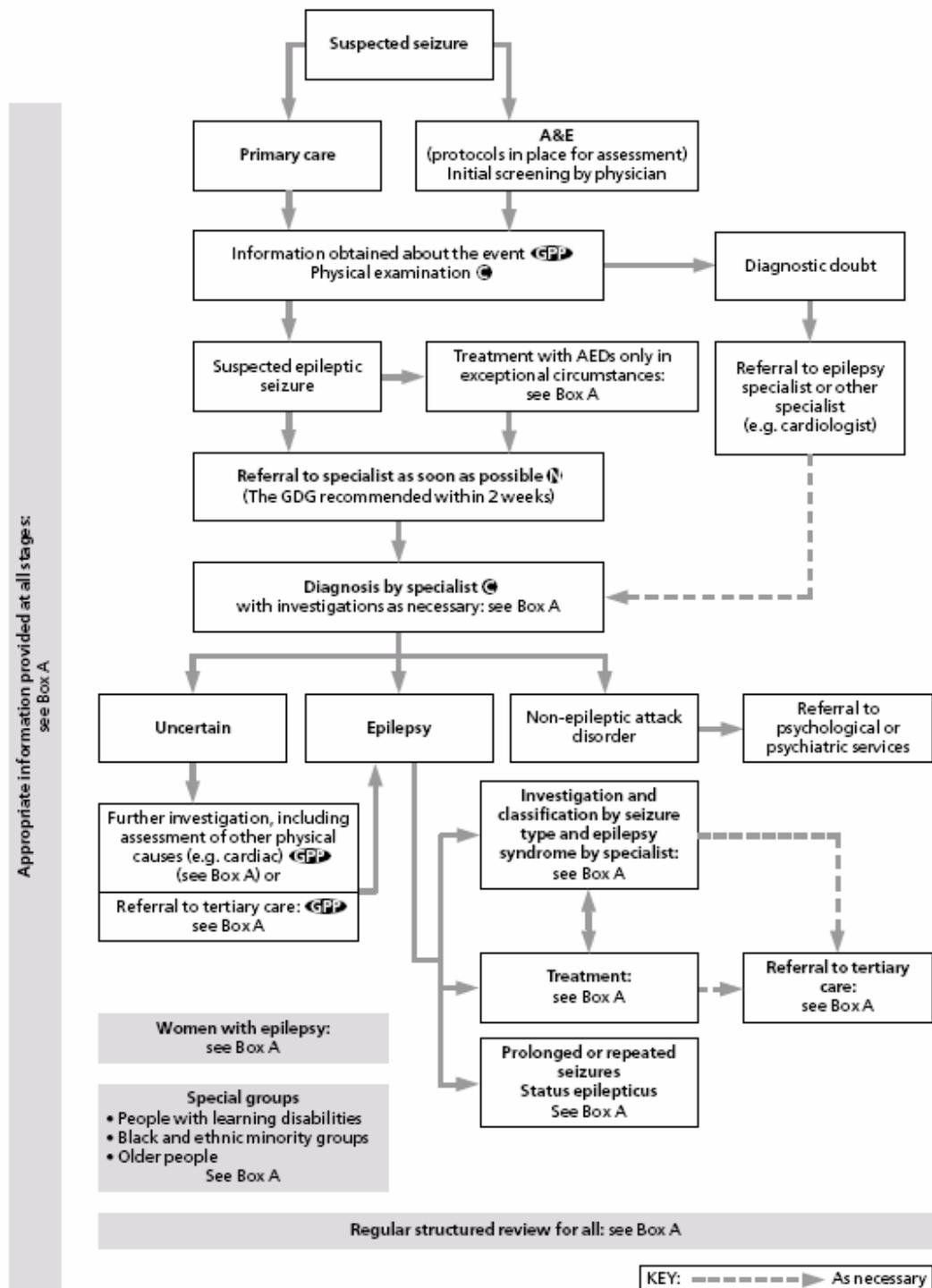
4.16.7 Treatment should be reviewed at regular intervals to ensure that individuals with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained. **[A (NICE)]**

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

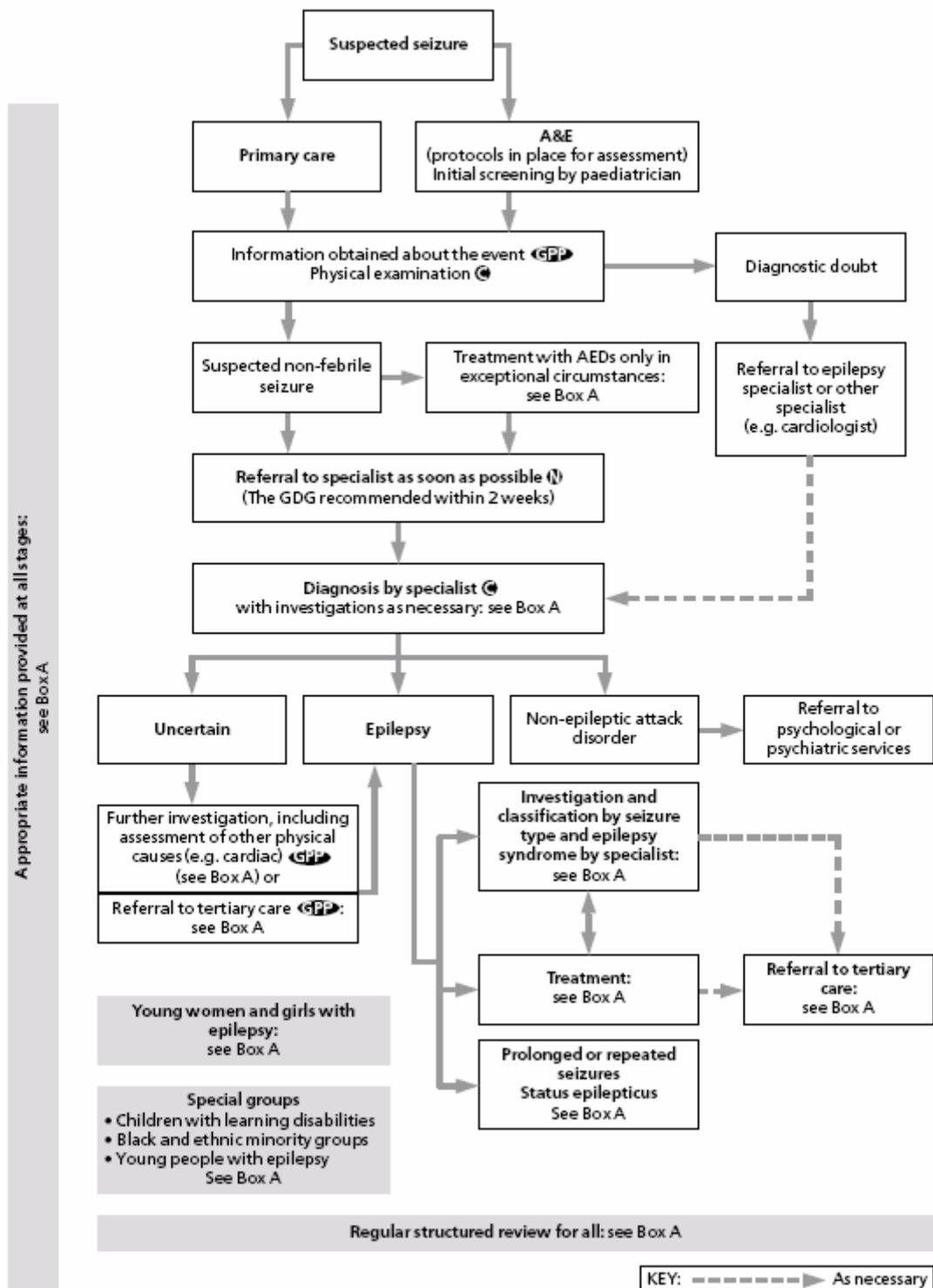
4.16.9 At the review individuals should have access to: written and visual information; counselling services; information about voluntary organizations; epilepsy specialist nurses; timely and appropriate investigations; referral to tertiary services including surgery, where appropriate. **[D]**

5 Outline epilepsy care algorithms

5.1 Outline care algorithm for adults



5.2 Outline care algorithm for children



Box A Cross-references for algorithms

	Page
Treatment with AEDs only in exceptional circumstances	203
Diagnosis and investigations	85 and 96
Further investigation	107, 113, 116, 123, 132, 136, and 137
Investigation and classification by seizure type and epilepsy syndrome	140
Referral to tertiary care	226
Treatment	153
Prolonged or repeated seizures; status epilepticus	245
Women or girls with epilepsy	280
Special groups	314, 331, 341, and 343
Regular structured review	347 and 355
Appropriate information	261

6 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.^f

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.

^f 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.

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.
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.

7 Principle of decision making

7.1 *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. **[D]**

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 2000³³

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.³³

8 **Diagnosis**

8.1 *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.

8.2 *Establishing the diagnosis of epilepsy*

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

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

It is recommended that all adults having a first seizure should be seen as soon as possible^u by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. **[A (NICE)]**

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

[A (NICE)]

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 unprovoked epileptic seizures; and, in people with epilepsy, classification of the disorder and identification of the cause so as to optimise treatment.³⁴

s For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy.

t For children, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.

u The GDG considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.

Secondary evidence

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

Primary evidence

Smith 1999⁵

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.⁵

Scheepers 1998³⁵

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.³⁵

8.3 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. **[C]**

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. **[B]**

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

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

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. **[C]**

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. **[GPP]**

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

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)

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.^{36;37} Unfortunately it is difficult to prepare an evidence-based review on the clinical diagnosis of epilepsy for reasons discussed below.

Secondary evidence

AHRQ 2001³⁸

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 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.'*³⁸

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^{39;40} reported that 609 of 613 children were assigned a syndromic diagnosis on the basis of clinical features.
- Arts, Geerts, Brouwer, and colleagues⁴¹ reporting on 466 children suggested the history alone yielded a 29 percent sensitivity and 89 percent specificity.
- Hoefnagels, Padblerg, Overweg, and colleagues⁴² 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 colleagues⁴³ 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 Tassinari⁴⁴ 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 2002⁴⁵

Since the AHRQ review³⁸, 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.⁴⁵

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.³²

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?*

8.4 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.

8.5 *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.

8.6 *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. **[GPP]**

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 adults⁴⁶ and children.^{47;48} 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.⁴⁹

Primary evidence

Newmark 1981⁴⁶

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.⁴⁶

Sheth 1994⁴⁷

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.⁴⁷

Woody 1985⁴⁸

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').⁴⁸

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).

9 Investigations

9.1 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.

9.2 *The role of EEG in making a diagnosis of epilepsy*

9.2.1 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?

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. [C]

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. [C]

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

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. [C]

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

Individuals requiring an EEG should have the test performed soon after it has been requested.^v [GPP]

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)

^v The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

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

Details

A recent definition of what constitutes a standard/'routine' interictal EEG has been provided in guidelines produced by the International League Against Epilepsy.⁵⁰

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.⁵⁰

Secondary evidence

Linzer 1997⁵¹

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.⁵¹

Fowle 2000⁵²

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.⁵² 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' discharges⁵³). It may also be normal in people with epilepsy.

Gilbert 2000⁵⁴

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.

AHRQ 2001³⁸

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.³⁸

Primary evidence

The primary papers reviewed here had methodological deficiencies according to criteria for diagnostic tests proposed by the *Evidence Based Medicine Working Group*.^{36;55}

Goodin 1984⁵⁶

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.⁵⁶

The results have been extracted from the paper and tabulated below.

Table 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		
	Epilepsy (n=764)	Not epilepsy (n=948)
Epileptiform activity	397	38
Normal	367	910
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 ^w	
Likelihood ratio for negative test	0.5 ^x	

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 1991⁴²

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).⁴²

^w Result defined as a large increase in pre-test to post-test probability

^x Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)

Table 2 Results of EEG in 119 individuals referred to a neurological department with one or more episodes of transient loss of consciousness

A) Results of interictal EEG		
	Seizure (n=45)	Syncope (n=73)
Normal	15	55
Localised epileptiform activity	10	4
Generalised epileptiform activity	8	0
Localised slow activity	12	14
B) Diagnostic value of epileptiform activity for a seizure		
Sensitivity	0.40 (18/45)	
Specificity	0.95 (69/73)	
Likelihood ratio for positive test (CI) ^{aa}	7.3 ^y (2.6 – 20.3)	
Likelihood ratio for negative test (CI)	0.6 ^z (0.5 – 0.8)	

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 2000⁵⁷

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

^y Result defined as a moderate increase in pre-test to post-test probability

^z Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)
aa CI- confidence interval

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).⁵⁷

Jan 2002⁵⁸

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). 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 3) 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.⁵⁸

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 3 Results of EEG for seizures vs non-epileptic paroxysmal events

A) Results of EEG		
	Seizure (n=154)	Non-epileptic paroxysmal event (n=40)
Focal/multifocal spikes on EEG	18	1
Generalised epileptiform discharges	12	0
Background EEG disturbances (focal & diffuse)	29	0
Normal	95	39
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 ^{bb}	
Likelihood ratio for negative test	0.76 ^{cc}	

Stroink 2003⁵⁹

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 seizures 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.

^{bb} Result defined as a large increase in pre-test to post-test probability

^{cc} Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)

9.2.2 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. [C]

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 2000⁶⁰

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.⁶⁰

Primary evidence

King 1998⁶¹

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%).⁶¹

9.2.3 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. **[GPP]**

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. **[C]**

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

When a standard EEG has not contributed to diagnosis or classification a sleep EEG should be performed. **[C]**

In children, a sleep EEG is best achieved through sleep deprivation or the use of melatonin^{dd}. **[GPP]**

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)

^{dd} Melatonin is not currently licensed in the UK.

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.^{38;52;62} Specific review articles are discussed below.

9.2.3.1 Early recording of EEG after seizure

Secondary evidence

No systematic reviews were identified.

Primary evidence

King 1998⁶¹

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%).⁶¹

Sundaram 1990⁶³

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.⁶³

9.2.3.2 Repeatedly performing EEGs

Secondary evidence

No systematic reviews were identified.

Primary evidence

Salinsky 1987⁶⁴

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.⁶⁴

9.2.3.3 Sleep and sleep deprivation EEGs

A narrative review which considered the earlier literature⁶⁵ and a recent critical review of the literature⁶⁶ 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.⁵²

Two prospective studies of the role of sleep and sleep deprivation were identified, both included in the Agency for Healthcare Research & Quality systematic review.³⁸

Secondary evidence

No systematic reviews were identified.

Primary evidence

Carpay 1997⁶⁷

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).⁶⁷

King 1998⁶¹

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).⁶¹

Schreiner 2003⁶⁸

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.⁶⁸

9.2.3.4 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.⁶⁹ As an alternative, children can be given oral melatonin to induce sleep.⁷⁰

No RCT evidence on the effectiveness of melatonin in children undergoing EEG assessment was identified.

9.2.4 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. [C]

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 adults⁷¹ and two on the diagnosis of non-epileptic attack disorders (NEAD).^{72,73}

Secondary evidence

AHRQ 2001³⁸

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.³⁸

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.⁷⁴ 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.⁷⁵ 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.⁷⁶
- 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.⁷⁷

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).⁷⁸
- 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'.⁷⁹

- 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.⁸⁰ 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.⁸¹

9.2.5 What is the role of provocation techniques and induction protocols?

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. **[C]**

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. **[GPP]**

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)

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 1996.⁷³

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.^{72;82}

Secondary evidence

No systematic reviews were identified.

Primary evidence

One RCT and four non-randomised studies were identified.

McGonigal 2002⁸³

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 stimulation. 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%).⁸³

Bhatia 1997⁸⁴

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.⁸⁴

Parra 1998⁸⁵

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.⁸⁵

Dericioglu 1998⁸⁶

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.⁸⁶

Benbadis 2000⁸⁷

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.⁸⁷

9.2.6 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. **[B]**

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)

Details

Secondary evidence

Four systematic reviews were identified.

Berg 1991⁸⁸

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.⁸⁸

Gilbert 2000⁵⁴

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.

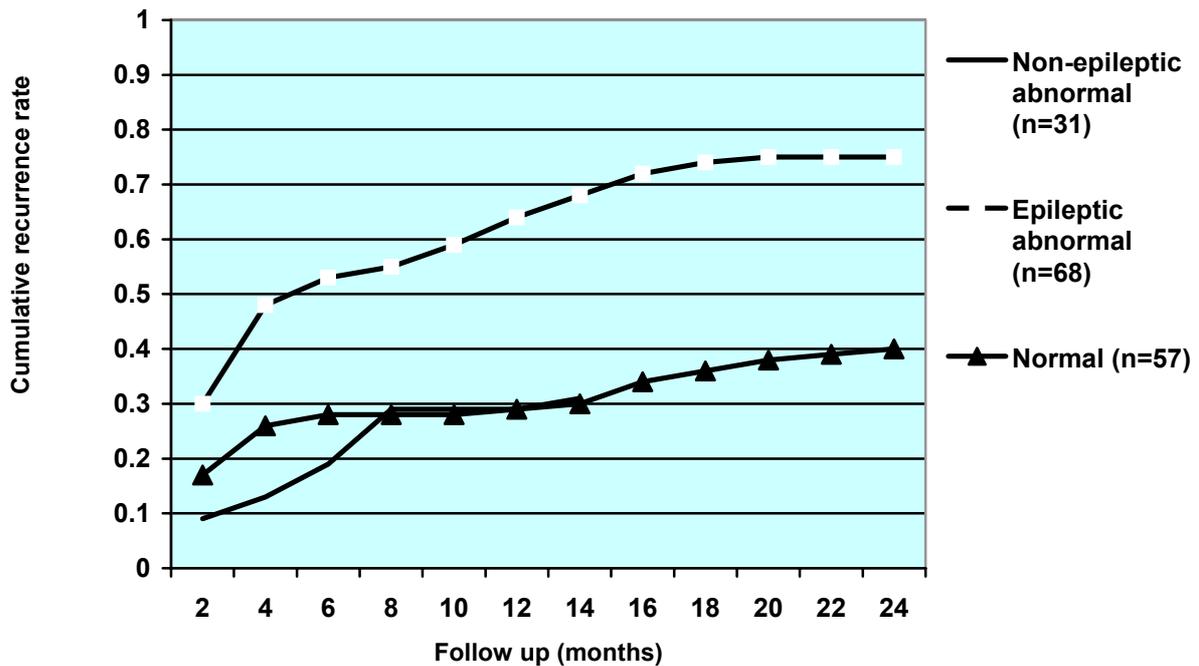
Four studies involving 831 children were included.

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.⁵⁴

Hirtz 2000⁶⁰

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.⁶⁰

Figure 1 Probability of seizure recurrence after a first unprovoked seizure as a function of the standard EEG⁸⁹ Modified with permission from Berg et al 2000

Gilbert 2003⁹⁰

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.⁹⁰

9.3 *The role of neuroimaging in the diagnosis of epilepsy*

Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. **[C]**

MRI should be the imaging investigation of choice in individuals with epilepsy. **[C]**

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. **[C]**

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

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. **[C]**

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

Individuals requiring MRI should have the test performed soon.^{ee} **[GPP]**

^{ee} The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

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).

Secondary evidence

Two systematic reviews of the literature were identified.^{38;60}

AHRQ 2001³⁸

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.³⁸

Hirtz 2000⁶⁰

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.⁶⁰

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 2000⁸⁹

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 4.

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.⁸⁹

Table 4 Frequency of neuroimaging and yield by epilepsy syndrome⁸⁹ Modified with permission from Berg et al 2000

Epilepsy Syndrome*	Total	Any Neuroimaging N (%)	MRI (±CT) N (%)	Abnormal† N(%) ‡	Etiologically Relevant † N(%)‡
Idiopathic localisation-related §	61	48 (78.7)	29 (47.5)	0 (0)	0 (0)
Symptomatic localisation-related	195	177 (90.8)	151(77.4)	50 (28.3)	43 (24.3)
Cryptogenic localisation-related	103	87 (84.5)	103(64.1)	4 (4.6)	0 (0)
Idiopathic generalised (all) ¶	126	62 (49.2)	51 (40.5)	5 (8.1)	0 (0)
Childhood absence	74	31 (41.9)	26 (35.1)	1 (3.2)	0 (0)
Juvenile absence	15	8 (53.3)	7 (46.7)	2 (25.0)	0 (0)
Juvenile myoclonic epilepsy	12	7 (58.3)	6 (50.0)	0 (0)	0 (0)
All other idiopathic generalised	25	16 (64.0)	13 (52.0)	2 (12.5)	0 (0)
Cryptogenic / symptomatic generalised	52	48 (92.3)	41 (78.8)	15 (31.3)	14 (29.2)
Infantile spasms	24	22 (91.7)	18 (75.0)	7 (31.8)	7 (31.8)
Lennox Gastaut	4	4 (100)	2 (50.0)	1 (25.0)	1 (25.0)
Dooze's syndrome	10	9 (90.0)	9 (90.0)	0 (0)	0 (0)
Other cryptogenic / symptomatic generalised	14	13 (92.9)	12 (85.7)	7 (53.8)	6 (46.2)
Undetermined (all)	76	66 (86.8)	51 (67.1)	6 (9.1)	5 (7.6)
With both focal and generalised features	5	5 (100)	3 (60.0)	0 (0)	0 (0)
With neither clearly focal or generalised features	71	61 (85.9)	47 (66.2)	6 (9.8)	5 (8.2)
Total	613	488 (79.6)	388(63.3)	80 (16.4)	62 (12.7)

* 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.

¶ Of 5 children with IGE, 3 had mild Chari I malformations, 1 had mesial temporal sclerosis, and 1 had a choroids fissure cyst.

Bunn 2002⁹¹

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.⁹¹

Dam 1985⁹²

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.

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).⁹²

Holt-Seitz 1999⁹³

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.⁹³

Jallon 1997⁹⁴

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.⁹⁴

Kilpatrick 1991⁹⁵

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.⁹⁵

King 1998⁶¹

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.⁶¹

Ramirez-Lassepas 1984⁹⁶

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.⁹⁶

Roberts 1988⁹⁷

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.⁹⁷

Syndromic diagnosis and classification

Atakli 1998⁹⁸

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.⁹⁸

Harvey 1997⁹⁹

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%).⁹⁹

Jallon 2001¹⁰⁰

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.¹⁰⁰

Lee 2002¹⁰¹

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%.¹⁰¹

9.4 *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. **[C]**

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. **[GPP]**

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. **[GPP]**

All investigations should be performed in a child centred environment. **[GPP]**

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 2001³⁸

This systematic review identified two relevant papers (Anzola¹⁰² and Neufeld¹⁰³ 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.^{36;55}

Diagnosis of epilepsy

Fein 1997¹⁰⁴

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%).¹⁰⁴

Shah 2001¹⁰⁵

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.¹⁰⁵

Tumani 1999¹⁰⁶

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%.¹⁰⁶

Differential diagnosis between epileptic and non-epileptic attacks

Alving 1998¹⁰⁷

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.

* These figures cannot be reconciled with the tables/data in the original paper.

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 μ U/ml), the figures were 34% and 44% respectively.¹⁰⁷

Epilepsy vs syncope

Anzola 1993¹⁰²

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 exceeding by +3 sd of the mean of P2, P3,P4) was 89% and the negative predictive value was 61%.¹⁰²

Lusic 1999¹⁰⁸

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)⁷⁵. 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.¹⁰⁸

Neufeld 1997¹⁰³

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 vasovagal 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 (3.33 μ kat/l) (on either admission or 24-26 hours later) and/or the elevation from the first to the second measurement of \geq 15mU/ml (0.25 μ kat/l), there were only 12% false negatives and 12% false positives.¹⁰³

9.5 **Cardiovascular tests as an aid to diagnosis**

A 12 lead ECG should be performed in adults with suspected epilepsy. **[GPP]**

In children a 12 lead ECG should be considered in cases of diagnostic uncertainty.

[GPP]

In cases of diagnostic uncertainty, a referral to a cardiologist should be considered.

[GPP]

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 2000¹⁰⁹

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.¹⁰⁹

9.6 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. **[D]**

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. **[D]**

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 2002¹¹⁰

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.¹¹⁰

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.

Kwan 2001¹¹¹

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.¹¹¹

10 Classification of seizures and epilepsy syndromes

10.1 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.

10.2 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. **[D]**

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. **[C]**

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

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).³

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.¹¹² 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.^{113;114} (Table 5, Table 6).

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 research⁴
- placing undue emphasis on the types of case referred to tertiary centres¹¹⁵
- placing undue emphasis on the role of the EEG at the expense of newer techniques such as MRI⁴
- not classifying epileptic seizures according to what a individual or eyewitness reports happens during a seizure (ictal semiology).¹¹⁶

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 2001.¹ The Task Force argued that it was not possible to replace the current international classifications^{113;114} 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 7). 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 8, Table 9 and Table 10. The Task Force also made suggestions as to how current terminology should be changed so as to make it more usable (Table 11) and these have been incorporated into the guideline glossary of terms.

Table 5 Classification of epileptic seizures according to clinical type**1. Partial (focal, local) seizures**

- 1.1. *Simple partial seizures* (consciousness not impaired)
 - 1.1.1. With motor signs
 - 1.1.2. With somatosensory or special-sensory symptoms (simple hallucinations, for example, tingling, light flashes, buzzing)
 - 1.1.3. With autonomic symptoms or signs (for example, epigastric sensation, pallor, sweating, flushing, piloerection and papillary dilatation)
 - 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)
- 1.2. *Complex partial seizures* (with impairment of consciousness)
 - 1.2.1. With simple partial onset followed by impairment of consciousness
 - 1.2.2. With impairment of consciousness at onset
- 1.3. *Partial seizures evolving to secondarily generalized seizures* (may be generalized tonic-clonic, tonic, or clonic)
 - 1.3.1. Simple partial seizures evolving to generalized seizures
 - 1.3.2. Complex partial seizures evolving to generalized seizures
 - 1.3.3. Simple partial seizures evolving to complex partial seizures and then evolving to generalized seizures

2. Generalized seizures (convulsive or non-convulsive)

- 2.1. *Absence seizures*
(impairment of consciousness alone or with: mild clonic, atonic or tonic components, automatisms and/or autonomic symptoms or signs)
- 2.2. *Atypical absence*
- 2.3. *Myoclonic seizures*
- 2.4. *Clonic seizures*
- 2.5. *Tonic-clonic seizures*
- 2.6. *Atonic seizures*

Unclassified seizures

Modified from: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures¹¹³ Reprinted by permission of the journal *Epilepsia*

Table 6 Classification of epilepsies and epileptic syndromes

<p>1. Localization-related (focal, local, partial) epilepsies and syndromes</p> <p>1.1. <i>Idiopathic</i> (listed in order of age of onset)</p> <p>1.1.1. Benign childhood epilepsy with centrotemporal spike</p> <p>1.1.2. Childhood epilepsy with occipital paroxysms</p> <p>1.2. <i>Symptomatic</i></p> <p>1.3. <i>Cryptogenic</i></p> <p>2. Generalized epilepsies and syndromes</p> <p>2.1. <i>Idiopathic</i> (listed in order of age of onset)</p> <p>2.1.1. Benign neonatal familial convulsions</p> <p>2.1.2. Benign neonatal convulsions</p> <p>2.1.3. Benign myoclonic epilepsy in infancy</p> <p>2.1.4. Childhood absence epilepsy (pyknolepsy)</p> <p>2.1.5. Juvenile absence epilepsy</p> <p>2.1.6. Juvenile myoclonic epilepsy (impulsive petit mal)</p> <p>2.1.7. Epilepsy with grand mal (generalized tonic-clonic) seizures on awakening</p> <p>2.2. <i>Cryptogenic or symptomatic</i> (listed in order of age of onset)</p> <p>2.2.1. West syndrome (infantile spasms)</p> <p>2.2.2. Lennox-Gastaut syndrome</p> <p>2.2.3. Epilepsy with myoclonic-astatic seizures</p> <p>2.2.4. Epilepsy with myoclonic absences</p> <p>2.3. <i>Symptomatic</i></p> <p>2.3.1. Non-specific etiology</p> <p>2.3.1.1. Early myoclonic encephalopathy</p> <p>2.3.1.2. Early infantile epileptic encephalopathy with suppression burst</p> <p>2.3.1.3. Other symptomatic generalized epilepsies not defined above</p> <p>2.3.2. Specific syndromes</p> <p>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</p> <p>3. Epilepsies and syndromes undetermined whether focal or generalized</p> <p>3.1. <i>With both generalized and focal seizures</i></p> <p>3.1.1. Neonatal seizures – <i>excluded from G/L</i></p> <p>3.1.2. Severe myoclonic epilepsy in infancy</p> <p>3.1.3. Epilepsy with continuous spike-waves during slow wave sleep</p> <p>3.1.4. Acquired epileptic aphasia (Landau-Kleffner syndrome)</p> <p>3.2. <i>Without unequivocal generalized or focal features</i></p> <p>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.</p> <p>4 Special syndromes</p> <p>4.2 Febrile convulsions</p> <p>4.3 Isolated seizures or isolated status epilepticus</p> <p>4.4 Seizures occurring only when there is an acute metabolic or toxic event</p>
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Modified from: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes¹¹⁴
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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 7 A proposed diagnostic scheme for people with epileptic seizures and with epilepsy

This diagnostic scheme is divided into five parts, or axes, organised to facilitate a logical clinical approach to the development of hypotheses necessary to determine the diagnostic studies and therapeutic strategies to be undertaken in individual patients:

- *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 8). 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 9), 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 10).
- [*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 ICDH-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 terminology¹
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Table 8 Axis 2 – Epilepsy seizure types (and precipitating stimuli for reflex seizures)

<ul style="list-style-type: none"> • Self-limited seizure types <ul style="list-style-type: none"> ○ <i>Generalized seizures</i> <ul style="list-style-type: none"> ▪ 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 ○ <i>Focal seizures</i> <ul style="list-style-type: none"> ▪ Focal sensory seizures ▪ Focal motor seizures ▪ Gelastic seizures ▪ Hemiclonic seizures ▪ Secondarily generalized seizures ▪ Reflex seizures in focal epilepsy syndromes • Continuous seizure types <ul style="list-style-type: none"> ○ <i>Generalized status epilepticus</i> <ul style="list-style-type: none"> ▪ Generalized tonic-clonic status epilepticus ▪ Focal status epilepticus • Precipitating stimuli for reflex seizures <ul style="list-style-type: none"> ○ <i>Visual stimuli</i> <ul style="list-style-type: none"> ▪ Flickering light -colour to be specified when possible ▪ Patterns ▪ Other visual stimuli ○ <i>Thinking</i> ○ <i>Music</i> ○ <i>Eating</i> ○ <i>Praxis</i> ○ <i>Somatosensory</i> ○ <i>Proprioceptive</i> ○ <i>Reading</i> ○ <i>Hot water</i> ○ <i>Startle</i>

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 terminology¹
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Table 9 Axis 3 – Epilepsy syndromes and related conditions

<ul style="list-style-type: none"> • Benign familial neonatal seizures • Early myoclonic encephalopathy • Ohtahara syndrome • Migrating partial seizures of infancy • West syndrome • Benign myoclonic epilepsy in infancy • Benign familial infantile seizures • Benign infantile seizures (non-familial) • Dravet's syndrome • Hemiplegic Hemiatrophy syndrome • Myoclonic status in non-progressive encephalopathies • Benign childhood epilepsy with centrotemporal spikes • Early onset benign childhood occipital epilepsy (Panayiotopoulos type) • Late onset childhood occipital epilepsy (Gastaut type) • Epilepsy with myoclonic absences • Epilepsy with myoclonic-astatic seizures • Lennox-Gastaut syndrome • Landau-Kleffner syndrome • Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS) • Childhood absence epilepsy • Progressive myoclonus epilepsies • Idiopathic generalized epilepsies with variable phenotypes <ul style="list-style-type: none"> ○ <i>Juvenile absence epilepsy</i> ○ <i>Juvenile myoclonic epilepsy</i> • Epilepsy with generalized tonic-clonic seizures only • Reflex epilepsies <ul style="list-style-type: none"> ○ <i>Idiopathic photosensitive occipital lobe epilepsy</i> ○ <i>Other visual sensitive epilepsies</i> ○ <i>Primary reading epilepsy</i> ○ <i>Startle epilepsy</i> • Autosomal dominant nocturnal frontal lobe epilepsy • Familial temporal lobe epilepsies • Generalized epilepsies with febrile seizures plus • Familial focal epilepsy with variable foci • Symptomatic (or probably symptomatic) focal epilepsies <ul style="list-style-type: none"> ○ <i>Limbic epilepsies</i> <ul style="list-style-type: none"> ▪ Mesial temporal lobe epilepsy with hippocampal sclerosis ▪ Mesial temporal lobe epilepsy defined by specific aetiologies ▪ Other types defined by location and aetiology ○ <i>Neocortical epilepsies</i> <ul style="list-style-type: none"> ▪ Rasmussen syndrome ▪ Other types defined by location and aetiology <p>CONDITIONS WITH EPILEPTIC SEIZURES THAT DO NOT REQUIRE A DIAGNOSIS OF EPILEPSY</p> <ul style="list-style-type: none"> • 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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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 terminology¹
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Table 10 Axis 4 - Aetiology. Classification of groups of diseases frequently associated with epilepsy seizures or syndromes**Progressive Myoclonic Epilepsies**

- for example, Ceroid lipofuscinosis

Neurocutaneous Disorders

- for example, Tuberous Sclerosis Complex; Neurofibromatosis

Malformations Due to Abnormal Cortical Developments**Other Cerebral Malformations****Tumours**

- for example, Gangliocytoma

Chromosomal Abnormalities

- for example, Partial Monosomy 4P or Wolf-Hirschorn Syndrome

Monogenic Mendelian Diseases with complex Pathogenic Mechanisms

- for example, Fragile X Syndrome

Inherited Metabolic Disorders

- for example, Nonketotic Hyperglycinemia

Prenatal or Perinatal Ischemic or Anoxic Lesions or Cerebral Infections Causing**Nonprogressive Encephalopathies**

- for example, Porencephaly

Postnatal Infections

- for example, Herpes Encephalitis; Bacterial Meningitis

Other Postnatal Factors

- for example, Head Injury; Alcohol and Drugs Abuse; Stroke

Miscellaneous

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 terminology¹

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Table 11 Definition of key terms¹

<i>Epilepsy seizure type</i> : 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)
<i>Epilepsy syndrome</i> : 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 <i>per se</i> , for instance, do not constitute a syndrome. (changed concept)
<i>Epileptic disease</i> : 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)
<i>Epileptic encephalopathy</i> : A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. (new concept)
<i>Benign epilepsy syndrome</i> : A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. (clarified concept)
<i>Reflex epilepsy syndromes</i> : 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)
<i>Focal seizures and syndromes</i> : Replaces the terms partial seizures and localization-related syndromes. (changed terms)
<i>Simple and complex partial epileptic seizures</i> : 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)
<i>Idiopathic epilepsy syndrome</i> : 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)
<i>Symptomatic epilepsy syndrome</i> : A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. (unchanged term)
<i>Probably symptomatic epilepsy syndrome</i> : 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)

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 terminology¹

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10.3 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 1984¹¹⁷

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.¹¹⁷

Grunewald 1992¹¹⁸

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.¹¹⁸

Montalenti 2001¹¹⁹

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.¹¹⁹

This has also been identified in other studies.^{118;120} 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.^{121;122}

11 Management of epilepsy

11.1 *Pharmacological treatment*

11.1.1 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 evidence base for the newer AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin) which were the subject of the Institute's Technology Appraisals has not been reviewed in detail, but the resulting recommendations have been incorporated into the guideline where appropriate (see Methods 2.7).

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.

11.1.2 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 B). **[A]**

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

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. **[D]**

Adults:

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. **[A (NICE)]**

Children:

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. **[A (NICE)]**

Vigabatrin is recommended as a first-line therapy for the management of infantile spasms. **[A (NICE)]**

Evidence statements

Evidence from randomised trials comparing newer and older antiepileptic drugs as monotherapy did not suggest differences in their effectiveness in seizure control. There was also insufficient evidence to distinguish between the different newer antiepileptic drugs for seizure control. (1a NICE)

Evidence was inadequate to support a conclusion that the newer drugs were generally associated with improved quality of life. (1a NICE)

Clinical effectiveness of individual drugs varies by seizure type and by epilepsy syndrome. (1a, 1b)

It was not possible to determine whether any one drug was more likely to bring about seizure freedom over the longer term than any other. (1a NICE)

Different preparations may vary in bioavailability or have different pharmacokinetic profiles. (IV)

11.1.3 Pharmacological treatment in the management of the epilepsies by drug

Two technology appraisals have been published on the use of newer drugs in adults and children with epilepsy. The remit of the evidence reviews produced to inform the guidance was to assess the effectiveness of newer drugs compared with older drugs. The following evidence reviews were produced for the older drugs and other drugs not included in the technology appraisals.

Only high quality systematic reviews of RCTs and high quality RCTs were included in the evidence reviews for this section.

The drugs to be included were taken from the National Society for Epilepsy website (<http://www.epilepsynse.org.uk/>). Two other drugs were added (felbamate and sulthiame) on the advice of the GDG. It was agreed that remacemide and zonisamide should not be included.

- Acetazolamide (ACZ)
- Carbamazepine (CBZ)
- Clobazam (CLB)
- Clonazepam (CLN)
- Ethosuximide (ESM)
- Felbamate (adults only) (FBM)
- Gabapentin (GBA)
- Lamotrigine (LMG)
- Levetiracetam (LEV)
- Oxcarbazepine (OXC)
- Phenobarbitone (PHB)
- Phenytoin (PHY)
- Piracetam (adults only) (PRC)
- Primidone (PMD)
- Sodium valproate (VPA)
- Sulthiame (children only) (STM)
- Tiagabine (TBG)
- Topiramate (TPM)
- Vigabatrin (VGB)

11.1.3.1 Acetazolamide (ACZ)

No systematic reviews or RCTs were identified that reviewed the effectiveness of acetazolamide in the management of the epilepsies.

11.1.3.2 Carbamazepine (CBZ)

Secondary evidence

Three Cochrane reviews were identified.¹²³⁻¹²⁵ Seven papers reporting possible RCTs (published since 1999) were assessed as potentially being relevant. However, on re-examining the abstracts, none of the 7 trials identified compared CBZ with PHB, PHY, or VPA as monotherapy in epilepsy.

Tudur Smith 2003¹²³

Tudur Smith and colleagues reviewed the effectiveness of CBZ compared to PHB monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised or quasi-randomised, blinded or unblinded controlled trials in children or adults were included.

Outcome measures were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and
- c. time to first seizure.

Individual patient data were available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met the inclusion criteria. Of these four trials, two recruited adults only (aged 13 to 82 years), one recruited adults and children (aged 2 to 68 years) and one recruited children only (aged 3 to 16 years).

The main overall results (hazard ratio HR, 95% CI) adjusted for seizure type were,

- a. time to withdrawal 1.63 (1.23 to 2.15),
(HR>1 indicates a clinical advantage for CBZ)
- b. time to 12 month remission 0.87 (0.65 to 1.17),
(HR>1 indicates a clinical advantage for PHB)
- c. time to first seizure 0.85 (0.68 to 1.05)
(HR>1 indicates a clinical advantage for CBZ)

The results showed that time to withdrawal was significantly improved with CBZ compared to PHB, suggesting that CBZ is significantly better tolerated than PHB. No overall difference between drugs was identified for the outcomes 'time to 12 month remission' and 'time to first seizure'. However, subgroup analyses for time to first seizure suggested an advantage with PHB for partial onset seizures (0.71, 0.55 to 0.91) and a clinical advantage with CBZ (1.50, 0.95 to 2.35) for generalized onset tonic-clonic seizures.¹²³

Tudur Smith 2003¹²⁴

This Cochrane study reviewed evidence comparing CBZ and PHY when used as monotherapy in people with partial onset (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures were included.

Outcomes were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission,
- c. time six month remission, and
- d. time to first seizure post randomisation.

Individual patient data were available for 551 participants from three trials, representing 63% of the participants recruited into the nine trials that met the inclusion criteria. Two of these trials recruited adults only (aged 13 to 82 years) and one recruited children only (aged 3 to 16 years).

Main results (HR 95% CI) were

- a. time to withdrawal of allocated treatment 0.97 (0.74 to 1.28),
(HR>1 indicates a clinical advantage for CBZ)
- b. time to 12 month remission 1.00 (0.78 to 1.29)
(HR>1 indicates a clinical advantage for PHY)
- c. time to six month remission 1.10 (0.87 to 1.39)
(HR>1 indicates a clinical advantage for PHY)
- d. time to first seizure 0.91 (0.74 to 1.12)
(HR>1 indicates a clinical advantage for CBZ)

The results suggested no overall difference between CBZ and PHY for these outcomes. However, the authors commented that confidence intervals were wide and the possibility of the existence of important differences had not been excluded.¹²⁴

Marson 2003¹²⁵ and Marson 2002¹²⁶

The objective of this review was to assess the evidence comparing CBZ and VPA monotherapy in adults and children with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures. Randomised controlled trials comparing CBZ and VPA monotherapy for epilepsy were included.

Outcome measures were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and

- c. time to first seizure post randomisation.

Individual patient data were available for 1265 individuals from five trials, representing 85% of those recruited into the eight trials that met the inclusion criteria. Of these five trials, three recruited adults only (aged 13 to 83 years) and two children only (aged 3 to 16 years).

The main overall results (HR 95% CI) were

- a. time to treatment withdrawal 0.97 (0.79 to 1.18)
(HR>1 indicates a clinical advantage for CBZ),
- b. 12 month remission 0.87 (0.74 to 1.02)
(HR>1 indicates a clinical advantage for VPA),
- c. first seizure 1.09 (0.96 to 1.25)
(HR>1 indicates a clinical advantage for CBZ)

The results showed no overall difference for these outcomes. However, a test for interaction between treatment and epilepsy type was significant for time to first seizure, indicating an advantage for CBZ in the treatment of partial seizures (1.22, 1.04 to 1.44). There was some heterogeneity and age was shown to be significantly linked with treatment effect. The authors suggested that the age distribution of adults classified as having a generalized epilepsy (36% and 44% in two trials had generalised epilepsy with onset over the age of 30 years) indicated that significant numbers of individuals may have had their epilepsy misclassified.^{125;126}

Another systematic review of AED (CBZ, PHY, VPA) efficacy and safety was identified.¹²⁷ This was an older review, published in 1997, and there were significant methodological flaws in the analysis. Therefore, only the results of the Cochrane reviews described above have been included.

Primary evidence

No RCTs were identified since the Cochrane reviews above.

11.1.3.3 Clobazam (CLB)

Secondary evidence

No systematic reviews were identified on the effectiveness of clobazam in the management of the epilepsies.

Primary evidence

One RCT of clobazam as monotherapy in children was identified.¹²⁸

Canadian Study Group for Childhood Epilepsy 1998¹²⁸

The Canadian Study Group for Childhood epilepsy compared the effectiveness of monotherapy clobazam (CLB) to carbamazepine (CBZ) and phenytoin (PHY) in children with epilepsy. Children aged 2-16 years with newly diagnosed epilepsy or previous failure of one drug (for poor efficacy or side effects) were assigned to one of two study arms and then randomised to CLB versus CBZ or CLB versus PHY. Eligible children had partial epilepsies or only generalized tonic-clonic seizures. The study was double blind. An intention to treat analysis assessed the primary endpoint, defined as the length of retention on the initial medication during the year after randomisation.

235 children were included: 159 randomised to CLB versus CBZ and 76 to CLB versus PHY. Altogether, in all study arms, 119 received CLB, 78 CBZ, and 38 PHY. Overall, 56% continued to receive the original medication for 1 year with no difference between CLB and standard therapy (CBZ and PHY). Of these 131 children, 39% (n=51) were seizure free for the 12 month period of the trial (23% of those taking CLB, 25% CBZ, and 11% taking PHY) Seizure control was equivalent for all three medications, as were side effects. PHY and CBZ induced more biologic side effects, such as rash, while CLB

induced slightly more behavioural effects. Tolerance developed in 7.5% of children receiving CLB, 4.2% with CBZ and 6.7% with PHY.¹²⁸

In a more detailed analysis of the cognitive and behavioural effects of CLB,¹²⁹ a subset of the children in the above trial underwent neuropsychological assessments at 6 weeks and 12 months after initiation. There were no statistically significant differences between the CLB and standard monotherapy groups on any of the measures. There was no evidence of deterioration in children who took CLB for the full 12 month period.¹²⁹

Four trials of CLB as adjunctive therapy in both adults and children were identified.

Aucamp 1985¹³⁰

Aucamp assessed the efficacy of CLB as add-on therapy in 12 institutionalised adults. All participants had uncontrolled seizures, defined as two or more seizures in the two weeks preceding the study period. The trial was a double blind, randomised cross-over design. Nine of the twelve participants became seizure free when taking CLB.¹³⁰

Keene 1990¹³¹

Keene and colleagues reported the results of a double-blind cross-over study comparing clobazam and placebo in the treatment of refractory childhood epilepsy. Participants were aged between 2 years to 19 years and had more than 4 seizures a month.

52% (n=11/21) of children had greater than 50% reduction in their seizure frequency when taking the clobazam. During the placebo phase no child recorded a greater than 50% reduction in seizure frequency. Only 2/21 children had behavioural changes on the drug sufficiently severe to require the child to drop out of the study prematurely. Drug interactions between clobazam and the other anticonvulsant medicines did not occur.¹³¹

Koeppen 1987¹³²

Clobazam was compared with placebo as antiepileptic adjunct medication in 129 therapy-resistant epileptic individuals mainly having complex partial seizures. The study was performed in five European countries according to a double-blind crossover design lasting 7 months and included 129 participants.

19% (n=20/129) of those receiving clobazam became seizure-free during the maintenance dose period. In contrast, freedom from seizures was not observed in any individual in the placebo group. The most frequent adverse reactions to clobazam were drowsiness and dizziness.¹³²

Schmidt 1986¹³³

The efficacy of CLB as adjunctive therapy was assessed in a double-blind trial in 20 adults with chronic complex partial seizures uncontrolled by maximally tolerable daily dosage of standard antiepileptic drug therapy. The mean number of seizures was statistically significantly lower during the three months of active treatment as compared with placebo. At the end of the third month, eight (40%) adults had a seizure reduction by more than 75%, including four (20%) who had complete control. Tolerance to the antiepileptic effect of clobazam was noted in 56% of individuals, and mild transient sedation occurred in 40%.¹³³

11.1.3.4 Clonazepam (CLN)**Secondary evidence**

No systematic reviews were identified that reviewed the effectiveness of clonazepam in the management of the epilepsies.

Primary evidence

One RCT was identified.¹³⁴

Mikkelsen 1981¹³⁴

In a double-blind randomised trial of CBZ and CLN in adults and children (age range 6 to 72 years) with newly diagnosed, untreated psychomotor epilepsy, 19 participants were allocated to CBZ, and 17 to CLN.

Five participants were withdrawn from the CBZ group, and 7 from the CLN group, and there was no significant differences between the groups in terms of number of withdrawals, timing of withdrawals, number of seizures to withdrawal, and side effects ($p > 0.20$).

For participants treated for at least one month, the median difference in the number of seizures between the two groups was not significant (95% CI – 0.3 to 0.4).¹³⁴

11.1.3.5 Ethosuximide (ESM)

No systematic reviews or RCTs were identified that reviewed the effectiveness of ethosuximide in the management of the epilepsies in adults.

One Cochrane review was identified for the use of ethosuximide in children with absence seizures¹³⁵ (Pharmacological treatment in the management of the epilepsies by syndrome).

No other RCTs of ESM in epilepsy were identified.

11.1.3.6 Felbamate (FBM)**Secondary evidence**

No Cochrane reviews or protocols were identified that consider the effectiveness of felbamate in the treatment of the epilepsies. One other systematic review was identified.

French 1999¹³⁶

The Quality Standards subcommittee of the American Academy of Neurology and the American Epilepsy Society published a practice advisory on the use of FBM for the treatment of various types of epilepsy. This was based on a review of the literature (only Medline searched – no other details were given). Of the 54 articles assessed as relevant, only nine studies were Class I evidence (defined as well-designed, prospective, blinded, controlled studies), of which seven related to the efficacy of FBM.

The practice advisory summarised the evidence as follows:

- FBM was found to be effective for
 - Partial seizures in adults aged 18 to 65 as adjunctive and monotherapy
 - Lennox-Gastaut syndrome as adjunctive therapy (see Lennox Gastaut syndrome (LGS)).¹³⁶

Primary evidence

No RCTs were identified.

11.1.3.7 Gabapentin (GBA)

The effectiveness of gabapentin is addressed in the Technology Appraisals for adults and children.

11.1.3.8 Lamotrigine (LMG)

The effectiveness of lamotrigine is addressed in the Technology Appraisals for adults and children.

11.1.3.9 Levetiracetam (LEV)

The effectiveness of levetiracetam is addressed in the Technology Appraisals for adults.

11.1.3.10 Oxcarbazepine (OXC)

The effectiveness of oxcarbazepine is addressed in the Technology Appraisals for adults and children.

11.1.3.11 Phenobarbitone (PHB)

Secondary evidence

Two Cochrane reviews were identified.^{123;137}

Tudur Smith 2003¹²³

Tudur Smith and colleagues reviewed the effectiveness of CBZ compared to PHB monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised or quasi-randomised, blinded or unblinded controlled trials in children or adults were included.

Outcome measures were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and
- c. time to first seizure.

Individual patient data were available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met the inclusion criteria. Of these four trials, two recruited adults only (aged 13 to 82 years), one recruited adults and children (aged 2 to 68 years) and one recruited children only (aged 3 to 16 years).

The main overall results (HR 95% CI) adjusted for seizure type were,

- a. time to withdrawal 1.63(1.23 to 2.15),
(HR>1 indicates a clinical advantage for CBZ)
- b. time to 12 month remission 0.87(0.65 to 1.17),
(HR>1 indicates a clinical advantage for PHB)
- c. time to first seizure 0.85(0.68 to 1.05)
(HR>1 indicates a clinical advantage for CBZ)

The results showed that time to withdrawal was significantly improved with CBZ compared to PHB, suggesting that CBZ is significantly better tolerated than PHB. No overall difference between drugs was identified for the outcomes 'time to 12 month remission' and 'time to first seizure'. However, subgroup analyses for time to first seizure suggested an advantage with PHB for partial onset seizures (0.71, 0.55 to 0.91) and a clinical advantage with CBZ (1.50, 0.95 to 2.35) for generalized onset tonic-clonic seizures.⁸⁸

Taylor 2003¹³⁷

In this Cochrane review, the effects of PHB compared to PHY when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types) were assessed. Randomised controlled trials in children or adults were included.

Outcomes were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and
- c. time to first seizure post randomisation.

Individual patient data were obtained for four of the ten studies meeting the inclusion criteria, amounting to 599 individuals, or approximately 65% of the potential data. Two trials were adults only (aged 14 to 81 years) and two children only (aged 2 to 18 years).

The main overall results were

- a. time to treatment withdrawal 1.62 (95% CI 1.22 to 2.14),
(HR>1 indicates a clinical advantage for PHY)
- b. time to 12 month remission 0.93 (95% CI 0.70 to 1.23) and
(HR>1 indicates a clinical advantage for PHB)
- c. time to first seizure 0.84 (95% CI 0.68 to 1.05)
(HR>1 indicates a clinical advantage for PHY).

These results indicate a statistically significant clinical advantage for PHY in terms of treatment withdrawal and a non-significant advantage in terms of 12 month remission. Results for time to first seizure suggest a non-significant clinical advantage for PHB.¹³⁷

Primary evidence

No further RCTs were identified.

11.1.3.12 Phenytoin (PHY)

Secondary evidence

Three Cochrane reviews were identified.^{124;137;138}

Tudur Smith 2003¹²⁴

This Cochrane reviewed evidence comparing CBZ and PHY when used as monotherapy in people with partial onset (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without

other generalised seizure types). Randomised controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures were included.

Outcomes were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission,
- c. time six month remission, and
- d. time to first seizure post randomisation.

Individual patient data were available for 551 participants from three trials, representing 63% of the participants recruited into the nine trials that met the inclusion criteria. Two of these trials recruited adults only (aged 13 to 82 years) and one recruited children only (aged 3 to 16 years).

Main results (HR 95% CI) were

- a. time to withdrawal of allocated treatment 0.97 (0.74 to 1.28),
(HR>1 indicates a clinical advantage for CBZ)
- b. time to 12 month remission 1.00 (0.78 to 1.29)
(HR>1 indicates a clinical advantage for PHY)
- c. time to six month remission 1.10 (0.87 to 1.39)
(HR>1 indicates a clinical advantage for PHY)
- d. time to first seizure 0.91 (0.74 to 1.12)
(HR>1 indicates a clinical advantage for CBZ)

The results suggested no overall difference between CBZ and PHY for these outcomes. However, the authors commented that confidence intervals were wide and the possibility of important differences existing had not been excluded.¹²⁴

Taylor 2003¹³⁷

In this Cochrane review, the effects of PHB compared to PHY when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types) were assessed. Randomised controlled trials in children or adults were included.

Outcomes were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and
- c. time to first seizure post randomisation.

Individual patient data were obtained for four of the ten studies meeting the inclusion criteria, amounting to 599 individuals, or approximately 65% of the potential data. Two trials were adults only (aged 14 to 81 years) and two children only (aged 2 to 18 years).

The main overall results were

- a. time to treatment withdrawal 1.62 (95% CI 1.22 to 2.14),
(HR>1 indicates a clinical advantage for PHY)
- b. time to 12 month remission 0.93 (95% CI 0.70 to 1.23) and
(HR>1 indicates a clinical advantage for PHB)
- c. time to first seizure 0.84 (95% CI 0.68 to 1.05)
(HR>1 indicates a clinical advantage for PHY).

These results indicate a statistically significant clinical advantage for PHY in terms of treatment withdrawal and a non-significant advantage in terms of 12 month remission. Results for time to first seizure suggested a non-significant clinical advantage for PHB.¹³⁷

Tudur Smith 2003¹³⁸

Tudur Smith and colleagues reviewed evidence comparing PHY and VPA when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults were included.

Outcomes were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission,
- c. time to six month remission and
- d. time to first seizure post randomisation.

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met our inclusion criteria. Of these five trials, one recruited adults only (aged 14 to 72 years), one recruited children only (aged 3 to 16 years), two recruited both (aged 3 to 64 years) and one recruited older subjects only (aged 61 to 95 years).

One important limitation was that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow-up. Hence results applied only to generalized tonic-clonic seizures.

The main overall results were as follows

- a. time to withdrawal of allocated treatment 1.10 (0.79 to 1.54)
(HR>1 indicates a clinical advantage for VPA)
- b. time to 12 month remission 1.04 (0.78 to 1.38)
(HR>1 indicates a clinical advantage for PHY)

- c. time to six month remission 0.89 (0.71 to 1.11)
(HR>1 indicates a clinical advantage for PHY)
- d. time to first seizure 0.92 (0.74 to 1.14)
(HR>1 indicates a clinical advantage for VPA).

The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found.¹³⁸

Another systematic review of AED (CBZ, PHY, VPA) efficacy and safety was identified.¹²⁷ This was an older review, published in 1997, and there were significant methodological flaws in the analysis. Therefore, only the results of the Cochrane reviews described above have been included.

Primary evidence

No further RCTs were identified.

11.1.3.13 Piracetam (PRC)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of piracetam in the management of the epilepsies in adults.

Primary evidence

One RCT was identified.¹³⁹

Koskiniemi 1998¹³⁹

This RCT compared the efficacy, tolerability, and safety of three daily regimens of oral piracetam in adults with progressive myoclonus epilepsy (Unverricht-Lundborg disease).

Twenty adults (12 men, eight women), aged 17 to 43 years, with classical Unverricht-Lundborg disease were enrolled in a multicentre, randomised, double blind trial of crossover design in which the effects of daily doses of 9.6g, 16.8g, and 24g of piracetam, given in two divided doses, were compared with placebo. The crossover design was such that individuals received placebo and two of the three dosage regimens of piracetam, each for two weeks, for a total treatment period of six weeks and thus without wash out between each treatment phase. The primary outcome measure was a sum score representing the adjusted total of the ratings of six components of a myoclonus rating scale in which stimulus sensitivity, motor impairment, functional disability, handwriting, and global assessments by investigators and individuals were scored. Sequential clinical assessments were made by the same neurologist in the same environment at the same time of day.

Treatment with 24g/day piracetam produced significant and clinically relevant improvement in the primary outcome measure of mean sum score ($p=0.005$) and in the means of its subtests of motor impairment ($p=0.02$), functional disability ($p=0.003$), and in global assessments by both investigator ($p=0.002$) and the individual ($p=0.01$). Significant improvement in functional disability was also found with daily doses of 9.6g and 16.8g. The dose-effect relation was linear and significant. More individuals showed clinically relevant improvement with the highest dosage and, in individuals, increasing the dose improved response. Piracetam was well tolerated and adverse effects were few, mild, and transient.¹³⁹

11.1.3.14 Primidone (PMD)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of primidone in the management of the epilepsies.

Primary evidence

One RCT was identified.

Mattson 1985¹⁴⁰ and Smith 1987¹⁴¹

A 10-centre, double-blind trial was conducted to compare the efficacy and toxicity of four antiepileptic drugs in the treatment of partial and secondarily generalized tonic-clonic seizures in 622 adults. Participants were randomly assigned to treatment with carbamazepine, phenobarbital, phenytoin, or primidone and were followed for two years or until the drug failed to control seizures or caused unacceptable side effects. Strict exclusion criteria limited confounding factors such as drug or alcohol abuse. Seizure freedom for tonic-clonic seizures was similar for all drugs (CBZ 48%, PHB 43%, PHY 43%, PMD 45%). Carbamazepine provided complete control of partial seizures (43%) more often than primidone (15%) or phenobarbital (16%) ($p < 0.03$).

Differences in failure rates of the drugs were explained primarily by the fact that primidone caused more intolerable acute toxic effects, such as nausea, vomiting, dizziness, and sedation. Decreased libido and impotence were more common in those given primidone. Phenytoin caused more dysmorphic effects and hypersensitivity. Control of tonic-clonic seizures did not differ significantly with the various drugs. A behavioural toxicity battery was performed whenever possible prior to administration of any antiepileptic drug and at 1, 3, 6, and 12 months after initiation of monotherapy. Significant differences in performance on all subtests of the battery were found between individuals with epilepsy and a control group matched by age, sex, and education. When the differential effects of all four drugs on behavioural toxicity were compared, few statistically significant differences emerged. However, carbamazepine consistently

produced fewer adverse effects on tests of attention/concentration and motor performance than did the other three antiepileptic drugs. Both carbamazepine and phenytoin were associated with significantly lower incidences of intolerable side effects than were primidone or phenobarbital.

Overall, carbamazepine and phenytoin were recommended drugs of first choice for single-drug therapy of adults with partial or generalized tonic-clonic seizures or with both.^{140;141}

11.1.3.15 Sodium valproate (VPA)

Secondary evidence

Three Cochrane reviews were identified.^{125;135;138}

Marson 2003¹²⁵ and Marson 2002¹²⁶

The objective of this review was to assess the evidence comparing CBZ and VPA monotherapy in adults and children with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures. Randomised controlled trials comparing CBZ and VPA monotherapy for epilepsy were included.

Outcome measures were

- a. time to withdrawal of allocated treatment,
- b. time to 12 month remission, and
- c. time to first seizure post randomisation.

Individual patient data were available for 1265 individuals from five trials, representing 85% of those recruited into the eight trials that met the inclusion criteria. Of these five trials, three recruited adults only (aged 13 to 83 years) and two children only (aged 3 to 16 years).

The main overall results (HR 95% CI) were

- a. time to treatment withdrawal 0.97 (0.79 to 1.18)
(HR>1 indicates a clinical advantage for CBZ),
- b. 12 month remission 0.87 (0.74 to 1.02)
(HR>1 indicates a clinical advantage for VPA),
- c. first seizure 1.09 (0.96 to 1.25)
(HR>1 indicates a clinical advantage for CBZ)

The results showed no overall difference for these outcomes. However, a test for interaction between treatment and epilepsy type was significant for time to first seizure, indicating an advantage for CBZ in the treatment of partial seizures (1.22, 1.04 to 1.44). There was some heterogeneity and age was shown to be significantly linked with treatment effect. The authors suggested that the age distribution of adults classified as having a generalized epilepsy (36% and 44% in two trials had generalised epilepsy with onset over the age of 30 years) indicated that significant numbers of individuals may have had their epilepsy misclassified.^{125;126}

Posner 2003¹³⁵

This reviews the use of VPA in childhood absences (see Childhood absence epilepsy (CAE)).

Tudur Smith 2003¹³⁸

Tudur Smith and colleagues reviewed evidence comparing PHY and VPA when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults were included.

Outcomes were

- a. time to withdrawal of allocated treatment,

- b. time to 12 month remission,
- c. time to six month remission and
- d. time to first seizure post randomisation.

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met our inclusion criteria. Of these five trials, one recruited adults only (aged 14 to 72 years), one recruited children only (aged 3 to 16 years), two recruited both (aged 3 to 64 years) and one recruited older subjects only (aged 61 to 95 years).

One important limitation was that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow-up. Hence results applied only to generalized tonic-clonic seizures.

The main overall results were as follows

- a. time to withdrawal of allocated treatment 1.10 (0.79 to 1.54)
(HR>1 indicates a clinical advantage for VPA)
- b. time to 12 month remission 1.04 (0.78 to 1.38)
(HR>1 indicates a clinical advantage for PHY)
- c. time to six month remission 0.89 (0.71 to 1.11)
(HR>1 indicates a clinical advantage for PHY)
- d. time to first seizure 0.92 (0.74 to 1.14)
(HR>1 indicates a clinical advantage for VPA).

The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found.¹³⁸

Primary evidence

No RCT evidence was found.

11.1.3.16 Sulthiame (STM)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of sulthiame in the management of the epilepsies in children.

Primary evidence

One RCT was identified that assessed sulthiame in the treatment of epilepsy.¹⁴² However, only 31% of the recruited participants completed the study. This is well below the accepted level of 80%. The age of the participants was not clear, so this was excluded.

11.1.3.17 Tiagabine (TBG)

The effectiveness of tiagabine is addressed in the Technology Appraisals for adults and children.

11.1.3.18 Topiramate (TPM)

The effectiveness of topiramate is addressed in the Technology Appraisals for adults and children.

11.1.3.19 Vigabatrin (VGB)

The effectiveness of vigabatrin is addressed in the Technology Appraisals for adults and children.

11.1.4 Pharmacological treatment in the management of the epilepsies by syndrome

Two technology appraisals have been published on the use of newer drugs in adults and children with epilepsy. The remit of the evidence reviews produced to inform the guidance was to assess the effectiveness of newer drugs compared with older drugs. The following evidence reviews were produced for effectiveness of drugs in specific epilepsy syndromes.

Only high quality systematic reviews of RCTs, and high quality RCTs were included in the evidence reviews for this section.

The literature was searched for evidence on the treatment of the following syndromes identified by the GDG as being relevant to this guideline:

- Benign epilepsy with occipital spikes (BCOS)
- Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)
- Childhood absence epilepsy (CAE)
- Continuous spike wave of slow sleep (CSWS)
- Infantile spasms
- Juvenile myoclonic epilepsy (JME)
- Landau Kleffner syndrome (LKS)
- Lennox Gastaut syndrome (LGS)
- Myoclonic astatic epilepsy (MAE)
- Severe myoclonic epilepsy of infancy (SMEI)

It should be noted that this list is not exhaustive.

11.1.4.1 Benign epilepsy with occipital spikes (BCOS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

11.1.4.2 Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)

Secondary evidence

No systematic reviews of the treatment for this syndrome were identified.

Primary evidence

Two RCTs were identified.^{143;144}

Rating 2000¹⁴³

Rating and colleagues aimed to evaluate the efficacy and tolerability of sulthiame (STM) as monotherapy in children with benign childhood epilepsy with centrotemporal spikes (BECTS).

Sixty-six BECTS children entered a 6-month double-blind trial and were randomised to receive either STM (5 mg/kg/day) or a placebo. All children had had two or more seizures during the 6 months preceding the trial and were aged 3-11 years.

The primary effectiveness variable was the rate of treatment failure events (TFEs) per group. TFEs consisted of a first seizure after a 7-day run-in period, intolerable adverse events (AEs), development of another epileptic syndrome, or termination of the trial by parents or the child.

Twenty-five of the 31 STM-treated children (81%) and 10 of the 35 placebo-treated children (29%) completed the trial without any TFEs ($p = 0.00002$). Most TFEs were seizures ($n=4$ for the STM group, $n=21$ for the placebo group). Parents requested termination of treatment for two placebo-treated children. Treatment was terminated in four children for administrative reasons. No child was withdrawn for AEs. While all children displayed at least one specific focus in either the awake or asleep EEG initially, 11 STM-treated individuals had a normal awake EEG and 10 had a normal asleep one after 6 months. The effects on EEG should be interpreted with caution as the trial was not designed primarily to investigate the effect of STM on EEG discharges (see Bast 2003).

The authors concluded that STM was remarkably effective in preventing seizures in children with BECTS. Children having 2 or more seizures during the past 6 months had a high risk of early recurrence of seizures.¹⁴³

Bast 2003¹⁴⁴

Using data from the RCT described above, Bast and colleagues evaluated the effects of STM on the EEGs of children with BECTS.

One-hundred seventy-nine sleep EEGs were recorded at screening and after 4 weeks, 3 months, and 6 months. EEGs were analysed by a blinded reviewer using a standard protocol for each EEG. This standard protocol collected data on general changes, specific epileptiform, and nonspecific focal and generalized changes. A classification system was defined depending on rating of pathologic EEG changes. Because of the higher number of treatment-failure events (i.e., seizures) in the placebo group, there was an increasing imbalance between the two groups regarding the number of recorded sleep EEGs over time (STM, 104; placebo, 74). A Wilcoxon-Mann-Whitney U test was used to describe differences in the grade of pathology during individual follow-up between the two groups.

The sleep-EEG was found to be normalized in 21 children treated with STM (12/21 transient) and in five treated with placebo (4/5 transient). In the STM group, the EEG showed a marked improvement during intra-individual course when comparing the

classification of follow-up EEGs at each time point with the screening EEG.

Comparable improvements were not observed in the placebo group (exact two-tailed p value at 4 weeks, $p < 0.0001$; at 3 months, $p = 0.0010$; and at 6 months, $p < 0.0001$).

STM had marked effects on the EEG in BECTS, which led to normalization in the majority of the children. Most of those whose EEGs were not normalized showed improvement in the grade of EEG pathology. Normalization persisted in >50% of children during the investigation. Spontaneous normalization in the placebo group reflected the wide spectrum of individual courses, which must be considered when analysing drug effects on EEG in BECTS.¹⁴⁴

11.1.4.3 Childhood absence epilepsy (CAE)

Secondary evidence

One Cochrane review was identified for the use of ESM, VPA or LMG in the treatment of absence seizures.¹³⁵

Posner 2003¹³⁵

The authors reviewed the evidence for the effects of ESM, VPA and LMG as treatments for children and adolescents with absence seizures, when compared with placebo or each other. Randomised parallel group monotherapy or add-on trials were included.

Outcome measures were

- a. proportion of individuals seizure free at 1, 6 and 18 months post randomisation;
- b. people with a 50% or greater reduction in seizure frequency;
- c. normalisation of EEG and/or negative hyperventilation test and
- d. adverse effects.

Four small trials were found,¹⁴⁵⁻¹⁴⁸ which were of poor methodological quality. No trials were found comparing valproate or ethosuximide versus placebo.

One trial¹⁴⁶ (29 participants) compared LMG with placebo using a response conditional design. Individuals taking LMG were significantly more likely to be seizure free than participants taking placebo during this short trial. A responder enriched design was used where participants responding to lamotrigine during a pre-randomisation baseline phase were randomised to continue lamotrigine or have it withdrawn. This trial therefore compared the effect of continuing versus withdrawing LMG. The results were as follows, in the initial open label dose escalation phase 71% of the participants became seizure free on LMG using a 24-hour EEG/video telemetry recording; in the placebo controlled phase 64% of the participants on LMG remained seizure free versus 21% on the placebo ($p < 0.03$).¹⁴⁶

Three studies compared ESM with VPA,^{145;147;148} but because of diverse study designs and populations studied, a meta-analysis was not undertaken.

For the chosen outcome 'seizure freedom', data at the time points specified (one, 6 and 18 months) were not available. Rather than not present any data for this outcome, results for individual studies were presented.

- a. proportion of individuals seizure free at 1, 6 and 18 months post randomisation
The relative risk (RR) estimates with 95% confidence intervals (CI) for seizure freedom ($RR < 1$ favours ESM) were:

(a) 0.70 (95% CI 0.32 to 1.51);

(b) 0.88 (95% CI 0.53 to 1.46);

(c) 1.93 (95% CI 0.87 to 4.25).

Hence none of these trials found a difference for this outcome. However, confidence intervals were all wide and the possibility of important differences was not excluded and equivalence could not be inferred.

- b. people with a 80% or greater reduction in seizure frequency

This outcome was only reported in one trial, and the RR was 0.70 (95% CI 0.19 to 2.59).

Again no difference was found, but the confidence interval was wide and equivalence could not be inferred.

c. people with a 50% or greater reduction in seizure frequency

This was reported in two trials. In one trial all participants achieved this outcome.

For the other trial the RR was 1.02 (95% CI 0.70 to 1.48).

Again no difference was found, but the confidence interval was wide and equivalence could not be inferred.

None of these studies found a difference between VPA and ESM with respect to seizure control, but confidence intervals were wide and the existence of important differences could not be excluded. The authors concluded that although individuals taking LMG were significantly more likely to be seizure free than participants taking placebo, overall there was insufficient evidence to inform clinical practice.¹³⁵

Primary evidence

Only one RCT that was not already included in the Cochrane review on absences was identified.¹⁴⁹

Trudeau 1996¹⁴⁹

The efficacy and safety of GBA monotherapy in newly diagnosed absence epilepsy was evaluated in two identical RCTs. 33 children were randomised to either treatment (n=15, dose range from 9.7 to 19.1 mg/kg/day) or placebo (n=18). No statistically significant baseline differences were found between the two groups. Seizure frequency was determined by baseline 24 hour EEG, which was repeated at the end of the 2 week treatment phase.

In an intention-to-treat analysis, data on two children was excluded due to a lack of a baseline EEG because of equipment malfunction. No statistically treatment differences (response ratio, p=0.141 or responder rate, p=0.344) were found between GBA and placebo. GBA did not decrease or increase absence seizures compared with placebo.

The authors suggested that the lack of effect may have been due to the study being underpowered (terminated early due to slow recruitment), the 2-week treatment period being too short, or subtherapeutic doses.¹⁴⁹

11.1.4.4 Continuous spike wave of slow sleep (CSWS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

11.1.4.5 Infantile spasms

Secondary evidence

One Cochrane review was identified.¹⁵⁰

Hancock 2003¹⁵⁰

Hancock and colleagues compared the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, subsequent epilepsy, control of the spasms and adverse effects. All randomised controlled trials (RCTs) of the administration of drugs to people with infantile spasms were included.

Outcomes included

- cessation of spasms,
- time to cessation of spasms,
- participants with cessation of spasms remaining spasm free,
- reduction in spasms,
- resolution of hypsarrhythmia,
- subsequent epilepsy rates, and
- adverse effects.

Eleven RCTs were included, which in total recruited 514 participants and tested eight different drugs. Overall, methodology of the studies was poor. No study assessed long-term psychomotor development or onset of other seizure types.

One small study¹⁵¹ found VGB to be more efficacious than hydrocortisone in stopping infantile spasms in a group of people with tuberous sclerosis. This study compared VGB (150 mg/kg/day) and hydrocortisone (15 mg/kg/day) in 22 infants with infantile spasms due to tuberous sclerosis, and found in the initial phase, all participants (11 infants) treated with VGB to be spasm free as compared to five of 11 infants (45%) treated with hydrocortisone giving a Peto odds ratio of 13.8 (95% CI 2.21 to 86.35). On average the 11 responders to vigabatrin took 4 days (range 0.5 to 14 days, median 2 days) to achieve complete cessation of spasms, whilst the 5 responders to hydrocortisone took an average of 13 days (range 3 to 30 days, median 23.5 days) giving a weighted mean difference of -8.8 (95% CI -19.2 to 1.6). 10 of the 11 infants who responded to vigabatrin remained spasm free; this information was not given for the five responders to hydrocortisone. Other effects were not reported.¹⁵¹

One underpowered study showed a trend for VGB to be more efficacious than placebo in stopping infantile spasms.¹⁵² Of the 40 participants, 7 of 20 (35%) participants treated with vigabatrin compared with 2 of 20 (10%) treated with placebo showed complete cessation of spasms, giving a Peto odds ratio of 4.1 (95% CI 0.9 to 17.5). Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study. There was a greater than 70% reduction in spasms in 40% of the group treated with VGB compared with 15% in the group treated with placebo. However, it was not clear from the paper to what proportion of the two groups of individuals these figures applied, whether the figures applied to the whole group or just those individuals in whom complete cessation of spasms was not achieved. Four of the seven participants who responded to vigabatrin relapsed and all the participants successfully treated with placebo relapsed. Overall only three participants treated with vigabatrin and no individual treated with placebo treatment remained spasm free within the four week study period giving a Peto odds ratio of 8.2 (95% CI 0.8 to 84). Effects on time taken to relapse were not reported as an outcome in this study. Five of the seven participants who were spasm free with vigabatrin showed resolution of hypsarrhythmia

on EEG, compared with one of the two participants who had become spasm free on placebo, Peto odds ratio 2.4 (95% CI 0.1 to 54.6). Other effects were not reported.¹⁵²

Two small studies^{153;154} when combined showed ACTH to be more efficacious than low-dose prednisone (2 mg/kg).

Baram et al¹⁵³ in their study compared ACTH with prednisone and found 7 (~ 50%) participants in both groups to have developed other seizure types over the period of follow up of 2 to 48 months. However, this comparison was confounded by the fact that some infants initially randomised to receive prednisone went on to receive ACTH within the follow up period. They did not report subsequent epilepsy rates at five years of age. Baram and colleagues¹⁵³ showed ACTH to be superior to prednisone with cessation of spasms in 13 of 15 (87%) participants and 4 of 14 (29%) participants respectively. Hrachovy and colleagues¹⁵⁴ compared 12 participants treated with ACTH with 12 participants treated with prednisone. In the initial phase of the trial 5 of 12 (42%) participants treated with ACTH had complete cessation of spasms and resolution of hypsarrhythmia on their EEG compared with 4 of 12 (33%) treated with prednisone. Combining the two studies, ACTH stopped the spasms in 67.5% of participants compared with prednisone in 31% of participants giving a Peto odds ratio of 4.2 (95% CI 1.4 to 12.4). Baram 1996,¹⁵³ found that, on average, the 13 responders to ACTH took 3.2 days (range 1 to 7 days, median 2 days) to achieve complete cessation of spasms, whilst the 4 responders to prednisone took an average of 4 days (range 2 to 7 days, median 3.5 days) giving a weighted mean difference of -0.8 (95% CI -3.3 to 1.7). In Baram 1996,¹⁵³ 2 of the 13 participants who responded to ACTH relapsed and none of the 4 responders to prednisone relapsed. Hrachovy 1983¹⁵⁴ found three of the five participants who responded to ACTH relapsed and one of the four responders to prednisone also relapsed. Overall, Baram 1996¹⁵³ found 11 participants who responded to ACTH remained spasm free and the four responders to prednisone also remained spasm free. In Hrachovy 1983,¹⁵⁴ two participants successfully treated with ACTH remained spasm free and three successfully treated with prednisone remained spasm free within the study period. The combined Peto odds ratio for these two studies is 2.6 (95% CI 0.8 to 8.1~). Baram 1996¹⁵³ showed ACTH to be superior to prednisone with resolution of hypsarrhythmia in 13 of 15 participants treated with ACTH compared to 4

of 14 of participants treated with prednisone giving a Peto odds ratio of 10.1 (95% CI 2.4 to 43.2). In Hrachovy 1983,¹⁵⁴ 5 of 12 participants treated with ACTH had resolution of hypsarrhythmia but this was not reported for the group treated with prednisone. Other effects were not reported.

One study also suggested that control of spasms occurred more frequently with high dose VGB as compared to low dose VGB.¹⁵⁵ 8 of 75 participants treated with low dose vigabatrin became spasm free as compared with 24 of 67 participants treated with high dose vigabatrin, giving a Peto odds ratio of 0.24 (95% CI 0.11 to 0.52). Effects on time taken to achieve cessation of spasms within the initial two week study period were not reported as an outcome in this study. But in an open follow up period of the study, where other treatment could be given (but details not provided) the authors found that the number of responders increased from 8% at 2 weeks, to 42% at 4 weeks, 55% at 2 months and 65% at three months. 8 of 75 participants treated with low dose vigabatrin had no evidence of hypsarrhythmia compared with 24 of 67 participants treated with high dose vigabatrin, giving a Peto odds ratio of 0.24 (95% CI 0.11 to 0.52). Other effects were not reported.

It was not possible to compare reduction in the number of spasms between the different treatments because of differences in methods of analysis. Overall, only 18 individuals were reported to have been withdrawn from the trial treatments due to adverse effects and 4 deaths were reported.

The authors concluded that no single treatment was proven to be more efficacious in treating infantile spasms than any of the others (other than VGB in the treatment of infantile spasms in tuberous sclerosis in one underpowered study).¹⁵⁰

Primary evidence

No RCTs were identified since the above reviews.

11.1.4.6 Juvenile myoclonic epilepsy (JME)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

11.1.4.7 Landau Kleffner syndrome (LKS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

11.1.4.8 Lennox Gastaut syndrome (LGS)

Secondary evidence

One Cochrane review was identified.¹⁵⁶

Hancock 2003¹⁵⁶

This review compared the effects of pharmaceutical therapies used to treat Lennox-Gastaut syndrome in terms of control of seizures and adverse effects. Many people who have this syndrome will already be receiving other antiepileptic medications at the time of their entry into a trial. However, for the purpose of this review only the effect of the single therapeutic agent being trialled (often as add-on therapy) was considered. All randomised controlled trials (RCTs) of the administration of drug therapy to individuals with Lennox-Gastaut syndrome were included.

Five RCTs were included, but the authors were unable to perform a meta-analysis, primarily because each trial studied a different therapy. However, even if two or more of the trials had considered the same therapy it would still have been difficult to combine the results. The studies had used different entry criteria and definitions (summarised under description studies) leading to heterogeneity between the groups. In addition the studies all used different outcome measures, for example one study only considered cessation or reduction of all seizure types whilst one considered a reduction in the number of absence, tonic and atonic seizures and another reported a reduction in drop

attacks, tonic-clonic seizures and all seizure types. Even when studies did report the same outcomes the results were often presented in different ways, for example one study gave the reduction in all seizure types as the percentage reduction in number of seizures for each participant, whilst another gave an overall reduction for all the participants combined.

The optimum treatment for Lennox-Gastaut syndrome remains uncertain and no study showed any one drug to be highly efficacious; LMG, TPM and FBM may be helpful as add-on therapy.¹⁵⁶

Primary evidence

No RCTs were identified as having been published since the Cochrane review.

11.1.4.9 Myoclonic astatic epilepsy (MAE)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

11.1.4.10 Severe myoclonic epilepsy of infancy (SMEI)

Secondary evidence

No systematic reviews of the treatment for this syndrome were identified.

Primary evidence

One RCT was identified.¹⁵⁷

Chiron 2000¹⁵⁷

The efficacy of stiripentol as add-on therapy in severe myoclonic epilepsy in infancy was evaluated in a randomised placebo-controlled trial involving 41 children taking valproate and clobazam. After a one month baseline period, children were assigned to either the treatment group (n=21) or the placebo group (n=20). Children were assessed every month during the two month double blind period. Seizure frequency was based on a diary maintained by parents and carers, and drug compliance based on the number of capsules returned. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double blind period compared with baseline.

Table 12 Comparison of stiripentol and placebo groups Modified from Chiron 2000¹⁵⁷ and reprinted with permission from Elsevier (The Lancet, 2000, 356, 1638-42)

	Stiripentol n=21)	Placebo (n=20)	Difference between groups
Responders (95% CI)	15 (71%) (52.1% to 90.7%)	1 (5%) (0% to 14.6%)	p<0.0001
Individuals who became seizure free (95% CI)	9 (43%) (21.9% to 65.9%)	0 (0.0% to 13.9%)	p=0.0013
Median (range) monthly seizures in double blind period	5 (0 to 27)	14 (2 to 23)	p=0.0063
Mean change from baseline of seizure frequency (95% CI)	-69% (-50% to -85%)	7% (25% to 11%)	p<0.0001

The frequency of responders was greater on stiripentol (71%, 95% CI 52.1% to 90.7%) than on placebo (5%, 95% CI 0% to 14.6%) with a high significance (p<0.0001). During the double-blind period, nine (43%) children on stiripentol but none on placebo became free of clonic (or tonic-clonic) seizures. In each group, one person had status epilepticus. Absolute seizure frequency was significantly lower on stiripentol than placebo (p=0.0063) after a decrease of 69% on stiripentol but an increase of 7% on placebo (p<0.0001). 21 children on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of co-medication was decreased in 12 of the 21 cases.¹⁵⁷

11.1.5 Side effects of antiepileptic drugs

The GDG agreed to use the information on side effects from both the National Society for Epilepsy website (<http://www.epilepsynse.org.uk/>) and the Summary of Product Characteristics for each drug. The tables are presented alongside the drug tables in Appendix B:

The tables are intended to make the prescriber aware of the side effects that are commonly caused by AEDs.

11.1.6 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'.¹⁵⁸

11.2 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. **[A (NICE)]**

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. **[A (NICE)]**

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. **[GPP]**

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. **[GPP]**

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.¹⁵⁹ However, participants may have tried several monotherapy regimes before inclusion, so this RCT was excluded. No other RCTs were identified.

Other evidence

Kwan 2000¹⁶⁰

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 ($p=0.25$).

Deckers 2003¹⁶¹

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.¹⁶¹ 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.¹⁶¹

11.2.1 When should AED treatment in adults and children be started?

Treatment with AED therapy is generally recommended after a second epileptic seizure.

[A]

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. **[GPP]**

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. **[B]**

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. **[GPP]**

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. (1a)

11.2.1.1 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 1991⁸⁸

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%).⁸⁸

Hirtz 2003¹⁶²

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.¹⁶²

Are there factors that increase the risk of recurrence?

The authors cited the findings of the Berg & Shinnar review⁸⁸ that the underlying aetiology and whether the EEG is normal or abnormal were consistently related to the risk of recurrence.¹⁶²

Primary evidence

Hart 1990¹⁶³

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).¹⁶³

Macdonald 2000¹⁰

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 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.¹⁰

11.2.1.2 In adults and children who present with a single seizure, does treatment with antiepileptic medication reduce the risk of further seizures?

Secondary evidenceBerg 1991⁸⁸

A systematic review of the risk of seizure recurrence following a first unprovoked seizure was undertaken by Berg & Shinnar in 1991.⁸⁸ Their literature review reviewed all relevant studies up to 1990. The authors identified one RCT¹⁶⁴ in which treatment of a first seizure was associated with a significant reduction in risk of recurrence.

Hirtz 2003¹⁶²

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 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.¹⁶⁴ 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.¹⁶⁴

In studies involving both children and adults, outcome was not provided based on age. One study¹⁶⁵ 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.¹⁶⁵

However, these results were not found in another randomised study¹⁶⁶ (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^{166;167}.

One study¹⁶⁶ 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 study¹⁶⁷ 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.¹⁶²

11.2.2 Who should start AED treatment in adults and children?

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

AED therapy in children should be initiated by a specialist. **[GPP]**

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. **[GPP]**

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 8 was considered by the GDG and formed the basis for the GPPs above.

11.2.3 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?

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. **[GPP]**

If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. **[GPP]**

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. **[GPP]**

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. **[GPP]**

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.

11.2.4 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. **[C]**

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

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. **[D]**

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. **[GPP]** (adults only)

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

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

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. **[A (NICE)]**

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)

Details

In adults/children with epilepsy, does 'routine' monitoring of

- AED blood levels
- side effects
- drug usage

lead to better outcomes (e.g. seizure recurrence, side effects) when compared with those who receive no monitoring or monitoring only when clinically indicated?

11.2.4.1 In adults and children with epilepsy, does 'routine' monitoring of AED blood levels lead to better outcomes when compared with those who receive no monitoring or monitoring only when clinically indicated?

Secondary evidence

AHRQ 2001³⁸

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 1998¹⁶⁸

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.¹⁶⁸

Primary evidence

Jannuzzi 2000¹⁶⁹

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.¹⁶⁹

Froscher 1981¹⁷⁰

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.¹⁷⁰

11.2.4.2 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

Deckers 1997¹⁷¹

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.¹⁷¹

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.¹⁷²

11.2.4.3 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.

11.2.5 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 above)
- using simple medication regimens
- positive relationships between healthcare professionals, the individual with epilepsy, and their family and/or carers. **[D]**

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. **[GPP]**

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?¹⁷³ '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.¹⁷⁴

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.¹⁷⁵

The authors reviewed the research evidence and identified the following factors associated with **adherence** to medication:

Table 13 Factors affecting adherence to medication regimens in people with epilepsy¹⁷⁵

Factors related to good adherence	Factors related to poor adherence
Aged over 60 years	Aged under 60 years
Aged over 19 years	Teenager (aged under 19 years)
Once-daily dose	Four-times daily dose
Feeling that it is important to take medication as prescribed	Feeling stigmatised
Finding the GP easy to talk to	Experience of side effects
Concerned about health or health risks	
Absence of barriers, such as costs, inability to obtain medication	

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.

11.2.6 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). **[A]**

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. **[A]**

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. **[D]**

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. **[GPP]**

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. **[GPP]**

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)

11.2.6.1 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 1994¹⁷⁶

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^{ff} 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).¹⁷⁶

Quality Standards Subcommittee of the American Academy of Neurology 1996¹⁷⁷

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.

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,

^{ff} 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.

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.¹⁷⁷

Sirven 2003¹⁷⁸

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.¹⁷⁸

Primary evidence (adults)

MRC AED withdrawal study group 1991¹⁷⁹

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 14.

Table 14 Influence of individual characteristics on seizure recurrence¹⁷⁹

Factor	Relative risk (95% CI) (multivariate model)
History of partial seizures, none generalized	2.51 (1.00, 6.30)
History of myoclonic seizures	1.85 (1.09, 3.12)
History of tonic-clonic seizures (primary or secondary)	3.40 (1.48, 7.84)
Seizures after start of treatment	1.57 (1.10, 2.24)
On more than one AED at randomisation	1.79 (1.34, 2.39)
Period seizure free at randomisation (years)	
3 - <5	0.67 (0.48, 0.93)
5 - <10	0.47 (0.32, 0.69)
10-	0.27 (0.15, 0.48)

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.¹⁷⁹

MRC AED withdrawal study group 1993¹⁸⁰

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 above¹⁷⁹ 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.¹⁸⁰

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 15 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.¹⁸¹

Table 15 Prognostic index for recurrence of seizures within one and two years after continuing AED treatment or starting slow withdrawal¹⁸⁰Adapted from MRC AED Drug Withdrawal Group 1993¹⁸⁰ and reprinted with permission from the BMJ Publishing Group (BMJ, 1993, 306, 1374-8)

Starting score (all individuals)	-175
Age 16 or older	Add 45
Taking more than one AED	Add 50
Seizures after start of AED treatment	Add 35
History of primary or secondarily generalized tonic-clonic seizures	Add 35
History of myoclonic seizures	Add 50
EEG in last year	
not available	Add 15
abnormal	Add 20
Period free from seizures (t: no. of years)	Add 200/t
TOTAL SCORE	T
Divide total score by 100 and exponentiate	$z=e^{T/100}$
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	$1-0.60^z$

11.2.6.2 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 1994¹⁸²

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.¹⁸²

11.2.7 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.
[GPP]

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.

11.3 *When should an individual with epilepsy be referred for assessment in a tertiary centre?*

11.3.1 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.¹⁸³

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

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. **[GPP]**

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. **[GPP]**

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. **[GPP]**

If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, individuals should be referred to tertiary services soon⁹⁹ 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 **[D]**

⁹⁹ The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

- management is unsuccessful after two drugs **[GPP]**
- the individual is aged under 2 years **[GPP]**
- an individual experiences, or is at risk of, unacceptable side effects from medication **[GPP]**
- there is a unilateral structural lesion **[GPP]**
- there is psychological and/or psychiatric co-morbidity **[GPP]**
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. **[GPP]**

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.

[D]

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

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. **[GPP]**

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

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 1999¹⁸⁴

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.'¹⁸⁴

Wiebe 2001¹⁸⁵

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.¹⁸⁵

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 1999¹⁸⁴

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.

11.4 *The role of non-drug treatments in the management of the epilepsies*

11.4.1 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 bio-feedback 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 is high in fat and low in carbohydrate and it has been suggested that this diet reduces seizure frequency. This diet is used mainly as an adjunctive treatment for children who continue to have seizures despite treatment with antiepileptic drugs.

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.

Only systematic reviews of RCTs and RCTs are included in these evidence reviews – the same approach as was used in the review of pharmacological treatment.

11.4.2 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. **[A]**

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. **[A]**

Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children with drug-resistant focal epilepsy. **[A]**

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.¹⁸⁶

Ramaratnam 2003¹⁸⁶

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.¹⁸⁶

Engelberts 2002¹⁸⁷

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.¹⁸⁷

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.

11.4.3 In adults and children with epilepsy, is the ketogenic diet effective in reducing seizure frequency?

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

The ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy. [C]

Evidence statement

There is no RCT evidence on the effectiveness of the ketogenic diet in people with epilepsy. Observational studies suggest a potential benefit effect in children with epilepsy. (III)

Details

Secondary Evidence

One Cochrane review was identified that addressed the use of the ketogenic diet in the management of the epilepsies.¹⁸⁸

Levy 2003¹⁸⁸

This review aimed to assess the evidence from RCTs regarding the effects of ketogenic diets for people with epilepsy.

However, no RCTs were found. The majority of reported studies of the effects of ketogenic diets were not randomised or controlled and were predominantly retrospective.

A Medline search for observational studies assessing the effects of ketogenic diets upon seizures was undertaken, and 20 studies were found. These studies indicated a potential beneficial effect, supporting the need for further study in randomised controlled trials.¹⁸⁸

Table 16 Observational studies of ketogenic diets with at least three months follow-up¹⁸⁸ Modified from Levy, Issue 3, Cochrane Library 2003. Copyright Cochrane Library, reproduced with permission

Trial	Design	Type of diet an number of recruited	Number reduction; with 50% seizure free			Adverse affects; number
			3 months	6 months	12 months	
Barborka 1927	Retrospective	Classical 100	44;?	43;?	36;8	
Berman 1978	Retrospective	Classical 8 MCT, 18	6;2	6;?		
Caraballo 1998	Prospective	Classical 14	7;0	7;0	7;0	Gastrointestinal;2 Fluid/electrolyte;1 Infection;1
Cusmai 1999	Prospective	Classical 41	13;6	10;3	3;?	
Debakan 1966	Retrospective	Classical 11	4;5	4;5	4;5	
Freeman 1998	Prospective	Classical 150	85;4	72;5	64;11	Gastrointestinal;5 Renal calculi;4
Hassan 1999	Retrospective	Classical 49 MCT,3	20;6			Behavioural;2 Gastrointestinal;1 Fluid/electrolyte;1
Helmholtz 1927	Retrospective	Classical 127	38;56	33;53	23;42	Behavioural;2 Gastrointestinal;4
Hopkins 1970	Retrospective	Classical 34	10;7			Gastrointestinal;1 Fluid/electrolyte;1
Huttenlocher 1971	Retrospective	MCT, 12	6;3	3;2	2;2	Gastrointestinal;5
Kinsman 1992	Retrospective	Classical 58	763;717	?;?	?;?	Fluid/electrolyte;7
Maydell 2001	Retrospective	Classical 143	59;21	60;24	54;23	Behavioural;20 Gastrointestinal;75 Fluid/electrolyte;15
Moreno Villares 2001	Retrospective	Modific MCT, 12	9;1	6;2	3;1	
Nordli 2001	Retrospective	Classical 32	4;0	13;6		Gastrointestinal;3 Fluid/electrolyte;1
Panico 2000	Prospective	Classical 13	10;4	8;3	8;4	Gastrointestinal;4 Fluid/electrolyte;1 Anaemia;3
Schwartz 1989	Prospective	Classical MCT, modified MCT total 59	51;?			Behavioural;1 Gastrointestinal;15 Fluid/electrolyte;0
Sirven 1999	Prospective	Classical 11	6;0	6;?		Behavioural;2 Gastrointestinal;11 Menstrual issues;9
Trauner 1985	Retrospective	MCT,17	4;10	4;9	4;7	Gastrointestinal;3
Veggiotti 1999	Retrospective	Classical 10	4;0	4;0	1;0	Behavioural;4 Candida;2 Fluid/electrolyte;2
Wilkins 1937	Retrospective	Classical 34	12;5	13;10	13;12	

Classical = classical ketogenic diet
MCT = medium chain triglyceride.

Primary evidence

No RCTs were identified.

11.4.4 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. **[A]**

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. **[A]**

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 review¹⁸⁹ and one technology appraisal¹⁹⁰ 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 children¹⁹¹ was published by NICE in 2004. The guidance is included in the guideline recommendations above.

Privitera 2003¹⁸⁹

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^{192;193} 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 trial¹⁹² 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 trial¹⁹³ 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.¹⁸⁹

Bryant 1998¹⁹⁴

This technology assessment was published prior to the publication of the E05 trial so conclusions about effectiveness are not presented. (See Cochrane review above)

Corabian 2001¹⁹⁰

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.¹⁹⁰

Raeburn 2003¹⁹⁵

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 1999¹⁹⁶

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.¹⁸⁹

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 economicsBryant 1998¹⁹⁴

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 1999¹⁹⁷

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.¹⁹⁷

12 Management of acute or prolonged seizures and status epilepticus in adults and children

12.1 Introduction

Prolonged seizures requiring emergency treatment are defined as convulsive seizures lasting 5 or more minutes. Serial seizures are defined as 3 or more seizures in an hour.

Status epilepticus is defined as a condition in which 'epileptic activity persists for 30 minutes or more'.¹⁹⁸ Generalised tonic-clonic status is a medical emergency that is associated with significant morbidity and mortality if not treated promptly. Therefore rapid diagnosis and treatment is crucial.

12.2 Are rectal/buccal benzodiazepines effective in the treatment of acute convulsive seizures in the community?

An individual who has prolonged convulsive (lasting 5 minutes or more) or serial seizures (three or more seizures in an hour) in the community should receive urgent care and treatment. **[A]**

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

Rectal diazepam is safe and effective in first-line treatment of prolonged seizures and is recommended in the majority of cases. **[A]**

For many individuals and in many circumstances, buccal midazolam^{hh} 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. **[GPP]**

Healthcare professionals should inform individuals, and their families and/or carers, that buccal midazolam is currently unlicensed. **[GPP]**

Care must be taken to secure the individual's airway and assess his or her respiratory and cardiac function. **[GPP]**

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. **[GPP]**

^{hh} Buccal midazolam is currently unlicensed for the treatment of prolonged or repeated seizures.

Evidence statements

Rectal diazepam is effective in terminating prolonged and serial seizures in adults and children in the community. (Ib)

A comparison of buccal midazolam versus rectal diazepam shows similar effectiveness. (Ib)

A comparison of intranasal midazolam versus rectal diazepam in children shows midazolam to be more effective (Ib)

Details

The use of IV drugs by paramedics and other trained personnel has been excluded.

Secondary evidence (adults and children)

No systematic reviews of the use of rectal or buccal benzodiazepines in adults were identified.

No systematic reviews of the use of benzodiazepines for acute seizures in children were identified.

Primary evidence

Cereghino 1998¹⁹⁹

Cereghino and colleagues evaluated the effectiveness and safety of a single-dose treatment for acute repetitive seizure (ARS) episodes (e.g., clusters) administered in a nonmedical setting by caregivers. A multicentre, randomised, parallel, double-blind study of a single administration of Diastat (diazepam rectal gel) for treating episodes of ARS was undertaken. ARS episodes and treatment criteria were defined for each individual at the start of the study. Caregivers were taught to determine ARS episode

onset, administer a predetermined dose of study medication, monitor outcome, count respirations, and record seizures and adverse events.

158 people were enrolled, of whom 114 had a treated ARS episode (Diastat, n=56; placebo, n=58). Diastat treatment reduced median seizure frequency ($p = 0.029$). More Diastat treated individuals were seizure free post-treatment (Diastat, 55%; placebo, 34%; $p=0.031$). Analysis of the time to the next seizure favoured Diastat treatment ($p<0.007$). The most common adverse event was somnolence.¹⁹⁹

Dreifuss 1998²⁰⁰

Dreifuss and colleagues conducted a randomised, double-blind, parallel-group, placebo-controlled study of home-based treatment for acute repetitive seizures. Individuals were randomly assigned to receive either rectal diazepam gel, at a dosage varying from 0.2 to 0.5 mg per kilogram of body weight on the basis of age, or placebo. Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. Adults received three doses -- one dose at onset, and two more doses 4 and 12 hours after onset. Treatment was administered by a care giver, such as a parent, who had received special training. The number of seizures after the first dose was counted for 12 hours in children and for 24 hours in adults.

Of 125 participants (64 assigned to diazepam and 61 to placebo) with a history of acute repetitive seizures, 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. Diazepam treatment was superior to placebo with regard to the outcome variables related to efficacy: reduced seizure frequency ($p<0.001$) and improved global assessment of treatment outcome by the care giver (frequency and severity of seizures and drug toxicity) ($p<0.001$). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children ($p<0.001$) and adults ($p=0.02$), but only in children was it superior with regard to improvement in global outcome ($p<0.001$). The time to the first recurrence of seizures after initial treatment was longer for those receiving diazepam ($p<0.001$). Thirty-five individuals reported at least one adverse effect of treatment; somnolence was the most frequent. Respiratory depression was not reported.²⁰⁰

Scott 1999²⁰¹

Scott and colleagues aimed to find out whether there are differences in efficacy and adverse events between buccal administration of liquid midazolam and rectal administration of liquid diazepam in the acute treatment of seizures. At a residential school with on-site medical facilities, 42 young people with severe epilepsy were enrolled. Continuous seizures of more than 5 minutes duration were randomly treated with buccal midazolam or rectal diazepam. If the seizure did not stop within 10 minutes, additional medication chosen by the attending physician was administered. Oxygen saturation and blood pressure were monitored for 30 minutes after treatment. The main outcome measures were efficacy, time from arrival of the nurse to drug administration, time from drug administration to end of seizure, and incidence of adverse cardiorespiratory events.

Buccal midazolam was used to treat 40 seizures in 14 students, and rectal diazepam 39 seizures in 14 students. Midazolam stopped 30 (75%) of 40 seizures and diazepam 23 (59%) of 39 ($p=0.16$). The median time from arrival of the nurse to administration of medication was 2 minutes. Time from administration to end of seizure did not differ significantly between the two treatments. No clinically important adverse cardiorespiratory events were identified in the two groups. Buccal midazolam was universally acceptable to the nursing and care staff.²⁰¹

Results for the adult participants in two of the RCTs^{199;200} presented above were re-analysed and published in 2002.²⁰²

Cereghino 2002²⁰²

Cereghino and colleagues evaluated the efficacy and tolerability of rectal diazepam gel in the treatment of acute repetitive seizures in adults.

The results of two multicentre, double-blind, placebo controlled trials (study 001 and study 003) were combined to give a sample size of 96 adults with a history of acute repetitive seizures, were randomised into two groups. Of these 96, 70 experienced acute repetitive seizures and received treatment ($n=31$) or placebo ($n=39$). There were no significant baseline differences between the two groups.

There was a significant reduction in seizure frequency in individuals who received rectal diazepam gel compared with the placebo group. The median number of seizures per hour in the rectal diazepam gel treated group was 0.00, vs 0.13 in the placebo group ($p=0.002$). In addition, significantly more rectal diazepam gel treated individuals remained seizure-free during the 12-- hour observation period (71% [22/31] vs 28% [11/39]). The rectal diazepam gel exerted a prompt therapeutic effect that persisted throughout the observation period. Time to next seizure was significantly longer in rectal diazepam gel treated than placebo-treated individuals ($p<0.001$). Global assessment as provided by the caregivers was in favour of rectal diazepam gel for both study 001 ($p=0.17$) and study 003 ($p=0.02$).

The proportion of people experiencing at least one adverse event was higher (32% [10/31]) in the rectal diazepam gel treated group than in the placebo-treated group (23% [9/39]). Somnolence and dizziness were the only central nervous system adverse events that occurred more frequently in those receiving rectal diazepam gel than in those receiving placebo.

The only serious adverse events occurred in two individuals in the rectal diazepam gel group who inadvertently received more than 180% of the intended doses. These resolved without incident. There were no reports of severe respiratory depression necessitating emergency medical care in either treatment group.²⁰²

Fisgin 2002²⁰³

One RCT was identified that compared the efficacy and side effects of rectal diazepam and intranasal midazolam in the treatment of acute convulsions in children.

In the diazepam group, the seizures of 13 (60%) individuals terminated in 10 minutes; however, 9 (40%) did not respond. In the midazolam group, 20 (87%) individuals responded in 10 minutes, but 3 (13%) did not respond. Midazolam was found to be more effective than diazepam, and the difference was statistically significant ($p<0.05$). The necessity of a second drug for the seizures that did not stop with the first drug was higher in the diazepam group than the midazolam group, and the difference was statistically significant ($p<0.05$). No serious complications were observed. However,

the treatment was administered by physicians in the emergency room, rather than by caregivers in the community.²⁰³

12.3 How should status epilepticus be managed in adults and children in the hospital setting?

1.1.2 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 C):

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure intravenous (IV) access in a large vein. **[GPP]**

Lorazepam should be used as a first-line treatment in status epilepticus (see Appendix C). **[D]**

Non-convulsive status is uncommon and management is less urgent. A suggested guideline can be found in Appendix C. **[GPP]**

Evidence statements

Intravenous lorazepam and diazepam are both effective in controlling tonic-clonic status epilepticus. (1b adults 1a children)

Lorazepam may be more effective than diazepam but the difference does not reach statistical significance. (1b)

12.3.1 How should convulsive status epilepticus be managed in adults and children in the hospital setting?

Details

There were several primary papers exploring the usefulness of neuron specific enolase as a marker of brain damage, but this was felt to be out of the scope of the guideline.

Secondary evidence

No systematic reviews on the management of status epilepticus in adults were identified.

Appleton 2002²⁰⁴

A recent Cochrane review on drug management for acute tonic-clonic convulsions, including convulsive status epilepticus, reviewed the evidence comparing diazepam, lorazepam, phenobarbitone, phenytoin, and paraldehyde in children. The definition of status epilepticus used was 'a generalized tonic-clonic convulsion lasting 30 minutes or more, or repeated tonic-clonic convulsions occurring over a 30 minute period without recovery of consciousness between each convulsion'. Main outcome measures included cessation of convulsion or episode of status epilepticus, number of additional drugs needed to stop the convulsion, rates of respiratory depression, and hospital admissions due respiratory depression. Only one trial was identified that compared lorazepam and diazepam given either intravenously or rectally, depending on venous access.

The authors concluded that there was no evidence to suggest that intravenous lorazepam should be preferred to diazepam as the first-line drug in treating acute tonic-clonic convulsions including convulsive status epilepticus in children. There was some evidence that rectal lorazepam may be more effective and safer than rectal diazepam, but the data were insufficient to indicate that lorazepam should replace diazepam as the first choice rectal drug in treating acute tonic-clonic convulsions and convulsive status epilepticus.²⁰⁴

Primary evidence

Allredge 2001²⁰⁵

Allredge and colleagues undertook a randomised, double-blind trial to evaluate intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus. Adults with prolonged (lasting five minutes or more) or repetitive generalized convulsive seizures received intravenous diazepam (5mg), lorazepam (2mg), or placebo. An identical second injection was given if needed.

Of the 205 participants enrolled, 66 received lorazepam, 68 received diazepam, and 71 received placebo. Status epilepticus had been terminated on arrival at the emergency department in more individuals treated with lorazepam (59.1%) or diazepam (42.6%) than those given placebo (21.1%) ($p=0.001$). After adjustment for covariates, the odds ratio for termination of status epilepticus by the time of arrival in the lorazepam group as compared with the placebo group was 4.8 (95% CI, 1.9 to 13.0). The odds ratio was 1.9 (95% CI, 0.8 to 4.4) in the lorazepam group as compared with the diazepam group and 2.3 (95% CI, 1.0 to 5.9) in the diazepam group as compared with the placebo group. The rates of respiratory or circulatory complications (indicated by bag valve-mask ventilation or an attempt at intubation, hypotension, or cardiac dysrhythmia) after the study treatment was administered were 10.6% for the lorazepam group, 10.3% for the diazepam group, and 22.5% for the placebo group ($p=0.08$).²⁰⁵

Leppick 1983²⁰⁶

Leppick and colleagues compared lorazepam with diazepam for the treatment of status epilepticus in a double-blind, randomised trial. Seventy-eight individuals with 81 episodes were enrolled. Participants received one or two doses of either 4 mg of lorazepam or 10 mg of diazepam intravenously.

Seizures were controlled in 89% of the episodes treated with lorazepam and in 76% treated with diazepam although this difference was not statistically significant. The times for onset of action of the medications did not differ significantly. Adverse effects occurred in 13% of the lorazepam-treated group and in 12% of the diazepam-treated group (assumed to be non-significant). Respiratory depression and arrest, the most

frequent adverse effects, were treated symptomatically; no adverse sequelae were noted.²⁰⁶

Treiman 1998²⁰⁷

Treiman and colleagues conducted a five-year randomised, double-blind, multi-centre trial of four intravenous regimens: diazepam followed by phenytoin, lorazepam, phenobarbital, and phenytoin. Individuals were classified as having either overt generalized status epilepticus (defined as easily visible generalized convulsions) or subtle status epilepticus (indicated by coma and ictal discharges on the electroencephalogram, with or without subtle convulsive movements such as rhythmic muscle twitches or tonic eye deviation). Treatment was considered successful when all motor and electroencephalographic seizure activity ceased within 20 minutes after the beginning of the drug infusion and there was no return of seizure activity during the next 40 minutes.

In an intention-to-treat analysis, the differences among treatment groups were not significant, either among those with overt status epilepticus ($p=0.12$) or among those with subtle status epilepticus ($p=0.91$). There were no differences among the treatments with respect to recurrence during the 12-hour study period, the incidence of adverse reactions, or the outcome at 30 days.²⁰⁷

No RCTs for the management of status epilepticus in children were identified post Cochrane review.

12.3.2 How should non-convulsive status epilepticus be managed in adults and children in the hospital setting?

No systematic reviews or RCTs were identified.

12.4 *How should refractory status epilepticus be managed in adults and children in the hospital setting?*

Treatment of refractory status epilepticus in secondary care should follow the suggested guidelines (see Appendix C). **[D]**

In adults, propofol or thiopental should be used to control refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

In children, midazolam or thiopental should be used to control refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

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

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

If either the whole protocol or intensive care is required the tertiary centre should be consulted. **[GPP]**

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

It should be noted that pentobarbital is not available in the UK for use in humans and so cannot be recommended as a treatment option in status.

Evidence statements

Midazolam and propofol and pentobarbital are all effective in controlling refractory status epilepticus in adults. (III)

Midazolam, diazepam, isoflurane, thiopental and pentobarbital are all effective in controlling refractory status epilepticus in children. (III)

A comparison of midazolam versus diazepam showed similar effectiveness in controlling refractory status epilepticus in children. (Ib)

Differences in costs for 24 hours treatment of benzodiazepines compared to barbiturates are small compared to savings produced by shorter treatment length and quicker return to consciousness. (III)

12.4.1 How should refractory convulsive status epilepticus be managed in adults and children in the hospital setting?

Details

Secondary evidence

No systematic reviews of RCTs were identified.

Primary evidence

Only one RCT on the management of refractory status epilepticus was found. The study population was children aged 2 to 12 years. No RCTs could be found for adults.

Singhi 2002²⁰⁸

One RCT was identified that compared the efficacy of continuous midazolam and diazepam infusion in the control of refractory status epilepticus in children aged 2 to 12 years. Refractory status epilepticus was defined as motor seizures uncontrolled after two doses of diazepam 0.3mg/kg and phenytoin infusion 20mg/kg. Children were randomised to either continuous midazolam (n=21) or diazepam infusion (n=19) in incremental doses.

Refractory status epilepticus was controlled in 18 (86%) and 17 (89%) in the midazolam and diazepam groups respectively. The difference was not significant. Median time to seizure control was 16 minutes in both groups, but seizures recurred significantly more

often in the midazolam group (57% vs 16% in the diazepam group, $p < 0.05$). Approximately half the children needed mechanical ventilation, and 40% had hypotension in both groups. The mortality was higher in the midazolam group (38% vs 10.5%) but the difference was not highly significant ($0.05 > p < 0.1$).²⁰⁸

No RCT evidence on thiopentone and phenobarbitone was identified.

Other evidence

Claassen 2002²⁰⁹

Claassen and colleagues compared the efficacy of midazolam, propofol, and pentobarbital in terminating seizures and improving outcomes in adults with refractory status epilepticus. Inclusion criteria were peer-reviewed studies of adults with status epilepticus refractory to at least two conventional AEDs. Main outcome measures were the frequency of immediate treatment failure, mortality, and titration goal (seizure suppression vs EEG background suppression). 28 studies were included, but there was no documentation of quality assessment. However, the authors did note limitations of review due to the small numbers of reported cases, publication bias, and the retrospective nature of the included studies. Other limitations noted were the lack of continuous EEG monitoring in many cases, and the changes in intensive care management over the time period of the review (1980 – 2001).

Summary statistics were calculated, but no details of the meta-analysis were given. However, included case series and reports did show that midazolam, propofol and pentobarbital were effective in controlling seizures.

Brown 1998²¹⁰

Brown and Levin reviewed the evidence relating to the mechanism of action, clinical efficacy, adverse effects, and therapeutic considerations of using propofol in the management of individuals with refractory status epilepticus. Most of the evidence described the use of propofol after other treatments failed or were not tolerated. The

initiation of propofol usually resulted in termination of seizure activity and/or EEG burst suppression within seconds that was sustained during drug use. Propofol was also well tolerated. The review concluded that although promising results had been seen, controlled clinical trials were necessary to assess the comparative efficacy, adverse effects, and clinical outcomes of propofol in refractory status epilepticus.

The majority of the included papers discussed the use in adults only, but there were two papers that described the use of propofol in children. One case report of a 9 month old child described how seizure activity was reduced within 30 seconds of administration and EEG burst suppression was documented during administration. Another paper described the use of propofol in 5 children aged 19 months to 19 years. Seizure activity resolved in all the children, and treatment was withdrawn within 20 minutes to 48 hours (from both reports) without a return of seizure activity.²¹⁰

Niermeijer 2003²¹¹

The evidence on the efficacy and safety of propofol in the treatment of refractory status epilepticus was reviewed. 22 articles were included, of which only two were non-randomised studies comparing treatments, and the rest were case series or reports.

The results of the two studies comparing the effectiveness of propofol with midazolam and high dose barbiturates in adults are shown below:

- Seizure control was achieved in 5 of the 8 (63%) treatments with propofol compared with 9 of 11 (82%) treatments with high dose barbiturates ($p=0.60$). Only one of the adults treated with propofol survived compared with 4 of the 8 treated with high dose barbiturates ($p=0.28$).²¹²
- Seizure control was achieved in 9 of the 14 (64%) adults treated with propofol compared with 4 of the 6 (67%) treated with midazolam ($p\geq 0.61$). There was no significant difference in mortality rates. However, for individuals with APACHE II scores of 20 or more, propofol was associated with higher mortality than midazolam ($p=0.05$).²¹³

Gilbert 1999²¹⁴ and Gilbert 1999²¹⁵

Gilbert and colleagues published two systematic reviews of the efficacy and mortality, and the complications and costs of the treatment of refractory generalised status epilepticus in children. Refractory status epilepticus was defined as continued status epilepticus despite receiving at least two anticonvulsants in appropriate doses. The study population was children aged 1 month to 18 years. Included study designs were case reports, and retrospective or prospective studies. 111 children from 12 studies published between 1983 and 1998 met the inclusion criteria.

Although summary statistics were presented, no details of the meta-analysis were reported. However, included studies did show that diazepam, midazolam, thiopental, pentobarbital and isoflurane were effective in controlling seizures.

Health economicsGilbert 1999²¹⁵

The study presented a review of the medical literature on complications and costs of treatment of refractory generalized convulsive status epilepticus in children.

The authors argued that complications and costs as presented in their study appeared to favour continuous infusion of a short-acting benzodiazepine such as midazolam a reasonable first choice. However, there is need for proper randomised trials because the authors believed that the published data included in the review contained non-treatment-related biases that precluded statistical comparisons or evidence based recommendations.

Of the bolus doses described in the literature, midazolam was the most expensive (\$9.34), followed by diazepam (\$2.80), pentobarbital (\$2.35) and thiopental (\$1.84). For continuous dosing, costs are presented per 24-hour period. Midazolam was the most expensive (\$239), followed by diazepam (\$228.69), thiopental (\$88.48) and pentobarbital (\$11.28).

They found that the differences in costs for 24 hours treatment of benzodiazepines compared to barbiturates were small compared to savings produced by shorter length of treatment and return to consciousness.²¹⁵

12.4.2 How should refractory non-convulsive status epilepticus be managed in adults and children in the hospital setting?

No systematic reviews or RCTs were identified.

13 Information needs of individuals, families, and carers

13.1 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.

13.2 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. **[C]**

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

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. **[GPP]**

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). **[GPP]**

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

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

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

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. **[GPP]**

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 review²¹⁶ 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 review²¹⁶ were presented with research identifying specific information needs at specific points on the care pathway was summarised.

Secondary evidence

Couldridge 2001²¹⁶

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:

- Epilepsy in general; diagnosis and treatment options; medication and side effects; seizures and seizure control; prognosis; injury prevention; psychological issues (especially stress); social security, driving and insurance; employment; life style and social issues.

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.²¹⁷
- 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.

13.3 *What information is required at different stages of the care pathway*

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. **[GPP]**

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. **[GPP]**

Evidence statement

*Information is needed on managing the condition in children with new onset seizures.
(III)*

Details

McNelis 1998²¹⁸

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.²¹⁸

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. **[D]**

Evidence statement

Adults want information about the reasons for tests, the results and meaning of these results. (III)

Details

Dilorio 1993²¹⁹

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.²¹⁹

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 2002²²⁰

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.²²⁰

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). **[C adults, GPP children]**

Individuals and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. **[GPP adults, C children]**

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 fears, and providing emotional support as soon as possible after diagnosis. (III)

Details

Averis 1996²²¹

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.²²¹

CSAG 2000¹¹

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.¹¹

Goldstein 1997²²²

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.²²²

May 2002²²³

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.²²³

Buck 1996²²⁴

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.²²⁴

Ridsdale 2002²²⁰

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.²²⁰

Ridsdale 1999²²⁵

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.²²⁵

Austin 2002²²⁶

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.²²⁶

Kennelly 2002²²⁷

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 2003²²⁸

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.²²⁸

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. **[C]**

The risk of SUDEP can be minimized by:

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

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

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.

[C]

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 2002²²⁷

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.'*²²⁷

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. **[GPP]**

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 1997²²⁹

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.²²⁹

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. **[C]**

Evidence statement

Individuals want accurate and balanced information on surgery. (III)

Swarztrauber 2003²³⁰

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.²³⁰

Special groups – see relevant sections

13.4 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 Report¹⁷ is presented and a further review article was identified that summarized the available evidence on the mortality associated with epilepsy up to 1996.²³¹

Secondary evidence

The National Sentinel Clinical Audit of Epilepsy-Related Death¹⁷

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.¹⁶ 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.²³²

SUDEP is defined²³³ 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 factors²³⁴ 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.²³⁵ 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 of SUDEP compared to people with fully controlled seizures.²³⁵ Tomson,²³⁶ 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.²³⁷ 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.^{234;235;238;239}

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 1997²³¹

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.²³¹

14 Women of childbearing age with epilepsy

14.1 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.²⁴⁰

14.2 ***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. **[C]**

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. **[C]**

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

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.²¹⁶

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.

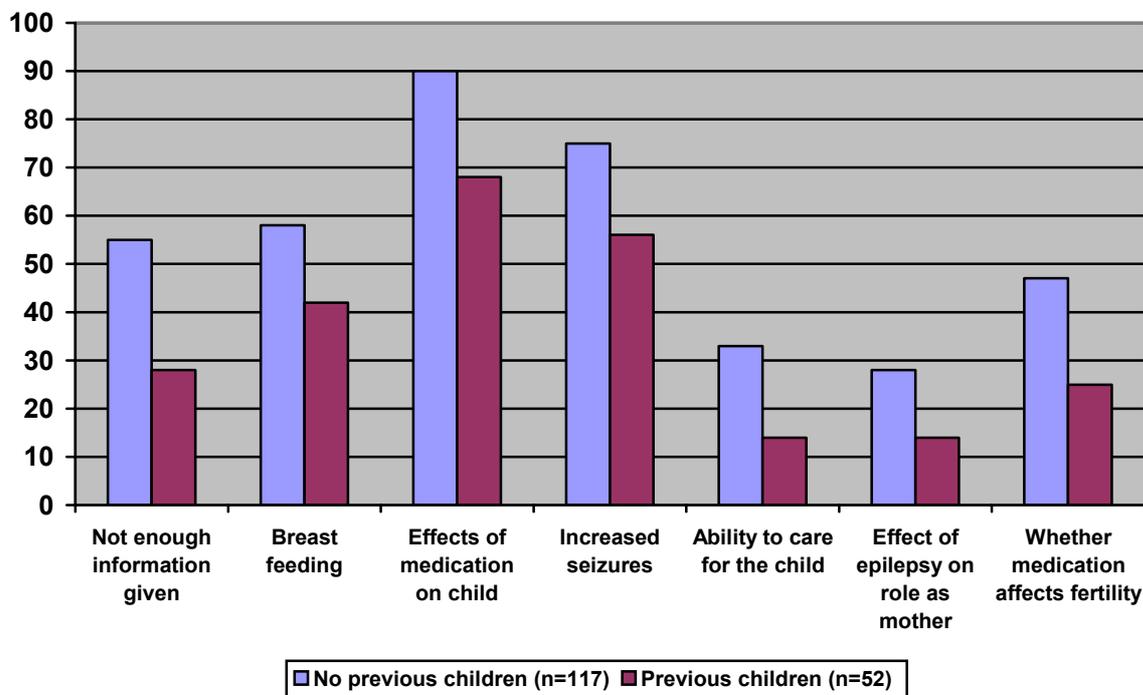
Since the publication of the systematic review described above²¹⁶, two large surveys of women with epilepsy were found.

Crawford 1999²⁴¹

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 Table 17).

Table 17 Concerns about pregnancy²⁴¹ 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.²⁴¹

Crawford 2003²⁴²

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 Table 18.

Table 18 Preferred time to receive information²⁴² 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.

Effect of Epilepsy on:	Diagnosis (%)	Before Puberty (%)	At Puberty (%)	Before considering pregnancy (%)	When considering pregnancy (%)	Approaching menopause (%)
Periods	35	32	15			
Contraception	25	6	30	15	2	1
Pregnancy	17	2	10	42	9	1
Risk of child developing epilepsy	19	1	5	41	15	
AEDs and pregnancy fetal development	16	1	5	43	13	
Menopause	19					58

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.²⁴²

14.3 *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. **[B]**

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. **[GPP]**

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%). **[C]**

In women of childbearing potential, the risk of the drugs (see Section on AEDs above) 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 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. **[A (NICE)]**

In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs (see Section on AEDs above) 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. **[A (NICE)]**

Prescribers should 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. **[GPP]**

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. **[GPP]**

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. **[GPP]**

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
- effectiveness
- side effects (see Section on)

Evidence statements, recommendations and reviews are presented for each of the four areas above. (For side effects, see Section on Pharmacological treatment)

14.4 *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 Table 19). 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 19 Seizure frequency during pregnancy and puerperium

Study	Participants	Number of participants	Definition of seizure rate change(s)	Increased	Unchanged	Decreased
Bardy 1987 ²⁴³	Women who had at least 2 epileptic seizures fulfilling the criteria of the WHO Dictionary of Epilepsy, with the first seizure occurring before pregnancy	154 pregnancies in 140 women	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	32%	54%	15% ⁱⁱ
Gjerde 1988 ²⁴⁴	Women who had epilepsy and used one or more AEDs for at least one year prior to pregnancy	78 pregnancies in 66 women	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	17%	67%	17%

ⁱⁱ Percentages may not add to 100% due to rounding errors

Study	Participants	Number of participants	Definition of seizure rate change(s)	Increased	Unchanged	Decreased
Schmidt 1983 ²⁴⁵	Women who had three or more verified epileptic seizures who completed the pregnancy	136 pregnancies in 122 women	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	37%	50%	13%
Tanganelli 1992 ²⁴⁶	Women with epilepsy	138 pregnancies in 97 women	Increased or decreased frequency defined as a 10% or more change during pregnancy when compared with the 9 months prior to pregnancy	17%	80%	3%
Tomson 1994 ²⁴⁷	Women who were treated with AEDs for epilepsy since the beginning of pregnancy	93 pregnancies in 70 women	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	15%	61%	24%

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^{243;245;246} 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 ($p < 0.001$).²⁴³

Increased seizures were seen in six pregnancies in the Schmidt study²⁴⁵ and non-adherence and sleep deprivation were associated with five of these.

Tanganelli and Regesta²⁴⁶ 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,²⁴³ seizures occurred during labour in 10 cases, an incidence nine times greater than the average.

Bardy²⁴⁸ 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.

14.5 *Teratogenic effects of AEDs whilst pregnant or breastfeeding*

The evidence relating to the teratogenic effects of AEDs was not reviewed in detail as this area was not a KCQ of the GDG and was addressed by the technology appraisals on the newer AEDs. It should be noted that this is an area where many important questions remain unanswered and further research is needed, notably by using prospective pregnancy registers.

A recent Epilepsy Research Foundation Workshop reviewed the evidence base in relation to AEDs and pregnancy and their findings, together with those of other studies, are summarised here.²⁴⁹

Pregnancy in women with epilepsy is known to be associated with a higher risk of congenital malformations.²⁵⁰⁻²⁵² However, congenital abnormalities are associated with the use of AEDs rather than the epilepsy itself.^{251;253}

The most common major fetal malformations associated with AEDs are: neural tube defects, orofacial defects, congenital heart abnormalities and hypospadias. Minor fetal malformations reported include: hypertelorism, epicanthic folds and digital hypoplasia. 'Fetal anticonvulsant syndromes', comprising typical dysmorphic craniofacial features and a range of musculoskeletal abnormalities have also been described in association with AED treatment in pregnancy.^{254;255}

Several factors have been identified to account for this increased risk, including the direct teratogenic effects of AED therapy and indirect effects of these drugs by interfering with folate metabolism. Little is known about the psychomotor development of children born to women with epilepsy because few prospective studies have been conducted. Retrospective studies suggest that impaired cognitive development may be associated with maternal drug therapy, notably valproate.²⁵⁶

Secondary evidence

NICE³¹

One technology appraisal of the effects of AED therapy in pregnancy was identified. The evidence base was summarised as follows:

'Few data are available on the use of newer antiepileptic drugs in pregnancy, and it is not yet possible to fully assess the risk of teratogenicity associated with them. Preliminary data from the UK Epilepsy and Pregnancy Register (based on the outcomes of 2028 pregnancies) suggest that the crude rates for risk of major congenital malformation were 4% (95% confidence interval 3.2% to 5.3%) in women taking one antiepileptic drug and 6.3% (95% CI, 4.3% to 9.1%) in women taking more than one. There are also data for a small group of women with epilepsy (5.9% of the total) who were not exposed to antiepileptic drugs during pregnancy. The crude malformation rate in this group was 0.9% (95% CI, 0.2% to 4.7%). For the older drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), and the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%). The risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%), but no risks were reported for any of the other newer agents. These data suggest that sodium valproate is associated with a statistically significantly higher risk of malformations than carbamazepine. Although the crude rate for lamotrigine was lower than for sodium valproate, the difference was not statistically significant.'³¹

No systematic reviews or prospective cohort studies on AEDs and breastfeeding were identified.

14.6 Effectiveness of AEDs whilst pregnant or breastfeeding

Secondary evidence

No systematic reviews of the effectiveness of AED therapy whilst pregnant or breastfeeding were identified. (See [Increased risk of seizures](#))

14.7 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. **[A (NICE)]**

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. **[A (NICE)]**

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

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. **[D]**

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

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). **[D]**

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

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

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. **[D]**

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.^{31;257}

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 2002²⁵⁸

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.{1163}

Oral contraception ('The pill')

Coulam 1979²⁵⁹

In 1979, Coulam and Annegers presented the results of a record review of 82 women with epilepsy who were also taking oral contraception.²⁵⁹ 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.

The authors then reviewed the literature on oral contraceptive failures in women taking AEDs or barbiturates. Including the women above described by Coulam and Annegers, there were 25 failures in women taking AEDs either as monotherapy or in combination.

Most women were taking the equivalent of 50mcgs of oestrogen, with a few taking 10mcgs of oestrogen, and one taking 80mcgs of oestrogen.

The authors concluded that the rate of oral contraceptive failure is higher among women taking AEDs.²⁵⁹

Back 1988²⁶⁰

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.²⁶⁰

No evidence was found on the most effective dose of oral contraception, or the most effective regimen. A recent guideline²⁴⁰ 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).²⁴⁰

Hormone-releasing intrauterine devices

Bounds 2002²⁶¹

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-years²⁴⁰, and was better than rates for barrier methods (15 to 20 per 100 woman-years).^{240;261}

Progesterone implants

Haukamaa 1986²⁶²

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{3655}

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.{3655}

The use of an increased dose was also proposed in another review of emergency contraception,²⁶³ 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'.²⁴⁰

14.8 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. **[B]**

Care of pregnant women should be shared between the obstetrician and the specialist. **[GPP]**

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. **[GPP]**

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). **[GPP]**

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)

14.8.1 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 2000²⁶⁴

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.²⁶⁴

Tanganelli 1992²⁴⁶

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%).²⁴⁶

Olafsson 1998²⁶⁵

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.²⁶⁵

14.8.2 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.²⁶⁶ 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
- the gestational age at scanning
- the skill of the operator
- the quality of the equipment being used
- the time allocated for the scan.

The guideline recommended that 'pregnant women should be offered an ultrasound scan to screen for structural anomalies, ideally between 18 to 20 weeks of gestation, by an appropriately trained sonographer and with equipment of an appropriate standard as outlined by the National Screening Committee'.²⁶⁶

14.9 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. **[D]**

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.²⁶⁷

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.²⁶⁷

No RCTs of different levels, or different timing of folic acid supplementation in women with epilepsy were identified.

A narrative review²⁶⁸ 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.’²⁶⁸

14.10 What are the dangers of seizures in women who are pregnant or post-natal?

In all women with epilepsy, seizure freedom during pregnancy should be sought. **[GPP]**

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). **[C]**

Women with generalised tonic-clonic seizures should be informed that the fetus 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. **[D]**

Women should be re-assured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury. **[D]**

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. **[GPP]**

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

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

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. **[GPP]**

Information should be given to all parents about safety precautions to be taken when caring for the baby (see Appendix D). **[C]**

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 Foundation²⁴⁹ 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.²⁴⁹

Effect of maternal seizures on the woman

The Confidential Enquires into Maternal Deaths in the United Kingdom²⁶⁹ 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.²⁶⁹

Effect of maternal seizures during labour

The expert workshop²⁴⁹ 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

Fox 1999²⁷⁰

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.²⁷⁰

14.11 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.

[D]

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.¹⁷²

14.12 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. **[C]**

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 2002²⁷¹

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.²⁷¹

14.13 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. **[D]**

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. **[GPP]**

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.²⁴⁰

14.14 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. **[GPP]**

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. **[GPP]**

Evidence statement

No evidence for the effectiveness of joint epilepsy and obstetric clinics could be found.

Details

No systematic reviews or RCTs were identified.

15 People with learning disabilities and epilepsy

15.1 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.²⁷²

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.²⁷³

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 field²⁷⁴ 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.²⁷⁴

15.2 Who should manage and treat epilepsy in people with learning disabilities?

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. **[GPP]**

Learning disabilities are a common association with epilepsy. The management and treatment of the epilepsy should be undertaken by a specialist, working within a multi-disciplinary team. **[C]**

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)

15.2.1 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 1989²⁷⁵

A cohort of 215 people (mean age 38 years \pm 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 ($p<0.005$).²⁷⁵

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 2002²⁷⁶

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%).²⁷⁶

This study compares specialists with non-clinical staff, not general physicians.

15.3 *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. [C]

It is important to have an eye witness account supplemented by corroborative evidence (e.g. a video account), where possible. (D)

Clear, unbiased reporting is essential. Witnesses may need education to describe their observations accurately. (GPP)

Evidence statements

Stereotypic behaviour and other abnormal movements may be confused with seizures. (III)

15.3.1 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 8.2 and no primary studies were identified that answered this question.

15.3.2 What are the practical difficulties in establishing the diagnosis in this group?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

DeToledo 2002²⁷⁶

'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.²⁷⁶

15.4 Are there difficulties in doing investigations in this group?

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

Facilities should be available for imaging under anaesthesia, if necessary. **[D]**

In the child presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. **[GPP]**

Evidence statements

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.

15.4.1 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 1994²⁷⁷

An EEG recording could not be made in 10 of 63 institutionalised individuals with learning disabilities due to 'co-operation problems'.

Consensus guideline recommendations

Anon 2001²⁷⁴

Kerr and colleagues recommended that:

- Facilities should be available for imaging under general anaesthesia.

15.5 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. **[D]**

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. **[A (NICE)]**

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)

15.5.1 Which drugs should be avoided in people with learning disabilities and epilepsy?

Details

Secondary evidence

The NICE technology appraisal of newer drugs for adults³¹ with epilepsy concluded that:

- Generally, little evidence was found on the use of these agents in specific subgroups, such as older people or adults with learning disabilities. No monotherapy studies in adults with learning disabilities were found, and only three studies of adjunctive therapy reported results exclusively from this population. There was some evidence from one study that both lamotrigine and gabapentin have some beneficial effects on behaviour in adults with learning disabilities.
- The Committee noted the lack of high-quality evidence on which to base recommendations on the most appropriate treatments for adults with learning disabilities.
- The Committee noted that the importance of regular monitoring of effectiveness and tolerability was the same for adults with learning disabilities as for the general population of people with epilepsy.³¹

Primary evidence

No further RCT evidence was identified.

Consensus guideline recommendations

Anon 2001²⁷⁴

The need to consider the side effect profile of AEDs, notably in relation to cognitive and behavioural effects, was emphasised.

15.6 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. **[B]**

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)

15.6.1 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 2000²⁷⁸

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.²⁷⁸

Annegers 1979²⁷⁹

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).²⁷⁹

Brorson 1987²⁸⁰

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%.²⁸⁰

Goulden 1991²⁸¹

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.²⁸¹

Sillanpaa 1975²⁸²

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.²⁸²

15.7 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. **[GPP]**

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. **[C]**

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)*

15.7.1 Is there increased mortality in people with learning disabilities and epilepsy?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Brorson 1987²⁸⁰

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.²⁸⁰

Forsgren 1996²⁸³

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 7 year 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.²⁸³

Forssman 1970²⁸⁴

A study 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).²⁸⁴

Nashef 1995²³²

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.²³²

15.7.2 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 2001²⁸⁵

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)²⁸⁵

16 Young people with epilepsy

16.1 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.²⁸⁶

16.2 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. **[C]**

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

[GPP]

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.

[GPP]

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. **[GPP]**

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.

16.3 *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?).¹⁷⁵

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.¹⁷⁵

16.4 Is there any evidence of effectiveness for any given strategies proposed to improve outcomes for adolescents?

The studies reported in the above systematic review¹⁷⁵ 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. **[D]**

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. **[D]**

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 1999²⁸⁷

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 2002²⁸⁸

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.

16.5 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. **[D]**

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 2001²¹⁶

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:

- 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

The review²¹⁶ identified one paper that dealt specifically with the experiences of young people with epilepsy.

Wilde 1996²⁸⁹

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.²⁸⁹

16.6 Should the diagnosis of epilepsy be revisited in this group?

The diagnosis and management of epilepsy should be reviewed during adolescence. [D]

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 1997²⁸⁷

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'.²⁸⁷

Expert evidence

Appleton 1999²⁸⁷

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.²⁸⁷

17 Older people

17.1 Introduction

Epileptic seizures are common in older people. In one UK study based on a large primary care computerized database the overall prevalence of epilepsy in people aged over 60 was 11.8 per 1000 and the overall annual incidence in those over 60 was 117 per 100 000.²⁹⁰ The majority of seizures in old age are either focal or focal in origin with secondary generalization.⁶

Cerebrovascular disease is the commonest cause of seizures in old age. Otherwise unexplained epilepsy occurring for the first time in old age may be an early presentation of cerebrovascular disease.^{6;291} As far as provoked seizures are concerned, common causes in this age group include iatrogenic seizures caused by existing drug therapy for other co-morbid conditions and alcohol.

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. **[A (NICE)]**

Specific issues in relation to the diagnosis and management of epilepsy in older people are not reviewed here.²⁹¹ The GDG decided that while the issue of epilepsy in older people was important it was not appropriate to include a separate section in the guideline on the diagnosis and management of epilepsy in this group.

The GDG felt strongly that older people with epilepsy should have access to the same range of investigations and treatment as any other group with epilepsy. The emphasis in the *National Service Framework for Older People* on rooting out age-related discrimination is noted here.²⁹²

Standard Two of the NSF around person-centred care includes the use of the Single Assessment Process, which will cut red tape and save older people

from having to provide the same personal details and discuss their needs with a range of different agencies. It will also make sure their needs and wishes lie at the heart of the process.²⁹²

All aspects of the NSF that are related to medicines management in older people are summarised in an accompanying report.²⁹³ All principles outlined in this report should be considered when prescribing for older people with epilepsy. However, as issues around medicines management in this group of individuals are not specific to AEDs, no additional recommendations have been made in this guideline.

There may be particular challenges in providing information and support for this group as there may be occasions where older people with epilepsy cannot make their own decisions due to decreased 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.²⁷³

18 People from black and minority ethnic groups

18.1 Introduction

The UK has a sizeable black and minority ethnic population.^{jj} 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.²⁹⁴

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.

^{jj}The 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.

18.2 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. [D]

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. [D]

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. [D]

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.

Details

No evidence was found in the Medicines Alliance review¹⁷⁵ or the Couldridge review²¹⁶ relating specifically to minority ethnic groups. One primary source of evidence was identified.²⁹⁵

Ismail and colleagues 2003²⁹⁵

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).

19 The care process for people with epilepsy

19.1 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).

19.2 *What features of the care process in primary care/shared care lead to improved health outcomes for adults and children with epilepsy?*

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

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. **[D]**

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. **[D]**

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. **[D]**

People with epilepsy should have an accessible point of contact with specialist services. **[GPP]**

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. **[GPP]**

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)

19.2.1 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.²⁹⁶

Primary evidence

SUDEP 2002¹⁷

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.¹⁷

Clinical Standards Advisory Group (CSAG) 2000¹¹*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.¹¹

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).¹¹

Primary care audits

Evidence is available on the quality of care provided in general practice through published audits conducted in the last ten years.²⁹⁷⁻³⁰¹ 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).²⁹⁸ 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%;²⁹⁸ 5%²⁹⁷) and the audit data were not disaggregated into adults and children.

19.2.2 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

19.2.2.1 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.^{11;17} 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 colleagues²⁹⁶ was excluded as this evaluated the opportunistic use of a prompt and reminder card in general practice as opposed to structured annual review.

19.2.2.2 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.^{11;302} The deployment of nurses trained in epilepsy care (specialist epilepsy nurses) working in primary care who could liaise with secondary care has been proposed.³⁰³

Secondary evidence

Bradley 2003³⁰⁴

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 RCT³⁰⁵ (and the follow-up paper³⁰⁶) 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 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 outcomes³⁰⁷ 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.³⁰⁴

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.

19.3 *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. **[D]**

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. **[D]** Children should have a regular structured review with a specialist. **[D]**

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.

[GPP]

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. **[D]**

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

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)

19.3.1 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 report¹⁷

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.¹⁷

Clinical Standards Advisory Group (CSAG) report 2000¹¹

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 studied³⁰⁸. 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.¹¹

Clinicians' perspectives on care

CSAG¹¹ 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 centripetal 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.¹¹

Independent Review of Paediatric Neurology Services In Leicester 2003³⁰⁹

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.³⁰⁹

Other primary evidence

Bradley 1999³¹⁰

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.³¹⁰

Reynders 2002³¹¹

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.³¹¹

19.3.2 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

19.3.2.1 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.¹¹ Specialised clinics have also been proposed by many authorities.^{11;302}

Secondary Evidence

Bowley 2000³¹²

In a recent narrative literature review of epilepsy in people with learning disabilities, no evidence of research in service delivery was identified.

Bradley 2003³¹³

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 epilepsy³¹³.

19.3.2.2 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,^{11;302} and detailed descriptions of the role have been proposed.

Secondary evidence

Bradley 2003³⁰⁴

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-being³¹⁴. 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 care³¹⁵ 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 expensive³⁰⁴.

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 2002³¹⁶

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 expensive³¹⁶.

Primary evidence

There were no RCTs identified as being published since the reviews presented above.

Health economics

Meads 2002³¹⁶

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.³¹⁶

19.4 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. **[GPP]**

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. **[GPP]**

It is recommended that all adults having a first seizure should be seen as soon as possible^{kk} by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. **[A (NICE)]**

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. **[A (NICE)]**

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

Evidence statement

No evidence of effectiveness for components of the care process for people with epilepsy in an A&E setting was identified.

kk The GDG considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.

19.4.1 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,³¹⁷ 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 report¹¹

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.¹¹

Other primary evidence

Ryan 1998³¹⁸

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.³¹⁸

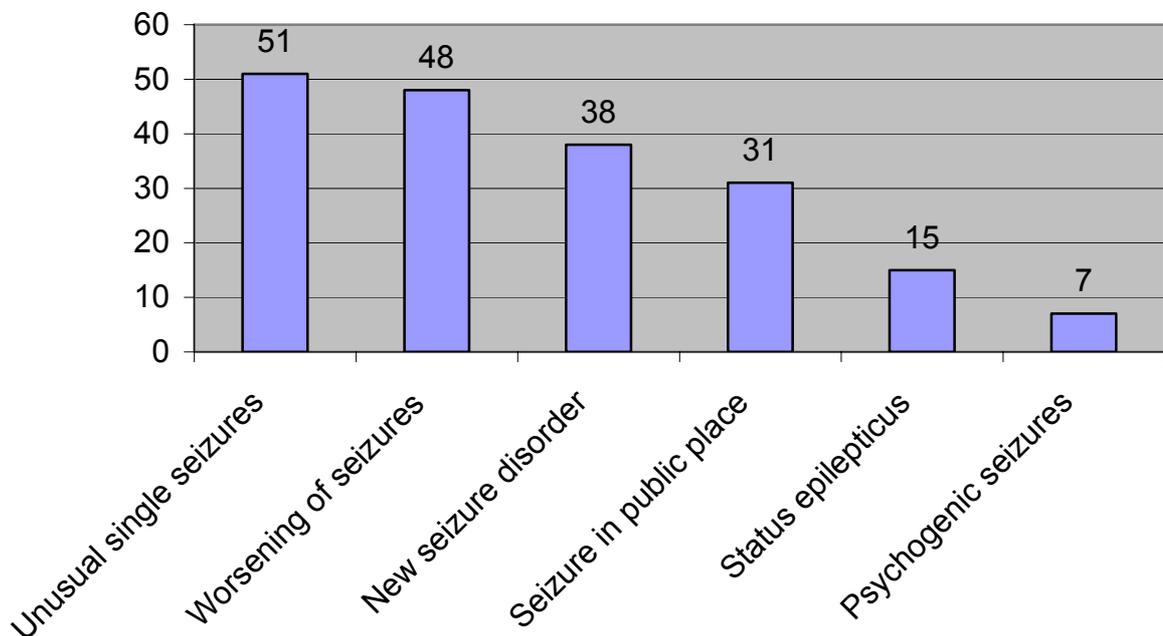
Reuber 2000³¹⁹

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 Figure 2). 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).³¹⁹

Figure 2 Causes of attendance³¹⁹ 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.³²⁰

19.4.2 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.

19.5 *How effective are individual/self management plans in adults and children with epilepsy?*

19.5.1 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.

19.5.2 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. **[GPP]**

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

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

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

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 1990³²¹

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 ($F(1,24)=4.18$, $p<0.05$).³²¹

May 2002²²³

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.²²³

Lewis 1990³²² and Lewis 1991³²³

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).³²²

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).³²³

Tieffenberg 2000³²⁴

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.³²⁴

20 Research Recommendations

- Large, population based studies are needed to assess current rates of misdiagnosis in both adults and children with epilepsy.
- Diagnostic studies are needed to establish the utility, sensitivity and specificity of structured questionnaires compared with a defined 'gold standard' to help medical practitioners differentiate between the common causes of attack disorders in adults and children.
- Economic evaluations are needed on the cost-effectiveness of investigations for the diagnosis of epilepsy in both adults and children. Economic evaluations that consider the incremental cost effectiveness of performing specific number of EEGs, or the cost effectiveness of video EEG as compared to EEG or MRI are needed to inform practice.
- Economic evaluations are needed into the cost effectiveness of training programmes for healthcare professionals (general practitioners, nurses and specialists) involved in the diagnosis of epilepsy.
- Diagnostic studies are needed to establish the utility, sensitivity and specificity of 24 hour ambulatory EEG, compared to standard and sleep/induced/deprived EEG in the diagnosis of suspected epilepsy and epilepsy syndromes.
- Large, population based cohort studies are needed to further investigate the prognosis of epilepsy in children, with a specific emphasis on the proportion of children who become refractory to drug therapy and become candidates for surgery.
- The use of steroids in the treatment of nonconvulsive status epilepticus should be evaluated in adequately powered RCTs that report all relevant clinical outcomes.
- RCTs are needed to establish the relative effectiveness of epilepsy clinics, in particular for special groups, when compared with usual care.

- The use of epilepsy specialist nurses in primary and secondary care and GPs with a special interest in epilepsy should be evaluated in adequately powered RCTs that report all relevant clinical outcomes for individuals with epilepsy.
- Qualitative studies are needed to explore both the process and outcome of risk communication in the consultation between healthcare practitioners and the individual with epilepsy and their carers. These should include the perspectives of all relevant parties.
- Qualitative studies are needed to determine the experiences of individuals from black and minority ethnic groups with epilepsy in relation to their health needs and beliefs and the role of healthcare professionals in providing culturally sensitive care.
- Qualitative and quantitative studies are needed to determine the experience of individuals with learning disabilities and in particular, to compare outcomes for people with epilepsy and learning disabilities managed by different groups of clinicians.
- Qualitative studies are needed about the information needs of individuals with epilepsy with respect to SUDEP. The research should focus on different groups of individuals, particularly children and their families.
- A large RCT of longer-term clinical outcomes and cost-effectiveness of standard and new antiepileptic drugs (SANAD) has been sponsored by the NHS R&D Health Technology Appraisal Programme. The study will compare monotherapy with clinicians' first-choice standard drug with appropriate comparators from the newer AEDs.

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